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# **Factors that Facilitate Regulatory Approval for Drug/Device Combination Products in the European Union and United States of America: A Mixed Method Study of Industry Views**

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**Submitted for the Degree of Doctor of Philosophy**

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## **Declaration**

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Doctor of Philosophy is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed: \_\_\_\_\_ Date: \_\_\_\_\_

Fiona Masterson

## **Abstract**

Drug/device combination products play a vital role in diagnosis and treatment of a wide range of disorders, including chronic disorders such as heart disease, cancer, respiratory disease, and diabetes. Doctors consider them a vital part of healthcare. The market for these products is growing. They include and combine products that originate in the pharmaceutical, biopharmaceutical, biotechnology, and medical device sectors. Thus they draw on different conventions and face complex regulatory processes. No single regulatory framework has prevailed for these products and obtaining timely regulatory approval has proven challenging. However, research on these processes is scarce and the experience of life sciences companies bringing them to market remains poorly understood. This thesis enters this gap, offering insight into the experiences of those involved in obtaining regulatory approval of drug/device combination products in the European Union and the United States, and providing a conceptual model which life sciences companies can use when seeking regulatory approval for drug/device combination products.

The thesis begins with a comprehensive review of European Union and the United States regulatory frameworks for drug/device combination products, the agencies involved in regulation for drug/device combination products, and the regulatory pathway of drug/device combination products taken in their journey to market. A review of the literature addressing regulatory processes of drug/device combination products in the European Union and United States follows. This review identifies a lack of research, quantitative or qualitative, focused on drug/device combination product regulatory processes.

Chapter five and six explores the experiences of those working on the regulation of drug/device combination products through a mixed methods research strategy based on a sequential exploratory design. The study utilised two phases of data collection – an initial qualitative phase followed by a quantitative phase. The participants in both phases of the study were senior, high calibre personnel with years of experience with drug/device combination product regulatory frameworks. Such people often do not discuss what they have learned from their work, because the life sciences industry is highly competitive; their

participation in the interviews and survey portions of the study will make this thesis of particular value to others in the industry, as well as researchers and policy makers.

The interviews identified a number of facilitating factors for obtaining regulatory approval in the EU and US markets, including: effective collaboration with partners involved with obtaining regulatory approval; effective management of regulatory relationships; smart leveraging of existing technology; and experience with regulatory processes. Participants also identified the impact of the type of drug/device combination product on its likelihood of gaining regulatory approval. A conceptual model was designed to depict these factors.

The survey questions reflected the issues the qualitative phase of the study had identified, and yielded results that corroborated the results of the interview phase. Surveys also identified elements that were not identified during the interviews such as having strong clinical data supporting a product, the product's primary mode of action being chemical rather than mechanical, the importance of comprehensive regulatory submission documentation, and engineering well designed products to address human factors. The initial conceptual model was revised to reflect these additional facilitating factors.

The analysis generally ruled out a meaningful interaction between organisation types and sizes (by annual sales and by number of employees) and the facilitating factors respondents identified. Three differences were as follows. Employees of contract research organisations more than other types of organisations felt early engagement with the Office of Combination Products in the United States had a determinative effect. Employees of smaller companies (1-10 employees) were more likely to emphasise partnerships than employees of larger companies. Finally, an analysis revealed that employees of smaller companies emphasised the importance of the components having regulatory approval prior to inclusion in the drug/device combination product more than their counterparts at larger companies. However, all three of these differences were a matter of degree; respondents in all groups considered the factors to be facilitating.

Chapter six found that no statistically significant difference exists between an organisation's type or size and obtaining regulatory approval in either the European Union or the United States. However, product type and market had a significant effect, with the most common types of combinations finding the greatest regulatory success. Drug eluting stents and pre-filled syringes dominate combination products and products were more likely to achieve regulatory approval than other types of products.

The study contributes to knowledge in a variety of ways. The development of a conceptual model to depict the facilitating factors for obtaining regulatory approval of a drug/device combination product provides a theoretical contribution. This model provides, for the first time, a comprehensive understanding of these factors, providing a foundation that could be adapted to reflect specific drug/device combination products in either the European Union or the United States. The exploratory sequential design the researcher employed provides a methodological contribution which future researchers may be able to apply to determining facilitating factors for other types of life science product groups. The research results make a policy contribution, in that policy makers can use them as a reference for developing regulation for drug/device combination products and innovative products in general. By interviewing and surveying senior personnel in a highly competitive sector of the life sciences industry, the research provides a significant contribution to practice. Due to the applied nature of this research, life science professionals can translate the facilitating factors and conceptual model identified in this research in seeking regulatory approval for combination products. Given the growing nature of this field, this application has the potential to transform the nature of healthcare delivery in both the United States and the European Union.

## List of Publications arising from the Thesis

### Journal Papers

MASTERSON, F. & CORMICAN, K. (2013b) Overview of the regulation of medical devices and drugs in the European Union and the United States. *Therapeutic Innovation & Regulatory Science*, 47, 715-722.

MASTERSON, F. & CORMICAN, K. (2013a) Elemental Essentials: Regulation of Combination Products in the USA and the EU. *Journal of Medical Device Regulation*, 10, 74-79.

### Conferences

MASTERSON, F. (2011b) An Investigation of the Successful Commercialisation of Combination Products. *18<sup>th</sup> International Product Development Management Conference*. Delft University of Technology, Delft, Netherlands.

MASTERSON, F. (2014) Regulation of Drug-Device Combination Products in Europe and the United States: Lessons from the Front Line. *Medical Devices Summit Europe*. Dublin, Ireland.

MASTERSON, F. & CORMICAN, K. (2012) Success Enablers for the Development and Commercialisation of Combination Products: An Exploratory Study. *19<sup>th</sup> International Product Development Management Conference*. University of Manchester, UK.

### Published Abstract

MASTERSON, F. (2011a) Best Practice Framework for Regulation of Combination Products in the EU. *Drug Information Journal*, 45, 1.

### Posters

MASTERSON, F. (2011). Combination Products: Regulation and Development Framework. *DIA's 23<sup>rd</sup> Annual EuroMeeting*. Geneva, Switzerland.

MATSERSON, F. (2010). An Investigation of the Successful Commercialisation of Combination Products. *College of Engineering and Informatics Research Day*. Galway, Ireland.

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I would also like to thank all the participants who took part in the interviews and the respondents who took the time to complete the questionnaire survey. You are extremely busy individuals and I appreciate greatly the time you took in allowing me to interview you and take my survey.

Finally, I would like to express my gratitude to the College of Engineering and Informatics, for awarding me a fellowship to undertake this Ph.D. Thank you for giving me this wonderful opportunity that would not have been possible without your assistance.

## **Dedication**

This thesis is dedicated to my family for all of their love and support.



## List of Abbreviations

<b>Abbreviation</b>	<b>Description</b>
ALBC	Antibiotic-laden bone cement
API	Active Pharmaceutical Ingredient
CBER	Centre for Biologics Evaluation and Research
CDER	Centre for Drug Evaluation and Research
CDRH	Centre of Devices and Radiological Health
CE	Conformité Européenne
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use
CI	Clinical investigations
CPI	Critical Path Initiative
CRO	Contract Research Organizations
DFU	Diabetic Foot Ulcers
DES	Drug Eluting Stent
DPI	Dry Powder Inhalers
EMA	European Medicine Agency
EU	European Union
EUDAME	European Database for Medical Devices
FD&C	Food, Drug & Cosmetic
FDA	Food and Drug Administration
GHTF	Global Harmonisation Task Force
HDE	Humanitarian Device Exception
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDE	Investigational Device Exception
ISO	International Standards Organisation
MAH	Marketing Authorisation Holder
MAA	Market Authorisation Application
MDD	Medical Device Directive
MDEG	Medical Device Expert Group

MOA	Mode of Action
NBOG	Notified Bodies Operations Group
NCE	New Chemical Entity
NPD	New Product Development
NSE	Not Substantial Equivalent
OJEU	Official Journal of the European Union
OCP	Office of Combination Products
PM	Personalised Medicine
PMA	Pre Market Approval
PMOA	Primary Mode of Action
pre-IND meetings.	Pre-Investigational New Drug Meeting
US	United States
QSR	Quality System regulation
RFD	Request for Designation
SA	Scientific Advice
SPSS	Statistical Package for the Social Sciences
R&D	Research and Development

# 1 Introduction

*This chapter provides the reader with a background to the research. The motivation for the research is discussed. Next the scope of the research is outlined. The research questions and objectives are presented followed by a summary of the research methodology utilised for the investigation. Following this, the structure of the thesis is presented.*

---

## 1.1 Introduction

Remember Jack and Jill, who went up the hill for water? Jack fell down, broke his crown and mended it with vinegar and brown paper. This rhyme is from 1765 and it alludes to a drug/device combination of cider vinegar (the drug) and brown paper (the device). Brown paper soaked in apple cider vinegar and put across the forehead can often stop a headache within a few minutes. Of course, the drug/device combination products that are available today are significantly more sophisticated. Nowadays regulations play a critical role; no drug/device combination product can appear on the market until it has navigated the complex regulations that govern this process. A key challenge for those involved in trying to obtain marketing authorisation for drug/device combination products is how to navigate these regulations combined from different areas of life sciences; namely the drug and medical device worlds. This study's objective is to determine the enabling factors that helped those who successfully navigate this process. Those interviewed and surveyed for this research were senior and experienced personnel from a variety of organisations involved with obtaining marketing authorisation for a drug/device combination products. Drug/device combinations cover a diverse range of products used by millions of people (Gopaldaswamy and Gopaldaswamy, 2008, Eaglstein, 2014). This is a growing market (Transparency Market Research, 2015, Paulsen, 2010), often providing creative solutions to complex problems (Smith and Uhl, 2009, Shmulewitz and Langer, 2006, Gladfelter, 2009, Cramer and Rastogi, 2007, Lei, 2000, Levin, 2011, Lilly, 2011). Little attention has been paid to this area of study in the literature (Naughton, 2001, Dubin, 2007, Muni et al., 2005) and therefore this study is both timely and important.

The remainder of this chapter outlines the context, rationale and motivation for the study. The aim and objectives of the research are presented followed by a summary of the approach utilised for the research investigation. Following this, the novelty of the research and contribution to knowledge are outlined and the structure of the thesis is presented. Finally, the structure of the succeeding chapters in this thesis is previewed.

## **1.2 Research Context and Background**

A drug/device combination product combines two or more single-entity products such as a drug combined with a medical device, a drug combined with a biologic, or a medical device combined with both a drug and a biologic. Throughout this thesis, the term “Drug” refers to what the European Union (EU) terms a “medicinal product” and the United States (US) terms a “prescription drug.”

The US regulations 21 CFR 3.2(e) state that combination products include:

“(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labelling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.” (FDA, 2006b)

EU legislation does not provide a formal definition but this term is freely used to describe products that consist of a drug and a device in the EU.

The major product types in the drug/device combination product market include drug eluting stents, orthopaedic combination products; wound care combination products, prefilled syringes, inhalers, nebulisers, metered dose inhalers, dry powder inhalers, transdermal patches and intraocular implants. The following paragraphs give an overview of each of these product groups. They illustrate how important having an understanding of the regulatory process, is given that these products are often at the cutting edge of technology.

### *Drug-Eluting Stents*

Drug-Eluting Stents (DES), an implantable drug/device combination product, are the most famous of the drug/device combination product categories (Kamath et al., 2006). So far, drug-eluting stents epitomize the pinnacle of the drug/device combination product market, harnessing the strengths of the medical device industry and those of the drug or biologics industries to develop innovative medical products that could not have arisen from either sector alone. Drug-eluting stents (DES) revolutionised treatment of atherosclerotic heart disease, including myocardial infarction and occlusive coronary artery disease (Zilberman et al., 2010). Stents are miniature, expandable tubes that are inserted during angioplasty into a blocked section of the coronary artery to open the artery and increase blood flow. All stents incur risk of scar tissue forming and narrowing the artery again, but drug-eluting stents are coated with drugs that prevent scar tissue from growing into the artery. Examples of drugs used include Sirolimus and Paclitaxel. The first generation DES, the CYPHER™ Sirolimus Eluting Coronary Stent (Johnson & Johnson) and the Paclitaxel Eluting TAXUS™ Stent (Boston Scientific) were introduced in 2003 and 2004, respectively (Kamath et al., 2006, Zilberman et al., 2010). Since their inception, DESs have significantly reduced the rate of

clinical restenosis as compared to bare metal stents and conventional balloon angioplasty (Bangalore et al., 2012). Four medical device companies, Abbott Laboratories, Boston Scientific Corp., Medtronic Inc., and Terumo Corp. dominate the global market, enjoying a peak of \$4.5 billion in sales in 2009 (Devices, 2012).

### *Orthopaedic Combination Products*

The most common drug device combinations products in the combination product sector is antibiotic-loaded bone cement (ALBC). The primary aim of ALBC is infection control (Bistolfi et al., 2011). It has been used for more than 30 years as a delivery device for antibiotics in the treatment of musculoskeletal infections. Cement was originally used as a spacer to preserve the joint space and soft-tissue tension for later reconstruction. The addition of it to the cement, results in their elution into the involved tissue area, thus aiding the prevention of infection. As use of ALBCs grew, doctors began to add antibiotics to the cement when reimplanting a previously infected total joint. This positioning at the surgical site allows the administration of a high concentration of the drug, which would cause complications and toxicity if administered venously. A combination of medical device and pharmaceutical companies dominate the antibiotic market. The three most prominent companies, with the largest market share are Schering-Plough, Merck, and Depuy.

### *Wound Care Combination Products*

Wound care products principal objectives are ensuring timely wound healing and effective infection control. The rapid spread of modern epidemics such as obesity and diabetes (both chief causes of chronic wounds) the increase in hospital-acquired infections, and an increasing aging population are driving demand for advanced wound care products (Singer and Dagum, 2008). Drug/device combination products typically provide treatment for burns or wounds caused by underlying illnesses, as these types of wounds usually require more specific therapies such as active or moist or wound therapeutic products. Created to treat wounds such as pressure ulcers and diabetic foot ulcers, products such as Advanced Moist Wound Healing Products (alginate dressing, hydrogel dressing), Active Wound Healing Products (Skin replacements, collagen dressings, cell-based replacement,) and Antimicrobial Dressings (Silver antimicrobial dressing, non-silver antimicrobial dressing) (Boateng et al., 2008, Lee

and Mooney, 2012, Ulbrecht et al., 2004, Aziz et al., 2012) serve a growing market. A mix of medical device and pharmaceutical companies dominate. These include 3M, ConvaTec, DermaSciences, Hollister Incorporated, Human Biosciences, Smith & Nephew, B. Braun Melsungen, Coloplast, Genzyme, and Mölnlycke Health Care.

### *Prefilled Syringes*

Syringe and vial is the most common delivery system for injection but has limitations; it is easy to make errors in preparation and delivery of drugs (Makwana et al., 2011). To address this, more advanced drug/device combination products like insulin pens were developed in the 1980s to allow for convenient, safe self-administration of drugs. Around the same time, autoinjectors such as EpiPen were also developed for emergency treatment of anaphylaxis. More recently, auto-injectors were developed for the delivery of drugs for the treatment of other chronic diseases such as rheumatoid arthritis and multiple sclerosis. To improve the safety and convenience of these devices, single-use disposable devices have emerged (Kumar and Rahman, 2012). Injectable devices traditionally were mainly intended for delivery of human growth hormones and insulin. Technological innovations, however, has lead to them being used as combination therapies for the delivery of a wide selection of drugs, for example reproductive hormones (Sanghai et al., 2014).

### *Inhalers*

Since ancient times pulmonary routes have been used to treat respiratory diseases. Ancient remedies included employing leaves from plants, vapours from aromatic plants, balsam, and myrrh. Targeting the delivery of a drug into the lungs is one of the most important aspects of local or systemic drug delivery systems (Hickey, 2013). The use of inhaled aerosols permits discerning treatment of the lungs, attaining elevated drug concentrations in the airway and reducing systemic adverse effects. Not only is aerosol therapy used to treat lung disease, but increasingly inhalation is being explored as a method for systemic drug delivery (e.g., inhaled insulin). Furthermore, inhaled drug delivery is used to treat pulmonary vascular disease in addition to pulmonary infection and airway diseases. The success of inhaled drugs depends not only on the formulation, but perhaps even more on the delivery device and the patient's

skill at using the device in the correct manner. A deficient technique leads to decreased drug delivery and potentially reduced efficacy. A significant disadvantage of inhaled drug delivery is that the correct use of inhaler devices requires specific techniques (Hess, 2005). The asthma market is estimated to be worth approximately \$6 billion worldwide, and consists largely of inhaled products—bronchodilators and corticosteroids. It is a growing market because the prevalence of asthma is growing, particularly in developed countries. The main suppliers (including AstraZeneca, 3M and GlaxoSmithKline) have developed enhanced delivery devices, in addition to dry powder formulations and optimal medication particle size to improve penetration into the lung.

### *Transdermal Patches*

Transdermal drug delivery systems consist of self contained, individual dosage forms which, when put directly on skin, deliver the drug(s), through the skin, at an optimal rate to systemic circulation (Jain, 1997). Transdermal drug delivery systems offer many advantages over standard pharmaceutical dosage forms, for example elimination of first pass metabolism, continuous drug delivery, decreased frequency of administration, decreased side effects, and enhanced patient compliance (Hadgraft and Lane, 2005). Developments in synthetic materials and patch design have resulted in patches that are more aesthetically acceptable to patients and that deliver controlled dosing of active compounds in a less invasive manner.

The FDA approved the first transdermal system for systemic delivery—a patch that elutes scopolamine to combat motion sickness—for general use in 1979. Ten years afterwards, nicotine patches were the earliest transdermal blockbuster, increasing the popularity of transdermal delivery. Transdermal drug delivery is used in a variety of areas, including pain management, endocrinology, and motion sickness. Estrogen patches are approved for menopausal indications in addition to post-menopausal osteoporosis. Pharmaceutical companies such as Novartis are the most active purveyors of transdermal patches.

### *Intraocular Implants*

Eye drops have existed at least since Cleopatra's times. Belladonna was used as a mydriatic in ancient Egypt. Eye drops had to be administered regularly, their ocular bioavailability is low.



The development of prolonged action dosage forms with improved ocular absorption addressed this problem, and the first polymeric inserts that release the drug over prolonged period were in use in the United Kingdom in the late 1800s. Since then there have been great improvements made with this innovative medical technology. Lomb, a polymeric ganciclovir implant, was used in the 1990s for opportunistic viral retinitis in AIDS patients. Most current research efforts are directed toward treating age-related ocular diseases. These age-related ocular diseases, including glaucoma and cataracts, continue to cause significant and sometimes complete loss of vision. As the population ages, double-digit growth will likely prevail in the ophthalmic devices sector. Globally, these micro sized and highly precise components and assemblies are among the largest and fastest growing micro medical and pharma micro device sectors. Pharmaceutical companies, including Alcon (now part of Novartis), Allergan, Inc., Bausch & Lomb Incorporated, Daiichi Pharmaceutical Co., Ltd., Genentech Inc., Inspire Pharmaceuticals Inc., ISTA Pharmaceuticals Inc., Johnson & Johnson (Vistakon Pharmaceuticals, LLC), Merck & Co., Inc, Pfizer, Inc., and Santen Pharmaceutical Co., Ltd., are the major players in this market.

It is clear that drug/device combination products cover a wide range of medical areas. This shows how the research undertaken here is extremely worthwhile as it is applicable to a wide variety of medical product categories. This is one of the motivations for this research which will be discussed in detail with others in the next section.

### **1.3 Research Rationale and Motivation**

There were four principal motivations for this research; including

- Research is not keeping pace with the rate of new combination product development
- The gap in knowledge of the enabling factors facilitating drug/device combination products getting marketing authorization
- The acknowledged impact of regulation on the speed at which a product is brought to market
- The researcher's own experience in the drug/device combination industry.

Each of these motivational factors will be discussed in detail in the subsequent section.

### ***Research is not keeping pace with the rate of new combination product development***

Since the approval of Johnson & Johnson's Cypher drug-eluting stent in 2003 and Boston Scientific's Taxus drug-eluting stent in 2004, drug/device combination products have attracted sizeable attention (Hill et al., 2004). Market research predicts the global market for drug/device combination products will grow to \$115.1 billion by 2019 (Transparency Market Research, 2015), witness a compound annual growth rate of 7.9% between 2013 and 2019, largely in inhalation devices, including intranasal and pulmonary systemic therapies. Projections also predict growth in transdermal delivery and drug-enhanced technologies—like stents, orthopaedics, and electrodes. In light of this there is a real need for an empirical assessment of the regulation process for all these new combination products.

A review of the relevant literature reveals a number of factors driving this growth; the aging populations (Bartfai and Lees, 2013, Lee, 2011), protection of franchises (Gibbs and DeMatteis, 2003) There is however, little literature on the factors that support obtaining regulatory approval of combination products. For this reason, this work is very timely.

The aging population and increase in chronic diseases is a key driver for the drug/device combination product market. A plethora of literature is available, which references the role of an aging population and the attending increase in chronic diseases as driving the need for new medical products (Lee, 2011, Bartfai and Lees, 2013, Krol et al., 2012, Dall et al., 2013). The most prevalent chronic diseases are heart disease, cancer, respiratory disease, and diabetes. Drug/device combination products are prevalent in treating and managing these diseases.

### ***Protection of Franchises***

The protection of franchises is another key driver of the drug/device combination product market. The literature also describes the influence of many so-called blockbuster drugs patents expiring and going generic in the growth of the development of drug/device combination products (Mehta, 2008, Gallie and Legros, 2013). The pipeline of new drugs is

too bare to fill the space and create a platform for future growth (Dimasi et al., 2010). Drug delivery technology is one of the resources open to a company seeking to preserve its market share in this kind of circumstance (Dolfsma, 2010). Examples of the successful use of advanced drug delivery technology to prolong the commercial viability of original brands have proliferated. For example, drugs like Sirolimus and Paclitaxel, which were initially indicated for the prevention of organ rejection and as an anti-tumour agent for the treatment of cancer, have established a new existence for the treatment of restenosis (a narrowing of a blood vessel) for patients that have received Drug Eluting Stents (Kamath et al., 2006).

### *Targeted Drug Delivery*

Targeted drug delivery is another driver of the drug/device combination product market. Many scholarly journals and trade magazines dedicated to the topic of targeted drug delivery have arisen in the past few years (for example *Advanced Drug Delivery Reviews*, *Drug Delivery: Journal of Delivery and Targeting of Therapeutic Agents* and *Journal of Drug Delivery*). The largest group of these types of products are drug/device combination products. All of these journals have had some articles relating to drug/device combination products, none however were focused on the regulatory aspect of drug/device combination products. Drug eluting combination devices facilitate targeted delivery of the Active Pharmaceutical Ingredient (API). Zilberman, Kraitzer et al. (2010) outline how targeted drug-delivery allows the consistent maintenance of API concentrations within an optimal therapeutic range (Zilberman et al., 2010). This targeting approach permits the delivery of higher therapeutic dosage while minimizing side effects. Some drugs exhibit greater efficacy in the form of a drug-delivery product combination product such as those that use transdermal patches for delivery (Prausnitz and Langer, 2008). This is noteworthy because as few as five out of 10,000 compounds developed reach clinical trials, and only one of these five receive approval for use (Friedman et al., 2010, Light and Lexchin, 2012). Zilberman, Kraitzer et al. (2010) suggest that some rejected drugs may be effective and safe when manufactured and delivered as a drug/device combination product. As a result, Elman, Patta et al. (2009) describe a new focus on developing devices that use new ways of introducing drugs into the body among medical device manufacturers. The expense of device development is significantly less than drug discovery, and the probable advantage of improving existing products and helping to achieve improved patient outcomes is extremely appealing (Elman et al., 2009).

Cipolla, Chan et al. (2010) discuss how the body takes drugs delivered by oral and parenteral routes systemically, which can lead to adverse side effects. Targeted delivery can therefore confer benefits. A good example is targeting of steroids through inhalation to target the treatment of respiratory disease such as asthma (Cipolla et al., 2010). Inhalers came into common use in the 1960s with the development of press-and-breathe pressurized inhalers, and, more recently, dry powder inhalers have been developed that have a number of benefits including ease of use. The inhaled drug Advair, marketed by GlaxoSmithKline, was the fourth largest selling drug in the United States in 2010 (Rosenberg, 2011). This illustrates that device technology can provide a good defence for innovative pharmaceutical companies against generic entrants, which is another reason devices may continue to grow in importance in the pharmaceutical industry.

### *Patient Compliance*

Another significant factor driving the drug/device combination product market is patient compliance (Wu and Grainger, 2006). Most healthcare practitioners agree that as the population ages, compliance becomes less certain and therefore more important due to forgetfulness (Claesson et al., 1999, Langer, 2008, Puts et al., 2014). Combination products offer convenience that increases compliance both in administration and purchasing (Biradar et al., 2006, Berg et al., 1993). In 2007, Merck introduced the EasyPod, an auto-injector device that was designed to improve patients' ease of daily use, reliability, and convenience (Fry, 2012, Dahlgren, 2008). The sophisticated delivery device optimized compliance and comfort factors for patients and gave Merck a significant increase in market share (Dahlgren et al., 2007, Dahlgren, 2008). Self-injection has gained particular attention (Fry, 2012). So-called micro needle systems offer an alternative to conventional delivery (a vial or syringe pre-loaded within a device) in the form of a patch with micro needles each measuring just a few hundred microns. Such delivery systems can help to alleviate fear of needles, as they are less imposing and offer greater flexibility of use. They are user-friendly and result in less pain at the injection site, which helps to increase compliance with treatment.

All of the drivers of drug/device combination products show the need for research in this area and therefore this research is clearly warranted and timely.

### ***Gap in Knowledge***

This thesis aims to go some way towards filling the gap in knowledge by directly interviewing individuals who have done this already or are in the process of doing it. Scholars have long pointed to the importance of regulation in bringing a product to the market swiftly and safely (Abraham and Lewis, 2000, Bren, 2001, Hilts, 2003, Willman et al., 2003, Beardsley et al., 2005). Despite being a central concern in conversations the experience of drug/device combination product regulation has not yet been examined empirically (Jefferys and Tsang, 2005, Waters, 2011, Naughton, 2001). Scholars acknowledge that combination products pose a regulatory conundrum for an industry familiar with products classified solely as a drug, device, or biologic (von Tigerstrom, 2008, Vamvakas et al., 2011, Tominaga et al., 2011, Lavendar, 2005). However, the empirical evidence in this regard is limited.

Furthermore there are no studies that examine the usability of the regulatory process for combination products from the perspective of the manufacturer. The coming together of hitherto independent industries has presented a unique challenge for the manufactures and regulatory agencies (Couto et al., 2012, Foote and Berlin, 2005). The regulation of drug and medical device products and biologics as separate entities has been studied extensively (McCulloch, 2012, Patel and Chotai, 2008, Korwek, 2007, Eichler et al., 2009, Wilmshurst, 2011, Rago and Santoso, 2008) but no such studies are available for drug/device combination products. Opinions are offered, but no empirical evidence provided. This study will address this significant gap. Research that does discuss combination products are descriptive in nature (Willis and Lewis, 2008a, Foote and Berlin, 2005, Kramer, 2007, Lauritsen and Nguyen, 2009, Willis and Lewis, 2008b). Experts agree that there is at present no clear strategy to regulate combination products (FDA, 2005, Foote and Berlin, 2005). The knowledge and compliance with regulatory requirement is a key to success in development and marketing of combination products. There is therefore a need to study this area.

### ***The acknowledged impact of regulation on the speed at which a product is brought to market***

The next motivation for this thesis is the impact regulation can have on the speed at which a product is brought to the market (Curfman and Redberg, 2011, Woosley, 2014, Fitzgerald,

2011). Perhaps no issue has drawn more attention in both the academic literature and the popular business press in recent years than the strategic value of getting new products to market quicker and the impact that regulation has on this process (Fargen et al., 2012, Frank et al., 2014, Grasela and Slusser, 2014, Slikker et al., 2012, Hourd and Williams, 2008). The benefits of reduced development lead times are well known (Urban and Hauser, 1993). In some contexts, even short delays in product introduction can be deadly if first movers have been able to gain a stronghold in the market (Lieberman and Montgomery, 1988, McNeilly, 2012, Tufano, 1989, Stalk, 1988). From high-tech to low tech drug/device combination products, the speed and efficiency with which a company can develop and implement an effective regulatory strategy shapes the overall cost, timeliness, and results of new product introductions, and the overall competitiveness success of the company (Grasela and Slusser, 2014, Curfman and Redberg, 2011). Obtaining regulatory approval in a timely fashion plays an integral role in the commercialisation strategy of any drug/device combination product.

#### ***The researcher's own experience in the drug/device combination industry.***

The final motivation for the study is the researcher's own interest in the enabling factors individuals that help navigate the regulatory processes drug/device combinations products. The researcher worked for a number of years for a drug/device combination product manufacturer and is aware of the difficulty in getting this type of product to the market both in the EU and US. The researcher is aware of both the commercial pressure that is on a company to get their product first to the market place as this gives the company a competitive advantage.

#### **1.4 Research Scope**

The research focuses on the EU and US regions. The rationale for this focus is firstly that the US and the EU are two of the most important markets for medical products in the world, secondly the US has specific regulations for combination products and finally the researcher has worked in an American multinational based in Ireland, and is familiar with the legislation from both regions.

## **1.5 Research Problem, Questions and Objectives**

### **1.5.1 Research Problem**

Drug/device combination products are an unusual product from a regulatory point of view, as they comprise products that originate in the pharmaceutical, biopharmaceutical, biotechnology, and medical device sectors, that differ conventionally. Consequently, combination products do not fit into a single regulatory framework and they are thus more complex than average products in terms of determining the optimum regulatory pathways involved with getting them to market (Zenios, 2009, Chowdhury, 2014a).

The regulatory frameworks for drug/device combination products are complex (Grignolo, 2013). The EU and US have different frameworks for drug/device combination products, with different institutions involved in the process. There is clearly a need to understand what laws are involved in making up this regulatory framework.

A number of scholars have discussed the complexity and the long periods involved with bringing a novel life sciences product like a combination product from idea to marketplace. They describe how few firms enter the area with the understanding of the regulatory issues and expertise needed in order to succeed (Mitri and Pittas, 2009, Kramer, 2007, Eselius et al., 2008, Juanola-Feliu et al., 2012). These papers however do not empirically test these assertions.

These industries are highly secretive about their practices, as this information would be viewed as a source of competitive advantage for them. By explicating individual experiences with the EU and US drug/device combination product regulatory frameworks through semi-structured interviews and a questionnaire, this dissertation seeks to identify the factors that facilitate obtaining timely regulatory approval for drug/device combination products. It is important to know these factors as it will help an organisation to manage the process of seeking regulatory approval more efficiently and effectively.

The life sciences sector comprises of organisations of different sizes. The experience of a large company versus the experience of a small company in obtaining regulatory approval of combination products might be vastly different. These considerations have not been investigated previously in the scholarly literature.

Research suggests that opinion leaders identify the regulatory environment is one of the key factors in successfully bringing an innovative medical product, like a drug/device combination product, to market (Shmulewitz et al., 2006, Altenstetter, 2013, Altenstetter and Permanand, 2007, Makower, 2011, Langer, 2003, Shmulewitz and Langer, 2006, McCulloch, 2012). However, a dearth of studies in this area has addressed these processes.

### **1.5.2 Research Questions**

In order to explore the research problem, the thesis focuses on four research questions:

**Number 1:** What are the US and EU regulatory frameworks for drug/device combination products? (Answered in Chapter 2)

**Number 2:** What does the literature say about the facilitating factors for obtaining regulatory approval of drug/device combination products in the EU/US? (Answered in Chapter 3)

**Number 3:** What are the facilitating factors for obtaining regulatory approval in the EU and/or US? (Answered in Chapter 5)

**Number 4:** Determine whether the factors identified in the interviews are agreed with in a larger sample? (Answered in Chapter 5 and 6)

**Number 4a:** Are there are there differing perceptions across organisations types, annual sales and number of employees regarding the different facilitating factors for obtaining regulatory approval in the EU and US?

**Number 4b:** Are there significant relationships between organisation types, sizes, product type, market and obtaining regulatory approval in the EU and US?



### **1.5.3 Research Objectives**

This research has five specific objectives, which relate to the different phases of the research:

#### **Phase One: Exploratory –**

- Capture the unique insider perception of individuals experienced with the regulation of drug/device combination product in the United States and European Union through semi-structured interviews.
- Develop a conceptual model of the facilitating factors identified through the interviews.

#### **Phase Two: Explanatory**

- Develop a questionnaire based on the perceptions of life science industry professionals from phase one and investigate these perceptions with a larger sample of professionals within the life sciences industry through a survey.
- Investigate the factors identified in the exploratory stage, with respect to the perceptions of importance of the factors between:
  - product type and market,
  - organization type,
  - organization size.

#### **Phase Three: Synthesis of Qualitative and Quantitative Phases**

- Synthesis the qualitative and quantitative phases in order to add depth and richness to findings
- Revise the conceptual model to reflect the results of the synthesis the qualitative and quantitative

### **1.6 Research Methodology**

A mixed method sequential exploratory study was conducted utilising a combination of qualitative and quantitative research methods (Figure 1). Ceracelli and Green et al. 1989 describe how using the mixed methods research methodology is an effective means of generating more “relevant, useful, and discerning inferences” from research (Greene et al., 1989). The first phase captured the unique insider perspective of individuals experienced with

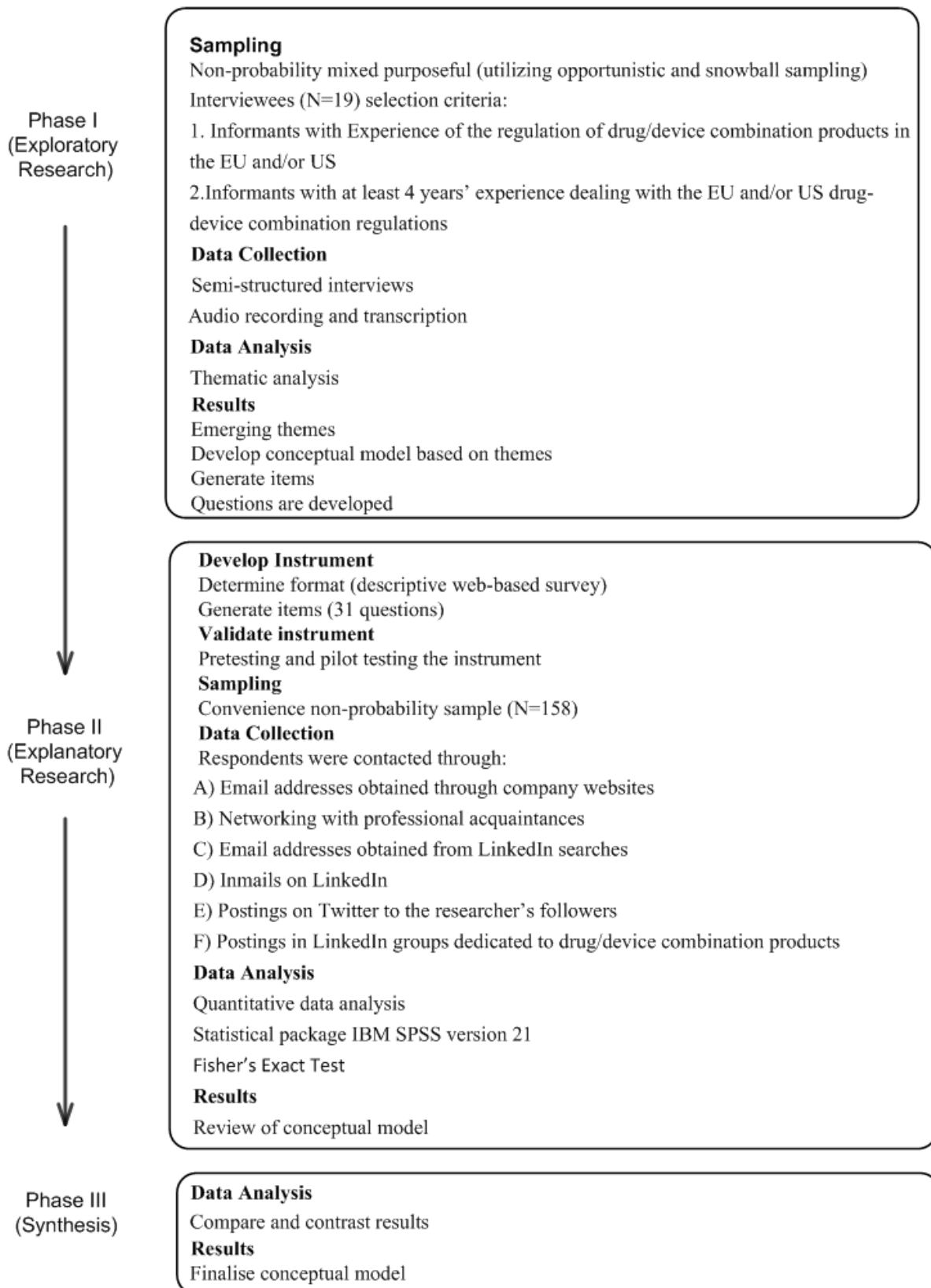
the regulation of drug/device combination product in the US and EU. The participant selection process employed a non-probability mixed purposeful sampling strategy, utilizing opportunistic and snowball sampling (Miles and Huberman, 1994, Denzin and Lincoln, 2005). Semi-structured interviews were conducted in conjunction with an analysis of relevant documents. To satisfy the exploratory nature of phase one, the researcher used a purposeful sample that would provide rich data. Nineteen interviewees with key informants in positions that have experience of obtaining regulatory approval of combination products. The inclusion of individuals involved at various stages of the development process, from research and invention to early-concept definition, development, regulatory approval, and post market feedback provided a holistic view of the process. Professionals from regulatory agencies, key stakeholders in the regulatory process, were also interviewed. Braun and Clarke (2006) procedure for thematic analysis was employed to analysis the interview transcripts. Thematic analysis was used to analyse classifications and present themes (patterns) that relate to the data following the procedures of Braun and Clark (2006). A conceptual model was developed to depict the themes that emerged from the analysis of the survey data (Figure 1).

The second phase of this study was confirmatory/disconfirmatory. The findings of the qualitative phase provided the necessary foundation for the quantitative phase. A descriptive web-based survey design was employed. The items were in the questionnaire (consisting of 31 questions) were developed based on the findings of the interviews. The questionnaire tested and explored, in a larger sample, the facilitating factors identified in the interviews. The participant selection process employed a non-probability mixed purposeful sampling strategy, utilizing opportunistic and snowball sample. 158 senior professionals participated in the survey. The responses of the web-based survey were used to ascertain whether the results contradicted, confirmed, or complemented the findings of the research interviews in a larger sample. The survey data were analysed using IBM SPSS Statistics version 21. Descriptive statistics (frequencies, percentages, skewness, kurtosis, histograms and cross tabulations) was run on the categorical variables. Next multivariate analysis was done by doing cross-tabulations in SPSS. The Fisher's Exact Probability Test was used to determine if there was a relationship between a number of the variables. Open-ended survey responses were transcribed and entered into an NVivo 10 software program. These were coded to group similar and identical answers and counts of these answers were reported in the results (Cooper et al., 2006).

In a mixed methods study results merged and integrated to provide interpretation about the overall results of this study (Creswell, 2008). The conceptual model that was developed at the end of the qualitative phase was revised to reflect the results from the quantitative phase.

Figure 1 depicts the procedure for sampling, data collection and analysis that was undertaken,

Figure 1 Procedure for Sampling, Data Collection and Analysis for the Study



## 1.7 Significance of the Research

This study has three areas of particular significance. First, six stakeholder groups will benefit from its insights, second, it makes a significant contribution to the literature on the regulatory approval of drug/device combination products, and, third, it presents novel research.

Firstly its relevance to stakeholders concerned that drug/device combination products obtain market authorisation in a timely fashion gives the study significance. Six distinct stakeholder groups have a reason to seek an understanding of the factors that facilitate marketing authorisation: (1) senior managers in manufacturing companies seeking to accelerate the regulatory approval of their drug/device combination products; (2) investors and life science entrepreneurs considering entering the market of drug/device combination products; (3) regulatory managers within organisations who are responsible for managing the process of seeking regulatory approval for combination products; (4) regulatory authorities involved with overseeing the regulatory frameworks for combination products; and (5) medical personnel and users drug/device combination products. (6) Policy makers. The paragraphs below describe the study's relevance to each of these stakeholder groups before describing the study's remaining areas of significance.

### *Stakeholder Benefit*

The first stakeholder group, senior managers in manufacturing companies seeking to bring their drug/device companies to market ahead of their competitors, stand to benefit greatly from the insights this study presents. A company that obtains timely regulatory approval for its combination product is in a position to beat competitors to market with new products, achieve rapid market penetration, offer more innovative and attractive designs, and protect its position from would-be imitators (Zenios, 2009, Mehta, 2008). In addition, senior managers involved in making the strategic decision as to where to market a product – in the EU or the US market or both – can benefit from this study. The experiences of other companies can inform these decisions.

The second stakeholder group is life sciences entrepreneurs and investors. They will receive a benefit analogous to senior managers in pharmaceutical and medical device companies. Understanding the challenges that the regulatory framework presents will be of particular help

to those entrepreneurs and investors who see the regulatory requirements as a barrier to entry (Chatterji, 2009, Shane, 2000). The study's findings will support informed decisions about entering the market or investing in companies that seek to enter this market.

The third stakeholder group are regulatory managers in drug/device combination companies. They can use this study to guide priority setting as their teams launch products. This research will help these teams pinpoint areas where problems might occur, thereby avoiding a regulatory strategy that might create critical delays in market authorisation that an inexperienced regulatory team could not have otherwise anticipated. This will also help identify specific problems likely to occur, to enable companies to provide extra attention or enhanced resource allocation when introducing the product into the EU and/or US market. Since combination products are comprised of two or more regulated components, even determining the correct regulatory process poses a challenge. Arguably, gaining a clear understanding of the proper regulatory process is the most critical step as it impacts all stages of the product development process, including: preclinical testing, clinical trials, marketing applications, manufacturing, quality control, and post-approval modifications.

Regulatory agencies stand to benefit just as much as the stakeholders seeking to profit in the combination product market from the current study. The research undertaken here shines a light on the experiences other stakeholders have in relation to regulatory agencies. In the US and European regulatory environment the four key players are the Food and Drug Administration (FDA) (FDA, 2012, Merrill, 1996), competent authorities, European medicines agency, and notified bodies respectively.

The fifth major stakeholder group that will benefit from this research are the medical personnel and users of drug/device combination products. Understanding the regulatory process for combination products will facilitate swift approval by the relevant regulatory authority and ultimately make them available for a physician to give to his/her patient. Regulatory requirements impact the time for product approval and subsequently largely determine when a patient can benefit from a product.

The sixth stakeholder group that will benefit from this research are policymakers. For the policy maker, this research can be a reference for those involved in developing regulation for drug/device combination products and how the users of the regulations are finding it. Policy developed based on its findings will ultimately improve regulatory environments.

### *Contribution to Literature*

Aside from the six stakeholder groups, another significance of this study is that it provides a novel contribution to the literature. Current literature acknowledges that developing and commercialising combination products is a uniquely challenging process (Zenios, 2009, Pietzsch and Paté-Cornell, 2008) but does not explore the process. No study available reports on the experiences of companies who have been successful in this arduous task. The current study addresses this gap.

### *Novel Research*

This study is also significant in its achievement of inducing companies that have brought new novel medical technologies to market to divulge their first hand experiences of the regulatory process. The medical technology sector is highly secretive. To date, neither qualitative nor quantitative research has been undertaken to explore the enablers and barriers to the obtaining regulatory approval for combination products in the EU or US. Drug/device combination products are a relatively small product group, and a small pool of people has first hand prior experience of the process. As the first research into this topic, this study makes a novel contribution to the literature. Senior personnel were interviewed and surveyed for this research. Getting access to these high calibre people in the highly competitive sector of the life sciences industry is not an easy task and the information they provided in their responses to the interview and survey questions is extremely valuable.

## 1.8 Structure of Thesis

The thesis consists of **six chapters**. This section provides a brief overview of each of these chapters.

**Chapter 1 – Introduction:** Chapter 1 introduces the context of the research problem. It outlines the rationale and motivations for the research. The scope of the research is discussed. The research objectives and questions are set out. This is followed by a presentation of the research methodology and finally the significance of this research is highlighted.

**Chapter 2 – Drug/Device Combination Product Regulation in the European Union and United States of America:** Chapter 2 answers research question 1. Chapter 2 summarises the current legislation and regulatory framework for the three product sectors — medicinal products, medical devices and drug/device combination products. This provides the context for the exploration of the main questions discussed in the interviews and survey.

**Chapter 3 – Literature Review.** Chapter 3 answers research question 2. Chapter 3 reviews the literature concerning the factors that impact getting a drug/device combination product onto the market in the EU and US. Chapter 3 also reviews the literature concerning the EU and US regulatory frameworks for drug/device combination. The review shows that there is a significant gap in the literature regarding the overall understanding of how the regulatory frameworks of drug/device combination products impact on obtaining regulatory approval. The chapter concludes by establishing the research gaps discovered in the literature review.

**Chapter 3 – Research Methodology:** Chapter 3 describes the methods of inquiry used (mixed-method), along with the rationale for this choice as well as practical aspects of the data gathering and analysis process. The study was conducted in two phases and employed a sequential exploratory design (Creswell 2003). The first phase involved qualitative data collection and analysis. In this phase nineteen semi-structured interviews were conducted with senior personnel in a variety of organisations that are involved in obtaining marketing authorisation for drug/device combinations products. The target sample included experienced



and senior regulators, combination product manufacturers, and contract research organisations personnel. The researcher employed thematic analysis to analyse classifications and present themes that relate to the data (Braun and Clarke, 2006). The researcher used a stepwise manner with three separate cycles of coding to analysis data in phase one, following the recommendations of Braun and Clarke (2006).

Phase two of this research used the quantitative methodology in the form of a survey. The choice of the descriptive survey approach is discussed in this chapter. Data collection techniques, survey design and survey data analysis (descriptive statistics and correlations) are outlined. The sample (N=158) who completed the survey were again senior and experienced personnel within their organisations (for examples senior managers, chief executives and directors). The quantitative phase was a complementary phase to the primarily qualitative phase. The aim of the quantitative phase was to test and explore, in a larger sample, the identified themes in the interviews. The results of a web-based survey were used to ascertain whether the results contradicted, confirmed, or complemented the findings of the research interviews.

**Chapter 4 - Qualitative Data Analysis:** Chapter 4 reports on the results of phase one of the study; the qualitative phase and thus answers research question 2. This chapter is structured around key themes that emerged from the thematic analysis of interviewee responses. More specifically, the chapter describes the enabling factors that the senior personnel interviewed perceive helped/helps them obtaining marketing authorisation for drug/device combination products.

**Chapter 5 - Quantitative Data Analysis:** Chapter 5 reports on the results of phase two of the research study, namely the quantitative study. Chapter 5 begins with descriptive statistics on the demographic characteristics and combination product experience of respondents. This is followed by a report on whether the results of the survey correlate with the themes identified in phase one of the study. Correlation between sets of data is a measure of how well they are related. Research questions 4, 4a and 4b are answered by using descriptive statistics, Fisher's Exact Test and the categorisation of the answers open responses questions.

**Chapter 6 – Conclusions/Discussions:** Chapter 6 is the concluding chapter of this thesis. This chapter fully integrates the findings of the qualitative and quantitative research

conducted. Each research question is answered. It highlights the key research findings of the study and presents a set of core messages for practice, policy and research. It also proposes further research. It presents the major conclusions of this research. Finally, the limitations of this research are discussed.

## **2 Drug/Device Combination Product Regulation in the European Union and United States of America**

*This chapter describes, in succeeding sections, the regulation, regulatory authorities, and guidance related to drug/device combination products in both the EU and US, the regulation and pathway to market for medical devices in the EU, the regulation and pathway for medical devices in the US, the regulation and pathway for drugs in the EU, and the regulation of drug/device combination products in the US. This chapter answers research question number one; what are the US and EU regulatory frameworks for drug/device combination products?*

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### **2.1 Introduction**

An effective regulatory framework is able to enhance a region's innovative potential, which, in its turn, can dedicate the pattern of the global industrial leadership in the industry (Porter and Stern, 2001, Mattli and Woods, 2009, Navaretti, 2004). Drug/device combination product manufacturers must comply with regulatory requirements in order to get an access to the European and US markets (Lumpkin et al., 2012, Burns, 2012). The review of regulations undertaken in this chapter will reveal that the regulation of drug/device combination products is complex, that much of the scholarship in this area focuses on the medical device and drug regulations and that there is a lack of knowledge about the enabling factors for obtaining regulatory approval of drug/device combination products in the EU and US.

This chapter summarises the current legislation and regulatory framework for the drug/device combination product sector; combination products, medical devices and medicinal products. An understanding of the relevant regulatory frameworks is essential in order to investigate the enabling factors in obtaining marketing authorisation. An understating of the regulatory frameworks is also necessary in order to develop meaningful and appropriate interview and

survey questions. This review of the regulatory frameworks also provides the context for the exploration of the questions discussed in the interviews and survey.

## **2.2 Regulation of Combination Products in the United States**

The regulation 21 CFR Part 3, *Product Jurisdiction* (FDA, 2006b) contains most US regulations for determining the status of a combination product and designates the FDA as the responsible party (Lauritsen and Nguyen, 2009, Sweet et al., 2011, Foote and Berlin, 2005). This regulation contains the definitions for a combination product, as well as the procedures for how the FDA will determine whether the Centre for Drug Evaluation and Research (CDER), the Centre for Devices and Radiological Health (CDRH), or the Centre for Biologics Evaluation and Research (CBER) will provide pre-market review and post-market control of a combination product.

The Medical Products and Tobacco Directorate within the FDA provides high-level co-ordination and leadership between the centres that are responsible for medical devices and the Office of Combination Products (OCP).

### **2.2.1 Office of Combination Products**

The Office of Combination Products (Foote and Berlin, 2005), established in 2002, has the following responsibilities:

- to designate the FDA centre for review and approval of a combination product;
- to act as the principal office for dealing with combination product issues for FDA reviewers and industry;
- to write guidance documents that clarify the regulation of combination products;
- to co-ordinate reviews involving more than one agency centre;
- to ensure consistency and appropriateness of the post-market regulation of combination products;
- to resolve disagreements regarding the timeliness of pre-market reviews of combination products;

- to revise agreements, guidance documents or practices specific to combination products;
- to submit annual reports to Congress on the Office's activities.

By selecting the FDA Centre assigned to a combination product, the OCP affects the regulatory pathways for each component of the product, including its pre-clinical testing, its marketing application, its clinical evaluation, adverse event reporting, post-approval modifications, and promotion and advertising (Sweet et al., 2011, Hamrell, 2006). However, OCP does not itself review combination products.

### 2.2.2 Assigning Jurisdiction for Review of Combination Products

The OCP assigns a centre based on the primary mode of action of the product, but the primary centre may consult and/or collaborate with other centres if constituents of the product lie outside the primary centre's realm of expertise (Hamrell, 2006). Inter- centre agreements established in the early 1990s allow for collaboration by describing how they distribute responsibilities (Eaglstein, 2014, FDA, 2009a). The OCP requests that sponsors contact them as early as possible to schedule a meeting to review the product and discuss primary centre assignment. Usually a manufacturer can determine which centre will review a product at the time of submission of the product, although, as the next section describes, there are exceptions.

### 2.2.3 Request for Designation (RFD)

If the classification of a product as a drug, device, biological product, or combination product is unclear or in dispute, a sponsor can file an RFD with the OCP to argue in favour of designation by a particular centre (Lauritsen and Nguyen, 2009). The RFD process is described in 21 CFR Part 3.7 (FDA, 2006a). The availability of product data determines the timing of filing; there must be enough reliable data on hand for the FDA to understand the product and uncover its primary mode of action (Hamrell, 2006).

#### 2.2.4 Combination Product Guidance Documents

Since the establishment of the OCP, the FDA has developed several guidance documents (Lavendar, 2005). The OCP website provides a list at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm122047.htm> (FDA, 2013). Currently-available guidance documents include:

- Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4;
- Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA (Biologics Licence Application), NDA [New Drug Application], or PMA (Pre-Market Approval application);
- Classification of Products as Drugs and Devices and Additional Product Classification Issues;
- Interpretation of the Term ‘Chemical Action’ in the Definition of Device Under Section 201(h) of the Federal Food, Drug, and Cosmetic Act;
- How to Write a Request for Designation;
- New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products;
- Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products;
- Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products;
- Minimal Manipulation of Structural Tissue (Jurisdictional Update);
- Early Development Considerations for Innovative Combination Products;
- Application User Fees for Combination Products;
- Current Good Manufacturing Practice for Combination Products (Draft Guidance);
- Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product.
- Heparin-Containing Medical Devices and Combination Products: Recommendations for Labelling and Safety Testing

FDA has developed these guidance documents to provide greater clarity for FDA reviewers and industry (Beaman and Wallace, 2009). They are principally intended to clarify parts of the regulations that are confusing the industry. FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidance documents outline the FDA's current views on a subject and should to be judged as recommendations. The use of the word "should" in FDA guidance documents denote that something is recommended or suggested, but is not mandatory.

### **2.3 Regulation of Combination Products in the European Union**

The EU does not have a special approval process for combination products, and no regulatory agency defines specific regulatory paths for combination products (O'Grady and Bordon, 2003, Kramer et al., 2012b). In relation to drug/device combinations, one of the most common types of combination products, EU legislation specifies that such products can be regulated as either medicinal products or medical devices (Wu and Grainger, 2006). For biologic/devices in which the biologic and device form a single integral product, the product is regulated under Directive 2001/83/EC, as amended, commonly known as the Medicinal Product Directive. If the biologic has an ancillary action, Directive 93/42/EEC, as amended, commonly known as the Medical Device Directive (MDD), applies. If a device is combined with tissue/cells it falls under the category of Advanced Therapy Medicinal Products (ATMPs). Regulation (EC) No 1394/2007 (European Commission, 2007) establishes the regulatory framework for ATMPs. If the product is a combination of a biologic/drug or drug/drug, it is regulated under Directive 2001/83/EC (European Commission, 2001), unless it is a fixed combinations, in which case CPMP/EWP/240/95 Rev 1 applies (Committee for Medicinal Products for Human Use, 2008). A fixed combination medicinal product is the combination of active substances within a single pharmaceutical form of administration.

#### **2.3.1 Regulations that Govern Drug/Device Combination Products**

If a drug/device combination product is classified as a medical device it is regulated by one of the following Directives (as transposed into member state law):

- Directive 93/42/EEC, as amended (i.e. the MDD) (European Commission, 1993);
- Directive 90/385/EEC, as amended, commonly known as the Active Implantable Medical Device (AIMD) Directive (European Commission, 1990);
- Directive 98/79/EC, as amended, commonly known as the *In Vitro* Diagnostic (IVD) Directive (European Commission, 1998).

If a product is classified as a medicinal product, it will be regulated by Directive 2001/83/EC, as amended (European Commission, 2001). Normally the procedures set out in each Directive do not apply cumulatively.

### **2.3.2 Classification of Drug/Device Combination Product**

The legislation specifies a number of scenarios for drug/device combinations as required by Annex I, Section 7.4 to the MDD (European Commission, 1993). The first scenario is a device that 'incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product'. Article 1(4) of the MDD it clear that such products are devices, provided that the action of the medicinal substance is ancillary to that of the device, as reflected in the product claim and as supported by the scientific data provided by the manufacturer of the devices. The medicine or drug used must already have regulatory approval for use in that particular application and intended use. Medical devices that incorporate medicines and are regulated as medical devices include catheters with anticoagulant coatings, drug-eluting coronary stents, and antiseptic wound dressings.

Article 1(3) of the MDD states that medical devices designed to administer a drug are regulated as medical devices. The medicinal product which the device is intended to administer must, of course, be approved according to the normal procedures for medicinal products. Examples of these products include drug delivery pumps, implantable infusion pumps, nebulisers, and jet injectors.

However, if the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single product is regulated as a medicinal product (Article 1(3), second subparagraph of the MDD). Examples of such products are pre-filled syringes, nicotine patches, and contraceptive implants.



In such cases the essential requirements of the MDD apply as far as the device-related features of the product are concerned (e.g. the mechanical safety features of a pre-filled syringe). The labelling, however, should comply with the requirements of Directive 92/27/EEC, which applies to medicinal products (European Commission, 1992).

### **2.3.3 Organisations Responsible for the Regulation of Drug/Device Combinations**

If a combination product is deemed a medical device, the competent authorities and notified bodies regulate it (Jefferys, 2001b, Kramer et al., 2012b, Kaplan et al., 2004). A competent authority ensures that the requirements of the MDD are applied. A member state and a Notified Body determines if a product or system meets applicable requirements for CE marking (Jefferys, 2001b). The Notified Body provides pre-marketing and routine conformity assessment services for a manufacturer's device and quality system.

If a combination product is deemed a medicinal product, the EMA and the competent authorities regulate it (Kingham et al., 1994). The EMA is responsible for scientific evaluation (Pignatti et al., 2004, Lisman and Lekkerkerker, 2005).

### **2.3.4 Drug/Device Combination Product Guidance Documents**

There are MEDDEV guidance documents available that provide information on this topic (European Commission, 2009). While MEDDEVs have no legal force, these documents facilitate common positions throughout the EU, and Member States usually expect manufacturers to follow them (Chowdhury, 2012b, Altenstetter, 2003). Examples of relevant MEDDEVs are:

- MEDDEV 2.1/1, *Definitions of 'medical devices', 'accessory' and 'manufacturer'*;
- MEDDEV 2.1/3 rev.3, *Borderline products, drug- delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative*;
- MEDDEV 2.14/1 rev.2, *Borderline and Classification issues. A guide for manufacturers and Notified Bodies*.

The MEDDEVs guidelines objective is to promote a common approach by manufacturers and Notified Bodies involved in the conformity assessment procedures according to the relevant annexes of the Directives, and by the Competent Authorities (Jefferys, 2001b). They are composed through a process of consultation with a range of stakeholders during which preliminary versions were disseminated and comments were taken and the documents revised. They indicate stances taken therefore by representatives of industry, Competent Authorities, Notified Bodies and industry.

### **2.3.5 ‘Borderline case’ as Opposed to a Combination Product**

The EU uses the term ‘borderline case’ to describe a product that appears to be related to multiple directives (Chowdhury, 2012b, Chowdhury, 2014a). *The Manual on Borderline and Classification* is a resource for companies developing products that may be borderline (European Commission, 2012). Written by the Borderline and Classification Working Group of the Medical Devices Expert Group, the manual explains the thinking of the European Commission on borderlines and classification. It also includes a number of specific cases and the reasons for classification in addition to the decision about the set of rules the product is regulated under. The expert panel consists of experts from all EU member states, EU representatives, and other stakeholders. It is not legally binding; it helps manufacturers and national regulatory authorities in making case-by-case decisions. It denotes the views agreed in this group where doubts have been raised over issues of classification and on issues of the line between MDDs and other regulatory regimes.

## **2.4 Regulation of Medical Devices in the EU**

The United States has been regulating medical devices since the mid 1930s; many if not most member countries in the European Union had similar regulations upon joining, but the EU’s process was formulated in the mid 1990s (Jarow and Baxley, 2014, Jefferys, 2001b, French-Mowat and Burnett, 2012). Chowdhury (2012) describes the regulatory frameworks in the EU as “a regulatory patchwork of European and national laws and guidelines operating concurrently with each other” (Chowdhury, 2012a).

Three EU directives govern the process, the Medical Devices Directive (European Commission, 1993), the Active Implantable Medical Devices (AIMD) Directive (European Commission, 1990), and the In Vitro Diagnostic (IVD) Directive (European Commission, 1998). The Medical Devices Directive covers the majority of medical devices, from simple non-sterile drainage containers to complex devices such as interventional cardiology catheters (Amato and Ezzell, 2014). The AIMD Directive governs powered implantable devices such as pacemakers, and the IVD Directive governs devices used in vitro for the examination of a specimen derived from the human body.

The Medical Device Directive defines medical devices as follows:

“Any instrument, appliance, apparatus, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of physiological process;
- control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.” (European Commission, 1993)

Medical devices vary greatly in complexity and application (Zenios, 2009). They can range from bandages and medical thermometers to magnetic resonance imaging machines and x-ray machines. The directive sets forth four classes of devices based upon contact time, invasiveness, and whether a device is active that correlates with the risk a patient incurs in the use of the device. Table 1 shows the different classifications, the corresponding risk levels, and examples of devices in each class.

Table 1 E.U. Classification of Medical Devices and Examples of Devices in each Class

<b>Class</b>	<b>Risk</b>	<b>Examples</b>
Class I basic	Low Risk	Reusable surgical instrument Nonsterile gloves
Class I (sterile)	Low Risk	Sterile dressings, non-medicated Sterile gloves
Class I (with a measuring function)	Low Risk	Volumetric urine bag
Class IIa	Medium Risk	Surgical blades <i>A hypodermic needle</i> <i>Suction equipment</i>
Class IIb	Higher Risk	Ventilators, orthopaedic implants Radiotherapy equipments
Class III	Highest Risk	Prosthetic joints Coronary Stent

Higher risk devices incur greater control by the state under the EU's multifaceted system in which a number of authorities, including private entities, have roles (Frank, 2003, Chowdhury, 2014b). The five authorities involved with the regulation of medical devices in the EU are:

1. The European Commission, the EU's executive body (Hix and Hoyland, 1999). The department within the Commission responsible for medical devices and drugs is the Directorate-General for Health and Consumer Protection (French-Mowat and Burnett, 2012)
2. Competent Authorities, a term that in the EU refers to a body with authority to act on behalf of the government of a member state (Higson, 2010). With respect to medical device directives, every member state has a competent authority that ensures implementation into national law and application within member countries. Competent authorities report to the Minister of Health in each member state and have responsibility for appointing and overseeing notified bodies, surveillance of medical devices on sale in their own member state, and the assessment of adverse incidents.

3. Notified Bodies: Notified bodies are privately-held for-profit organizations that certify medical devices under contract to competent authorities (Jefferys, 2001a, French-Mowat and Burnett, 2012). They assess manufacturers' compliance with the requirements of European medical device law, signifying compliance by granting certificates and monitoring it through regular audits. The scope of their role depends on the class of the product. In the case of a Class III device, for instance, the Notified Body will examine the product design and audit the quality system. These bodies do not scrutinize Class I devices unless they are sold sterile and have a measuring function, and then they only examine aspects.

Unlike in the US, manufacturers are not obliged to undergo governmental review in order to get access to the market in Europe (Tobin and Walsh, 2011). While the European Commission, competent authorities, and notified bodies together have a comparable role to the FDA's inspection branch, they have no enforcement powers.

4. Authorised Representative: The European Commission defines an authorised representatives as "any natural or legal person established in the Community who, explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacture with regard to the latter's obligations under" the Medical Devices Directive (European Commission, 1993b).

5. Manufacturer: The European Commission (1993) defines a manufacturer as "the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party". By permitting delegation to a third party, this definition employs flexibility while retaining the principle that even if the legal manufacturer delegates virtually all manufacturing tasks, the entity retains responsibility for any noncompliance, even if it rises from the actions or failings of a subcontractor (French-Mowat and Burnett, 2012).

### 2.4.1 Medical Device Pathway to Market in EU

In order to market medical devices in the EU, manufacturers must obtain CE marking certification and affix the CE marking. The process of obtaining the CE mark is described comprehensively in the literature (Tobin and Walsh, 2011, Kaplan et al., 2004, Schnoll, 2007). CE is an abbreviation of French “Conformité Européenne” meaning “European Conformity.” This mark is not a assurance of safety. It signifies that the manufacturer claims that the device complies with the relevant *Essential Requirements* in the directives (Schnoll, 2007). It also signifies that the product can be freely marketed anywhere in European Union without further control.

The *Essential Requirements* in the Medical Device Directive 93/42/EEC can be separated in two sections: the first relates to a series of general requirements for safety and performance that are applicable to all devices. The second is a list of specific and technical requirements related to design and manufacturing that apply to some devices but not others. Manufacturers have to demonstrate and document compliance with the regulations and issue a declaration of conformity. Class I sterile devices typically require the involvement of a Notified Body to obtain a CE mark. Class III devices require clinical studies, barring when data already exists.

Manufacturers can provide devices for clinical investigation and those that are custom made without the CE mark. Clinical investigations are investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device. Custom made device are intended for the sole use of a particular patient. They have to follow Annex VIII of the Medical Device Directive regarding the Statement Concerning Devices for Special Purposes (European Commission, 1993) and declare that their products conform to the *Essential Requirements*. Clinical data must demonstrate the device’s safety and that it performs as intended by the manufacturer. In this context, data can include everything from bench testing to clinical trials in humans. Manufacturers may compile data from the literature or fund clinical investigations. In the latter case, manufacturers must abide the standard ISO 14155 (ISO, 2012) and a competent authority must pre-approve the clinical trials.

## 2.5 Regulation of Medical Devices in the United States

The current US definition of medical devices appears the Title 21 Code of Federal Regulations (21 CFR) of the Federal Food, Drug and Cosmetics Act (FDC Act) (FDA, 2006b):

“An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and that does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and that is not dependent upon being metabolized for the achievement of any of its primary intended purposes.”

Title 21 Code of Federal Regulations Part 800 to Part 1299 sets forth most contemporary US regulation of medical devices and the FDA’s responsibility for oversight (Sweet et al., 2011). However, regulation of medical devices in the US began in 1938 and reflected the technologically relatively simple devices then on the market (Jarow and Baxley, 2014, Munsey, 1995, Merrill, 1994, Monsein, 1997, Merrill, 1996). The passage of the Federal Food, Drug, and Cosmetic Act in that year created the FDA and gave it gave the FDA multiple responsibilities and authorities for drugs and medical devices, including the authority to designate and seize adulterated or misbranded products and hold manufacturers accountable (Merrill, 1994, Monsein, 1997). This process revealed the high cost of an entirely reactive model and lawmakers began to see the increasing need for premarket review of problematic devices as the market grew. The Drug Amendments of 1962 responded to an increasing need for premarket review of devices, and the 1976 Medical Device Amendment mandated testing and FDA approval of all medical devices (Sweet et al., 2011).

The Medical Device Amendment set forth three classes of medical devices that required distinct regulation levels for safety and effectiveness based on the level of risk to the patient,

the intended use, and the indication for use (Monsein, 1997, Merrill, 1996). Class I devices are defined as non-life sustaining and receive the lowest level of regulatory control. These products are the least complicated and their failure poses little risk. Class II devices are more complicated and present more risk than Class I, but are also non-life sustaining. These may be subject to specific performance standards. Class III devices sustain or support life, so that their failure is life threatening. These products are subject to performance standards that are more stringent than Class II devices. Table 2 shows the different classifications, the corresponding risk levels, and examples of devices in each class:

Table 2 U.S. Classification of Medical Devices and Examples of Devices in each Category

Class	Risk	Examples
Class I	Low Risk	Tongue Depressor Elastic Band Hospital beds
Class II	Medium Risk	Absorbable suture Blood pressure cuffs
Class III	Highest Risk	Implantable Pacemaker Pulse Generator Pacemaker Battery coronary stent

Class I are subject to *General Controls*, the most stringent of which include *Establishment Registration* by the manufacturers, distributors, repackagers, and relabellers; listing in the FDA database; good manufacturing practices; labelling of the medical device; and a 510(k) Premarket Notification. However, premarket notification and good manufacturing practices do not apply to the majority of Class I devices (Merrill, 1996).

Class II medical devices have more risk than a Class I device and require a higher level of regulatory control. In addition to all *General Controls*, they are subject to *Special Controls*. *Special Controls* include additional labelling requirements, mandatory performance standards, and post-market surveillance. Some Class II devices are exempt from premarket notification; however, they are subject to limitations if they present a new intended use or questions new issues of safety and effectiveness (Merrill, 1996).



Class III medical devices include any device used to support or sustain life or prevent impairment and any device that presents a potential for increased risk of illnesses or injury to the patient, except those that qualify for 510(k) submission. This form of premarket approval application (PMA) that states that the device is substantially equivalent to a device that is currently on the market (has been cleared through a 510(k) review) merits classification as a Class II device, and clearing for commercialisation following the 510(k) submission. All others must seek other forms of PMA to be deemed approved (Merrill, 1996).

A device the FDA deems as not *substantially equivalent* in spite of this submission, (did not meet the requirement for a 510(k)), or that does not have a *predicate* (a device that has been cleared through a 510(k) review) to compare to for pre-market review also falls into the Class III category. Devices that meet the requirements for the 510(k) are given the designation of “*cleared*”, devices that undergo a Class III review and meet the requirements are given the designation of “*approved*” (Merrill, 1996, Muni et al., 2005).

The Center for Device and Radiological Health (CDRH), a department within the FDA, regulates manufacturers, repackages, re-labellers, developers of investigational medical devices and importers of medical devices (Maisel, 2004, Muni et al., 2005). The FDA assesses new medical device products before they are marketed for conformance to mandatory engineering bench tests, design, and clinical trials in patients or gathering data from animal trials; and by inspection and enforcement activities at device manufacturing plants (Merrill, 1996). They also collect and monitor adverse effects from marketed products and investigations, and take actions to prevent injury or death.

### **2.5.1 Medical Device Pathway to Market in the United States**

Manufacturers have four options when they market medical devices—securing the FDA’s declaration of exemption, 510(k) preapproval, premarket approval (PMA) and the humanitarian device exemption (HDE) (Sweet et al., 2011). Clinical studies of investigational devices must adhere to the FDA’s investigational medical device exemption regulations.

The *General Controls*, which apply to all medical devices, require manufacture under a quality assurance program, suitability for the intended use, adequate packaging and proper labelling, and filing of establishment registration and device listing forms with the FDA.

The 90-day 510(k) process enables most Class II devices to be released to the market, but some need only comply with General Controls and Special Controls. Special Controls include performance standards, guidance documents, or implementation of post-market surveillance.

Class II devices typically require PMA. This process resembles the design dossier that European Class III devices must have. It is the most comprehensive type of device marketing application. FDA regulations provide 180 days to review the PMA and make a determination, but the process can take between 6 months and 2 years, given factors such as the report of clinical studies, quality of documents, and the amount of time necessary for the manufacturers to respond to FDA concerns.

Previous to the FDA Modernization Act of 1997 (Federal Drug Administration Modernization Act, 1997), if an innovative device was found *not substantially equivalent* (NSE), it was classified as Class III. This created a conflict between the need to be innovative and a more complex commercialization process, a disincentive for innovation. A present, the *De Novo* process permits the reclassification of devices to Class I or Class II, providing a straightforward route to market for novel low risk devices. This process, which has to begin within 30 days of an NSE letter, has a review period of 60 days and, if the device is classified into Class I or II, the applicant may market the device. However, if the FDA will not reclassify the device, it cannot be marketed until the applicant has obtained an approved PMA.

Manufacturers select the *De Novo* strategically for some products (Santos et al., 2012). The device's market and other barriers to market entry influence the decision. For example, if there is deficient patent protection, manufacturers can gain from a Class III classification because it will create a barrier to market entry to competitors. *The Humanitarian Device Exemption* (HDE) is a particular pathway for Class III devices designed to target diseases that impact less than 4,000 patients in the United States per year. This pathway's objective is encourage the development of medical devices for use in the treatment or diagnosis of diseases that occur in small populations.

An investigational device is a medical device which is the subject of a human research study to evaluate its safety and/or effectiveness. A company developing an investigational medical

device can only conduct clinical studies of the device in the US if they obtain an *Investigational Device Exemption* (IDE) from the FDA.

## **2.6 Regulation of Drugs in the EU**

The internal market principle of the free movement of goods throughout the EU covers drugs. Article 1 (2) of European Council Directive 65/65/EEC defines a drug as follows (European Commission, 1965):

“Any substance or combination of substances presented for treating or preventing disease in human beings or animals. Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a drug.”

The directive states that a manufacturer may place a drug on the EU market only when the regulatory authority of a member state issues a *marketing authorisation* for its own territory or the European Commission grants an authorisation for the entire EU.

The Council Directive 65/65/EEC of 26 January 1965 replaces national legislation that regulated drugs in individual member states.

Extension and developments of the 1965 directive include the establishment in 1995 of a new system for authorising drugs entered into law, on in which marketing authorisation might occur by one of two procedures, Centralised and Mutual Recognition. The European Medicines Agency (EMA) administered the Centralised Procedure and member state competent authorities were responsible for the Mutual Recognition procedure. The EMA, a decentralised agency of the EU located in London, UK, evaluates medicines and consequently plays a pivotal role in the approval of pharmaceutical products in the EU. As an analogue to

the FDA, it not a law enforcement agency, but oversees all drugs authorised for use within the EU, maintains relevant databases, and coordinates pharmacovigilance. Manufacturers who wish to bypass the EMA can seek national authorisation alone for a product to market it in only one member state. New pharmaceutical regulations that came into force in 2005, Directive 2004/27/EC (European Commission, 2004), provided another option to authorise drugs within the EU: the Decentralised Procedure.

The European Commission is the EU civil service. The pharmaceutical sector currently is in the Directorate-General Health and Consumers. The European Commission also chairs both the Pharmaceutical and Standing Committees. The former is the pharmaceutical sector's policy making unit; the latter is the Commission's decision-making arm for refusing or granting authorisation.

### **2.6.1 The Route to Market for EU Drugs**

The majority of conventional drugs approved for marketing in Europe receive recognition under the Mutual Recognition Procedure. The member state regulatory agency evaluates the data and issues initial marketing authorisation which other member states must recognise. If a drug is already available in more than one member state, manufacturers may seek authorisation in multiple states and therefore generated identical marketing authorisations, therefore, can result in multiple, identical marketing authorisations. The current legislation allows the Mutual Recognition Procedure only for products that already have a marketing authorisation from one member state.

The Decentralised Procedure, this is also applicable to the majority of conventional drugs. The evaluation is also performed by one national regulatory agency, but the *marketing authorisation* is usually granted in other member states only after all member states involved reach agreement.

Human medicines derived from biotechnological processes, medicines developed for treatment of rare disorders (orphan drugs), and drugs which contain an active substance authorised in the Community after 20 May 2004 and which are for the treatment of cancer, AIDS, diabetes, or neurodegenerative disorders, must undergo the Centralised Procedure. Under this procedure, the Committee for Drugs for Human Use (CHMP) evaluates a given drug's data at the European level. This process results in one Community or European *marketing authorisation* that is valid throughout all EU member states. The EMA administers the Centralised Procedure; however, the actual licence takes the form of a decision issued by the European Commission.

Regardless of the registration procedure employed, the EU grants marketing authorisation to a single party, the Marketing Authorisation Holder (MAH), which must be established within the European economic area. The MAH can market the product as stipulated in the authorisation, so long as it fulfils its obligations. These include maintaining the marketing authorisation to reflect technical and scientific progress, releasing the product onto the market in accordance with EU law (through a qualified person) and providing pharmacovigilance and scientific information.

## **2.7 Regulation of Drugs in the US**

The birth of FDA guardianship and the origins of drug and medical product regulation began with a large medical calamity (Rago and Santoso, 2008, Merrill, 1994). In 1937 over 100 people in the US, mainly children, died of diethylene glycol poisoning as a result of the use of a sulfanilamide elixir, which used the chemical as a solvent without any safety testing (Ballentine, 1981). At that time, selling potentially toxic drugs was legal. In the absence of toxicities testing, scientific literature review, and other types of testing, the impetus for speedy market placement cost many lives. This led to the introduction of the Federal Food, Drug and Cosmetic Act (FD&C) in 1938 (Merrill, 1994). The law defines drugs by their intended use, as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of

disease” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals” [FD&C Act, sec. 201(g)(1)].

The thalidomide disaster in Europe in the 1950s led to the vast expansion of the oversight that began in 1938. Thalidomide was a sedative and hypnotic that first went on sale in Germany in 1956. Between 1958 and 1960 it led to the birth of an estimated 10,000 babies with phocomelia in 46 countries worldwide. While the FDA had never approved the drug for sale in the US, the incident spurred a call for more regulation in the United States (Rago and Santoso, 2008).

The evaluation of new drugs occurs within the FDA’s Center for Drug Evaluation and Research (CDER).

### **2.7.1 The Route to Market for US Drugs**

In the US, the FDA drug approval process has seven stages: preclinical testing, investigational new drug applications (IND), Phase I clinical trials (Turner, 2010), Phase II clinical trials (Turner, 2010), Phase III clinical trials (Turner, 2010), and new drug application (NDA) (Molzon, 2003, Turner, 2010).

Preclinical testing involves laboratory and animal studies must to prove the biological activity of the drug against the targeted disease and safety evaluation before testing on humans can begin.

The IND follows preclinical testing. The IND comprises of the results of earlier experiments; where, how, and by whom the new studies will be executed; the chemical makeup of the compound; any toxic effects revealed in the animal studies; how it is believed to perform in the body; and the manner by which the compound is manufactured. The IND must also be reviewed and approved by the Institutional Review Board where the studies will be performed. The IND becomes effective if the FDA does not reject it within 30 days.

Phase I clinical trial studies are normally the earliest tests of a drug under development in healthy volunteers. These studies require about 20 to 80 volunteers. The tests establish a drug's safety profile, in addition to the safe dosage range, how the drug is absorbed, distributed, metabolised, and excreted, and the duration of its action. The duration of Phase I trials is approximately 1 year (Food and Drug Association, 2012).

Phase II clinical trials generally involve 100 to 300 volunteer patients who suffer from the disease for which the drug is anticipated for. This phase is usually designed to identify the minimum and maximum dosages. Using a controlled design, they assess the drug's effectiveness and reveal common side effects (Food and Drug Association, 2012). Phase II on average takes approximately 2 years.

Phase III clinical trials are large, definitive, randomized trials. This phase investigates the effectiveness in addition to the safety of the new drug. Phase III trials usually involve 1,000 to 3,000 patients in clinics and hospitals. Patients receive the list of possible side effects derived in the Phase II study but also may report additional side effects. Phase III typically takes 3 years.

Subsequent to the Phase III clinical trials, the drug manufacturer analyses all the data from the studies and files an NDA with the FDA. The NDA comprises of all of the data collected before and during the drug approval process from all the preceding stages of the application. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed. Once the FDA decides that they will file and review the FDA the average review time for the FDA. The way that FDA calculates the NDA review time has been increasingly controversial. FDA includes only the time that it has the full NDA under review and excludes the time that the applicant is obtaining information that is requested by the agency. The FDA does not keep statistics showing the full time from NDA submission to approval. It is known however that the review of the NDA typically lasts one to two years (Dowden et al., 2012). All told, the usual journey for a drug from discovery to market in the US takes approximately nine years although some processes can be quicker or slower (Dowden et al., 2012).

The second section of this chapter provides an identification of the literature that discusses the regulatory frameworks for drug/device combination products, medical devices and pharmaceutical with a focus on literature that discusses the EU and US regulatory frameworks

for those products. The focus on this type of literature is necessary as it is the focus of this thesis. Following this review the gaps in the current scholarship about the EU and US regulatory frameworks for drug/device combination products will be identified. These are the gaps in knowledge that this thesis will fill.

## **2.8 Conclusion**

This chapter addressed the research on the regulatory frameworks relevant to drug/device combination products.

Drug-device combination product regulations have created a complex process to approval. This insight confirms the views of other commenters (Grignolo, 2013, Hamrell, 2006). The complexity reflects in part the wide variety of items categorized as drug-device combination products. Drug-device combination products can range from a simple bandage with silver ions that inhibit bacterial growth and speed healing time to high-tech life-saving implants like drug-eluting coronary stents. The fact that regulation involves both the medical device and drug regulations frameworks in both regions increases the complexity. Developers that seek to distribute combination products in both the EU and the US also face different approaches to oversight in each region, even though the two jurisdictions have largely similar regulations for medical devices. The US market is controlled through a centralised agency, the FDA, whereas the EU is much more decentralised and includes commercial organisations who charge fees to the manufacturers, notified bodies. Decentralisation also distinguishes the EU's approach to drugs from the US approach. The EU's use of three separate registration procedures—centralised, decentralised and national—exemplifies the complexity that results from this difference.

In conclusion, this chapter aimed to provide an overview of the regulatory framework for drug/device combination products (encompassing the regulatory frameworks for medical device and drugs in the EU and US). It presented the directives and federal laws that govern the approval of these products. The next section describes the literature on the EU and US drug/device combination product regulatory frameworks.



### **3 Literature on the European Union and United States of America Drug/Device Combination Product Regulatory Frameworks**

*This chapter reviews the literature on the regulatory frameworks relevant to the research in relation to both the EU and the US contexts. It identifies the gaps in the current literature which this thesis will fill. This chapter answers research question number two; What does the literature say about the facilitating factors for obtaining regulatory approval of drug/device combination products in the EU/US?*

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#### **3.1 Introduction to Literature on the Regulatory Frameworks**

Research suggests that opinion leaders identify the regulatory environment is one of the key factors in successfully bringing an innovative medical product, like a drug/device combination product, to market (Shmulewitz et al., 2006, Altenstetter, 2013, Altenstetter and Permanand, 2007, Langer, 2003, Shmulewitz and Langer, 2006, McCulloch, 2012, Makower, 2011). However, a dearth of studies in this area has addressed these processes. This section addresses that research and explains how the research undertaken in this thesis complements it.

The review casts a wide net. Drug/device combination products can be classified as drugs, as medical devices or, in the United States, as combination products. Therefore discussions of each of these regulatory frameworks fall into the scope of this chapter.

Literature discussing the regulatory frameworks related to drug/device combination products can be found in a variety of subject areas, including: regulatory science (Jefferys and Tsang, 2005), political science (Altenstetter and Permanand, 2007, Altenstetter, 2013, Fox and Zuckerman, 2014, Sorenson and Drummond, 2014, Merrill, 1994), innovation (Foote and Berlin, 2005), product development (Santos et al., 2012), medicine (Horton, 2012a, Maisel, 2005, Lewi and Frame, 2012), translational medicine (Novack, 2009), pharmaceutical

medicine (DiMasi et al., 1997, Lumpkin et al., 2012, Jefferys, 2001a, Sweet et al., 2011), pharmaceutical science (Putzeist et al., 2012, Gispen-de Wied and Leufkens, 2013), cardiac medicine (Kaplan et al., 2004, Mehran et al., 2004), law (Vinck et al., 2011, Horton, 1995, Lavendar, 2005, Foote and Berlin, 2005), biotechnology (Singh et al., 2010) and strategic management (Beardsley et al., 2005). This diverse range of areas examining the regulatory frameworks suggest wide interest in the subject matter, even as the number of studies focusing exclusively on drug/device combinations regulatory frameworks is small (Chowdhury, 2012b, Jefferys and Tsang, 2005, Foote and Berlin, 2005).

Section 3.2 describes commentary on medical device regulatory framework. Section 3.3 addresses research exploring the drug regulatory framework. Section 3.4 addresses research on the drug/device regulatory framework. In all cases, some studies discuss both the EU and US frameworks and some discuss only one or the other. Section 3.5 concludes by discussing literature focused on other innovative branches of medicines

## **3.2 Investigations of the Medical Devices Medical Device Regulatory Frameworks**

As Chapter 2 describes, both the EU and the US regulatory frameworks classify some drug/device combination products as medical devices and therefore subject them to the medical device regulatory approval process.

### **3.2.1 EU Medical Device Regulatory Framework**

Research addressing the EU framework falls into three categories: those examining the framework's effectiveness in ensuring product safety (Horton, 2012, Dhruva and Redberg, 2012, Horton, 2012a, Campillo-Artero, 2013, Lewi and Frame, 2012, Woods, 2012), those that seek to offer insight to policy makers (Altenstetter, 2010, Altenstetter, 2003), and literature describing the directives that constitute the EU medical device regulatory frameworks and the regulatory agencies involved in overseeing them (Altenstetter, 2003,

Frank, 2001, Altenstetter, 2010, Kaplan et al., 2004, McAllister and Jeswiet, 2003, Schnoll, 2007, Sweet et al., 2011).

Studies relating to how the regulatory framework ensures product safety, consists the bulk of the literature on the device frameworks, driven by highly publicised failures of medical device products such as metal-on-metal hip replacements and breast implants (Heneghan, 2012, Cohen and Billingsley, 2011, Sedrakyan, 2012). Wilmshurst condemns the EU medical device regulatory framework as “unsatisfactory, unscientific and in need of a major overhaul” (Wilmshurst, 2011). A series of articles published in the British Medical Journal on this topic described the evaluation pathway for medical devices as far less defined than pharmaceutical regulation (Cohen, 2013, Cohen, 2012a, McCulloch, 2012, Cohen and Billingsley, 2011). They highlight that manufacturers can sell any medical device on the open market if it has a CE mark, and regulation does not require clear evidence of functionality and safety. To the extent that these studies focus on particular products, none reference drug/device combination products, but their findings remain relevant since some combination products are classified as medical devices.

Christa Altenstetter describes the dynamics of the EU regulatory framework with the objective of influencing policy makers (Altenstetter, 2003, Altenstetter, 2010, Altenstetter, 2013). Her work discusses topics such as the future prospects for EU medical device regulation and regulatory responsibilities of the member states. Altenstetter (2010), while accepting convergence and internationalisation of medical device regulation, maintains that national states and national authorities have an important role in formulating regulatory framework that is appropriate for local conditions. In her opinion the medical device industry and their products are too diverse for uniform requirements to be workable. This view could also be valid for drug/device combination product products.

The third body of literature related to regulation the EU medical device regulatory frameworks describe the directives and regulatory agencies that guide the process (Altenstetter, 2003, Frank, 2001, Altenstetter, 2010, Kaplan et al., 2004, McAllister and Jeswiet, 2003, Schnoll, 2007). These articles do not focus on the drug/device combination regulatory frameworks. Schnoll (2007) and Frank (2001) give a comprehensive overview of directives that constitute the EU medical device regulation for medical devices. Altenstetter

articles are in the field of social science and law. They focus on the harmonisation of global medical device regulations. Kaplan, Baim et al. 2004 compare the regulatory approval pathways for medical devices in the EU and US. The comparisons are as a result of discussions with the inventor, entrepreneur, industry, clinical, and regulators of new interventional device. In their opinions there are 1- to 3-year delay in the introduction of new medical devices into clinical practice within the United States as compared with Europe.

### **3.2.2 US Medical Device Regulatory Framework**

There is considerably more literature available on the US medical device regulatory frameworks than the EU frameworks, but this scholarship does not include articles that focus on drug/device combination products. The four main areas relating to the US medical device regulation most frequently discussed in the literature are: the effectiveness of the US medical device regulatory framework ability to ensure product safety (Hines et al., 2010, Dhruva and Redberg, 2012, Dhruva et al., 2009); the impact of regulations on the time to market for a new medical device (Makower, 2011, Makower J. et al., 2010, Phillips et al., 2006); articles that navigate the laws that constitute the regulatory framework (Jarow and Baxley, 2014, Merrill, 1994, Kramer et al., 2012b, Monsein, 1997); and the role of the FDA in overseeing US medical device regulation (Diehl et al., 2010, Sweet et al., 2011, Maisel, 2012, Monsein, 1997, Merrill, 1996, Eisenberg, 2006).

Dhruva, Bero et al. (2009) focus on premarket evaluation and post-market surveillance regulatory requirements for medical devices in the United States. They argue that there are weaknesses in the premarket evaluation and post-market surveillance systems. Hines, Lurie et al. 2010; Dhruva and Redberg 2012; Kramer, Xu et al. 2012 report similar findings.

In a review that intersects two of the categories outlined above, Kramer, Xu et al. 2012 performed a systematic review of original studies assessing medical device approval and post-market surveillance in the European Union and United States prior to July 2011. They established that merely 20 studies evaluated the medical device approval process regardless of

an wide-ranging search. A number of studies were published in the peer-reviewed literature and indicate that regulatory reforms will be required to encourage superior quality evidence in studies of the highest-risk devices. These improvements could include more use of randomisation, blinding, and active controls. However, the review includes a number of non peer-reviewed studies undertaken by medical device companies that criticise device approval for being too time-consuming. Industry representatives have referred to these self-published reports to advocate increased regulation would be harmful to patient care and economically unwise (Makower J. et al., 2010). Markower (2011), in responding to these reports, provides a study in the second area of literature, focusing on the impact of regulatory processes on time to market.

A third area of literature addresses the role of the FDA in overseeing US medical device regulation (Eisenberg, 2006, Diehl et al., 2010, Sweet et al., 2011, Maisel, 2012, Monsein, 1997, Merrill, 1996). Merrill traces the evolution of drug and device regulation. Merrill's paper suggests that external pressures and internal practices are inexorably bringing device regulation closer to the drug model. Eisenberg 2006 and Diehl, Tierney et al. conclude that the FDA struggle to keep pace with the regulating of new innovative medical technology products, including some drug/device combination products. Sweet Schwemm et al. 2011 highlight the difficulties the FDA experience when trying to classify a new type of medical technology that crosses product borders. They outline the discusses the role of the Office of Combination products in classifying combination products. They describe problems that can arise when trying classifying combination products in the US. They gave an example of a situation in which a product that may be thought of as a drug (e.g., heparin flush) is regulated as a device. They discuss how the opposite can also be true.

In addition to research that addresses the EU and US regulatory frameworks separately, a number of studies compare and contrast the EU and US medical device regulatory frameworks. None of these focuses on drug/device combination products. The research includes investigation as to which is the better regulatory framework for medical devices (Redmond, 2004, Kaplan et al., 2004, Wilmschurst, 2011, Putzeist et al., 2012, Kramer et al., 2012a, Sorenson and Drummond, 2014). In a recent entrant into the debate, Sorenson and Drummond (2014) explore the impact of the distinction between the FDA's regulation of medical devices from that in Europe, arguing it is significant that Notified Bodies do not test

for efficacy or clinical benefit of devices, and rarely provide information to the public on the data reviewed, or even when they approve a product. Other studies compare the EU and US device premarket review process (Gottlieb, 2011, Cohen, 2012a). Gottlieb (2011) argues that the European approach is better since many devices get approved first there, but Cohen (2012) counters with cases of recent safety problems with devices in Europe as evidence that European regulation of devices should be reinforced.

### **3.3 Investigations of the Drug Regulatory Frameworks**

Scholarly work that focuses exclusively on drug regulatory frameworks focuses on topics such as methodologies of drug approvals and drug safety withdrawals (Abraham and Lewis, 2000), how the pharmaceutical regulatory framework affects the time to market for new chemical entities (Woodcock and Woosley, 2008, Woodcock, 2012), what drugs are being approved by the FDA (DiMasi et al., 1997, Barratt et al., 2012, Mullard, 2014, Mitka, 2012), the role of regulatory authorities in drug regulation (Wonder, 2014) and describing the individual regulatory frameworks (Rawat and Gupta, 2011, Moore, 2003, Mathieu et al., 2002).

Other studies compare the US and EU pharmaceutical regulatory frameworks (Paul, 2001, Wood, 2006, Tsuji and Tsutani, 2010, Tsuji and Tsutani, 2008, Ramesh et al., 2011). Most of these articles compare pharmaceutical regulatory approval times. Dr. DiMasi is one of the prolific scholars on this topic (DiMasi et al., 1997, Kaitin and DiMasi, 2010, DiMasi et al., 2013, DiMasi, 2014).

### **3.4 Investigations of the Regulatory Frameworks for Drug/Device Combination Products**

Literature relating to the regulatory frameworks for drug/device combination products explore the regulatory processes (Waters, 2011, Foote and Berlin, 2005, Jefferys, 2001b, Gopaldaswamy and Gopaldaswamy, 2008, Lewis, 2010, Siegel, 2008, Sweet et al., 2011,

Kapoor, 2013), or examine regulatory processes related to specific combination products (Levine et al., 2008, McGowan and Stiegman, 2013, Kulkarni, 2011). A small body of literature discusses whether the regulation for combination products is adequate.

Books that are dedicated to discussing drug delivery systems (Wen and Park, 2011, Wang and Singh, 2013) or describing how to bring a combination product to market (Gopaldaswamy and Gopaldaswamy, 2008, Lewis, 2010) are not scholarly explorations but guidebooks. In another article outside the scholarly literature Kapoor (2013) describes how combination products are regulated in the United States and the challenges manufacturers face. Office of Combination products staff members have written articles for scholarly journals describing the US regulatory framework for combination products, but these do not constitute peer reviewed literature (Lauritsen and Nguyen, 2009).

Fewer publications address the EU regulatory framework for drug/device combination products. Jeffery (2001) argued that the boundary between medical devices and medicinal products can be a difficult one, and that recent developments in technology have increased confusion (Jefferys, 2001b). A few articles address the EU system in relation to the US system without focusing on combination products (Kramer et al., 2012b, Redmond, 2004, Kramer et al., 2012a).

Articles addressing specific combination products include Levine (2008) and McGowan and Stiegman (2013), which discusses the FDA regulatory pathways for knee cartilage repair products, Novack (2009), which addresses US regulation of ophthalmic drug delivery combination products and Gryziewicz (2005) which focuses on a specific ocular drug/device combination product.

Levine (2011) and McGowan and Stiegman (2013) both focus on cartilage repair therapy products. They both conclude that the path to regulatory approval for a cartilage repair therapy is challenging and time-consuming. They acknowledge that appropriate clinical trial planning and consideration to the details can ultimately conserve companies' money and time by ensuring a product is brought to the market by quickest route possible.

Novack (2009) in his discussion on regulatory aspects of ophthalmic drug delivery also highlights the difficulty in determining the classification of a combination product. Gryziewicz

(2005) also discusses these difficulties in his article. Gryziewicz was a director of regulatory affairs at Allergan inc. Allergan is a significant manufacturer of drug/device combination products for treating glaucoma and retinal disease. The article discusses a drug that is delivered to the retina via an implantable device. The FDA classifies this product as a drug, as the intended outcome of therapy depends on the pharmacologic action of the drug, and the implant's sole function is to deliver the drug to the back of the eye. The injector that delivers the drug is already on the market and is classified as a medical device and regulated as such by the FDA. Gryziewicz found that determining which FDA centre is primarily responsible for the review of their combination product's application posed a problem.

Kulkarni (2011) also focuses on ocular products, reviewing the product summary basis of approvals for two newly approved products, specifically Ozurdex™, a dexamethasone containing intraocular drug delivery system for the management of macular edema and Lucentis™, a recombinant, humanized monoclonal IgG1 antibody indicated for neovascular age-related macular degeneration. His conclusions resemble Gryziewicz's.

Avery and Liu (2011) explore the current regulatory regime in relation to Smart Pills, a form of ingestible combination product, and find it "flawed" (Avery and Liu, 2011). They recommend that the FDA should provide further guidance on requirements regarding clinical trial design, data submission, marketing approval and drug-diagnostic co-development. They argue that the FDA should simplify current regulations and create a new center with jurisdiction over combination products. They believe that these initiatives will solve many regulatory problems facing innovative combination products. They propose that instead of following the drug and device frameworks, the new centre could design and regulate according to the underlying technology. They predict that under the new regulatory scheme, review time will be greatly reduced and the process will become more efficient. Phillips et al. 2006 holds similar views to that of Avery and Liu (2011). Phillips et al. 2006, using a methodology similar to that of the current study, interviewed individuals with experiences of developing diagnostics and biomarkers, arguing that US regulatory processes require reform to improve speed to market.

Couto et al. (2012) argue, in relation to US regulation of drug-eluting stents and transdermal patches, that drug/device combination products introduced a new dynamic to regulatory approval and provide valuable lessons for the development of new generations of combination



products. Identifying the determination of the FDA regulatory centre that will oversee a product's approval as the main obstacle to introducing a new kind of combination product, they argue that the first product of a new class of combination products presents a learning opportunity for the sponsor and the regulator. When that first product is approved, the leading regulatory centre is determined, and the ambiguity about the entire class of combination products is significantly lowered. The sponsor that is responsible for the new class of combination products takes a key position in decreasing this uncertainty by counselling the decision on the primary purpose of the combination product.

A few studies comment on the adequacy of the current combination product regulatory framework, but none are part of the peer reviewed literature. In November 2013, the Drug Information Association chaired a meeting on combination products. Speakers were from the FDA and the drug and diagnostic industries. Attendees had a knowledge of the regulatory framework of drug/device combination product development and regulation, while stressing the main developmental roadblocks facing combination product developers in the European Union and United States (Tsourounis et al., 2014). Tsourounis et al. (2014) described the meeting, at which attendees highlighted the importance of continual transparency and cooperation amongst combination product developers, regulators, and other stakeholders as a means to streamline the global combination product development and review process to guarantee the availability of innovative quality new products that are safe and effective.

Footnote and Berlin 2005 evaluated the FDA's efforts since 1990 to accommodate combination products, stating that the traditional response to innovation may not be suited to combination products. They found that statute and regulation focuses on definitions to distinguish between types of products as they emerge, and that the FDA then stretches the limits of the definitions as new products evolve until Congress revises the old definitions to reflect changes in product types. They argue that defining a product by the FDA's determination of its primary mode of action is frequently imprecise because it may be unclear at the time of an investigational application which mode of action provides the most important therapeutic action and some products have two different equally critical modes of action. New technologies and products often straddle the definitional boundaries provided in the Food, Drug, and Cosmetic Act (FDCA), and the definitional focus of the statutory scheme has caused a "silo effect," forcing rigid compartmentalization where it is often inappropriate.

### **3.5 Investigations of Innovative Branches of Medicine**

Drug/device combination products, as discussed in Chapter 1, often incorporate emerging, innovative technologies. There is a body of literature that focuses on other innovative branches of medicine like regenerative medicine based therapeutic products (Singh et al., 2010, Messenger and Tomlins, 2011), tissue engineering (Brévignon and Singh, 2008, Brévignon-Dodin, 2010, Hellman et al., 1998, Kent et al., 2006) nanotechnology (Bawa, 2008, Sandoval, 2009), stem-cell products (von Tigerstrom, 2008) and nanotechnology (Paradise et al., 2009, Paradise et al., 2008, Rollins, 2009, von Tigerstrom, 2008). Most of these articles argue that the regulatory processes currently in place are inadequate to address these new types of products. Several discuss the gap between regulations and similar innovative emerging medical technologies (Marchant, 2011, Lumpkin et al., 2012, Lavendar, 2005, Abraham and Davis, 2007, Woodcock, 2012).

The articles do not investigate the actual experience of the companies dealing with the regulatory frameworks. No surveys exclusively focus on drug/device combination products and none focus on the experiences of companies dealing with the regulatory frameworks.

### **3.6 Conclusion**

This chapter addressed the research on the regulatory frameworks relevant to drug/device combination products. It identified a lack of peer-reviewed quantitative or qualitative studies that focus on drug/device combination products, in contrast to a fair amount of literature on the regulatory frameworks for medical devices and pharmaceuticals. Most of the research found fell into two categories: medical device regulation in the United States and its impact on bringing products to market and the safety of the EU medical device regulations. A number of these articles focus on the process that determines which FDA centre will take the lead when reviewing a product, an issue of particular importance to combination products and warranting more investigation in relation to them. This thesis will attempt to correct this deficiency through interviewing and surveying individuals with this firsthand knowledge of these regulatory frameworks. Small companies developing ideas for innovative products face

a confusing regulatory process and this thesis will illuminate their path. Helping patients get access to combination products quickly is growing in importance, given an aging population.

There is a dearth of literature regarding manufacturer's perceptions of their experience of the regulatory frameworks. The next section will describe the research methodology used to undertake the research done for this thesis, which was particularly aimed at filling this particular gap.

## **4 Research Methodology**

*This chapter describes, in succeeding sections, the research design (mixed method), data collection (both qualitative and quantitative), data analysis (thematic analysis, descriptive statistics, cross tabulations). The final section discusses synthesis of the qualitative and quantitative findings.*

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### **4.1 Introduction**

This chapter presents the research design, data collection, and analysis procedures that were undertaken for this dissertation. The exploratory design had two sequential phases. Section 4.2 discusses the scientific paradigms on which the research is based and then proceeds to describe the mixed method approach taken. It explains why the chosen research methodology suits the research questions. Section 4.3 discusses the qualitative research methodology, including the interview protocol, the sampling strategy, and the data management and analysis. Section 4.4 describes the quantitative methodology, including instrument development, the sampling strategy, testing of the instrument, and survey administration and analysis. Section 4.5 discusses the method for evaluating the quantitative research and describes the ethical considerations adopted in this research. Section 4.6 summarises the chapter. Figure 1 in Chapter 1 depicts the procedure for sampling, data collection and analysis that was employed in this study.

### **4.2 Research Design (Mixed Method Sequential Exploratory)**

This thesis uses a mixed methods research design, collecting, analyzing, and mixing both quantitative and qualitative research to understand the research problem (Bryman, 2006, Creswell and Clark, 2007, Miles and Huberman, 1994, Brewer and Hunter, 2006, Tashakkori and Teddlie, 2010, Creswell, 2008). The approach, which Tashakkori and Teddlie (2010) call

mixed methodology and Bryman (2012) calls multi-strategy, is well-suited to the research at hand. As a research methodology, mixed methods was identified in 1959 by qualitative researchers Campbell and Fiske, who described it as an effective means to measure a psychological trait. The method existed long before this labelling identification, but Campbell and Fiske's work prompted a growth in the method's use and its adoption across a wide range of disciplines. Almost two decades later, Denzin (Denzin, 1978) introduced the term "triangulation" to describe a method of combining data sources to study the same social phenomenon and seek convergence across qualitative and quantitative methods. A year later, Jick (1979) described triangulating data sources as a means of alleviating the weakness of one method by drawing in the strength of another approach, noting that all methods have limitations and biases. There are a number of different mixed method typologies; the Triangulation Design (Creswell et al., 2003), the Embedded Design (Creswell et al., 2003, Greene et al., 1989), the Explanatory Design (Creswell et al., 2003, Tashakkori and Teddlie, 2010, Morgan, 1998), and the Exploratory Design (Morgan, 1998, Greene et al., 1989). Each research methodology has its own distinct objective, procedures, philosophical assumptions, weaknesses, strengths, challenges, and variations.

A sequential exploratory design methodology is used in this research (Brewer and Hunter, 2006, Tashakkori and Teddlie, 2010, Bryman, 2006), which means it is conducted in two phases and seeks to explore a particular phenomenon. Like most studies using sequential exploratory design, it collects and analyzes qualitative data, followed by quantitative data collection and analysis (Bryman, 2006, Castro et al., 2010, Erzberger and Kelle, 2003). The phenomenon explored here is the process of obtaining regulatory approval for drug/device combination products.

#### **4.2.1 Rationale for Choice of Research Design**

There are several reasons why using a sequential mixed method approach was deemed as suitable for this research; it "provides such a wealth of data that researchers discover uses of the ensuing findings that they had not anticipated" (Bryman, 2006, p. 110). In addition, the

mixed method approach was selected in order to preserve the purpose of triangulation (seeking convergence of results or corroboration between quantitative and qualitative data), complementarily (discovering distinct aspects of a problem, illumination of the results from the one method with the results from the other), and expansion (adding breadth and scope to the problem) (Greene, Caracelli & Graham, 1989). The mixed-methods approach provided the researcher with the opportunity to develop a richer understanding of the research findings and a higher level of confidence in their accuracy. This mixed methods design allows one to develop common themes through interviews and to enhance and clarify those findings with data collected through a questionnaire.

The exploratory research phase of this study seeks to increase the understanding of the research problem at the outset of the study; the explanatory research phase seeks to confirm the understanding at the conclusion (Mertens, 2011, Jick, 1979, Leech et al., 2010, Betz, 2010). In the exploratory research phase, the researcher articulates his or her understanding of the research questions and its purpose (Robson 2002, Lewis, Thornhill, et al. 2007). As the research questions in this study address the experiences of individuals in obtaining regulatory approval of their drug/device combination products in the EU and US, the rationale for the exploratory research phase, at the outset, is that it constitutes what Robson (2002) calls a “little-understood” situation, an opportunity “to seek new insight, to ask questions, to assess phenomena in a new light, to generate ideas and hypotheses for further research,” which is particularly suited to this approach (Robson, 2002, pp. 270-271). The object of the exploratory stage is a better understanding of these experiences, which may include identifying the contextual factors that influence the patterns that emerge (Morgan, 1998, Onwuegbuzie and Leech, 2006, Tashakkori and Teddlie, 2010).

In contrast to exploratory research, explanatory research objective is to account for a problem or a situation (Robson, 2002), i.e. investigate the relationship between the identified and explored variables. It often follows exploratory research as a means of improving the understanding of concepts obtained from the exploratory research (Bryman, 2006, Tashakkori and Teddlie, 2010). The explanatory research of this study investigates the patterns that emerge during the exploratory research as well as patterns that emerge in the second phase. That is to say, the researcher obtains a more comprehensive insight of the patterns in the first

phase and develops an informative but tentative conceptual framework at the outset of the second phase.

#### **4.2.2 Developing the Mixed Methods Analysis**

A mixed methods approach can be used as a way of moving the analysis forward, with one method being used to inform another. The researcher introduces the new method specifically to address research issues arising in the use of another method (Tashakkori and Teddlie, 2010, Teddlie and Tashakkori, 2009)). For this research, the analysis of the interview findings guided the development of the questionnaire. Combining the findings of the two approaches helps to provide a complete picture of the factors influencing obtaining regulatory approval of drug/device combination products in the EU and US (Denscombe, 2010). Researchers also tend to regard one method as the main and the other as the subsidiary counterbalance or check (Teddlie and Yu, 2007, Azorín and Cameron, 2010, Brewer and Hunter, 2006, Bryman, 2006, Burgess, 1986). Based on the findings of the interviews, the researcher developed an questionnaire to check and verify the interview findings. The qualitative data was the most important material for the investigation.

### **4.3 Qualitative Research Methodology (Phase One)**

In section 4.3.1 the researcher explains how this study was conducted; describing each step and the decisions the researcher had to make to pursue the research.

#### **4.3.1 Data Collection Technique (Semi Structured Interviews)**

This exploratory study aimed at capturing the unique insider perspective of individuals experienced with the regulation of drug/device combination product in the United States and European Union. The researcher conducted semi-structured interviews in 2011 and 2012.

Burgess (1986) emphasises the importance of interviews as a research method in that interviews provide the “opportunity for the researcher to probe deeply to uncover new clues, to open up new dimensions of a problem, and to secure vivid, accurate inclusive accounts that are based on personal experiences” (Burgess, 1986, p. 107) . Weiss (1995) suggests a number of reasons why interviews are superior to other methods: including that the method provides detailed descriptions, it integrates multiples perspectives, it allows the development of a holistic description, it enables the researcher to learn how events are interpreted.

Each of these attributes present advantages to the current study. In the absence of prior research, interviews provide the most appropriate method to explore the experience of seeking to obtain regulatory approval for the drug/device combination products.

#### **4.3.2 Sample Size**

Nineteen semi-structured interviews were conducted during 2011 and 2012, at which point theoretical saturation was reached. Using the principle that if no new data were to emerge, data collection should cease (Corbin and Strauss, 2008).

#### **4.3.3 Instrument – Interview Protocol**

Three interview protocols were created, one each for regulators, combination product manufacturers, and contract research organisations personnel (Appendices A-C respectively). Although conceptually similar, each contained questions specific to their respective groups. The wording and phrasing of questions is of central importance when using interviews to gather data (Weiss, 1995). The wording of a question can bias the interviewee’s response, for example by putting pressure on them to present themselves in a flattering light. Context can solicit a response that might omit the most relevant answer.

The researcher used a check list to develop the question wording (Frey and Oishi, 1995):

- “Use language that is comprehensible to the target population



- Keep the wording neutral
- Ask about one concept or issue per question
- Include enough information so that respondents can give meaningful answers (that is, so that most respondents don't say, "I don't know")
- Provide response answers that are exhaustive and mutually exclusive"

To ensure that the questions in the protocol were relevant, two pilot interviews were carried out with individuals in the target sample, a Product Development Project Manager and a Regulatory Manger. Both were involved in obtaining regulatory approval of a drug/device combination product in the EU and/or the US.

Following the pilot interviews, each participant was asked for feedback on the questions. Based on this feedback, time management emerged as a major problem because of the number of questions. Consolidation of redundant questions, adjustment or removal of ineffective questions, and rewording of unclear or confusing questions improved the protocols. The project manager suggested the rearrangement of the sequence of questions in order to make the interview flow more natural.

Open-ended questions were augmented by follow-up and clarifying questions. The interview protocol comprised three sets of questions. These were:

- (1) Questions about the respondent's firm/organisation: type of organisation and number of employees.
- (2) Questions about the participant's level of experience with drug/device combination products.
- (3) Questions about the respondents' experience obtaining regulatory approval of drug/device combination products in the EU and/or US.
- (4) Questions eliciting the respondent's opinions: their experience of the EU and/or US regulatory frameworks for drug/device combination products.

All interviews were recorded with participants' permission, using a smart phone and brief notes, with the consent of interviewees. Interviews lasted 40–60 minutes. Sixteen interviews were conducted in person, and three were conducted using Skype. Three individuals were unavailable for in-person interviews due to work pressures.

#### **4.3.4 Sampling Method – Non-Probability Mixed Purposeful**

The participant selection process employed a non-probability mixed purposeful sampling strategy, utilizing opportunistic and snowball sampling (Miles and Huberman, 1994, Denzin and Lincoln, 2005, Patton, 1990). Opportunistic sampling involves the researcher capitalizing on opportunities during the data collection stage to select participants for the study. Snowball sampling involves asking participants who have already been selected for the study to recruit other participants. This sampling method was chosen as it enabled the selection of “information rich” sample, and therefore greater insights (Easterby-Smith et al., 1991, Patton, 1990). Patton describes “information rich” participants as “Information-rich cases are those from which one can learn a great deal about issues of central importance to the purpose of the research”. In the case of this study a relatively small but experienced and knowledgeable group (N=19) were interviewed. These high calibre, well informed participants were “information rich” about drug/device combination products and thus provided more valuable information rather than gathering standardized information from a large, statistically representative sample.

Potential interviewees were targeted at four international conferences and one professional association's annual meeting (table 3). Two of the conferences focused on combination products, two were medical technology conferences, and the annual meeting was for a pharmaceutical industry professional association. The medical technology conferences and annual meeting both had a number of tracks focusing on combination products. Attending these conferences/meetings facilitated and accelerated the processes of identifying participants to interview (opportunistic sampling). The researcher approached expert speakers in the field of combination products who spoke at these conferences directly for interviews.

Table 3 Conferences and Annual Meetings Attended for Recruiting Interviewees

<b>Conference/Annual Meetings</b>	<b>Location</b>	<b>Date</b>
Medtech 2010	Galway, Ireland	October 2010
BIOMEDevice	Paris, France	February 2011
DIA EuroMeeting	Geneva, Switzerland	March 2011
Converging in Ireland Conference	Dublin, Ireland	May 2011
MedTech 2011	Cork, Ireland	October 2011

This method of sampling ensured:

- A desired representative sample of opinions of the regulation of drug/device combination products.
- Individuals from a variety of organisations participated.
- A geographically dispersed sample.

The participants' received participant information sheets (Appendix D) prior to the interview that explained the purpose of the research. Potential participants were given a day to decide whether they would like to participate and to seek more information regarding the research. Participation in the research was voluntary.

#### **4.3.5 Sample**

In order to ensure interviewees were 'information rich' (Patton, 1990) the researcher used the following selection criteria:

1. The informant must have experience of the regulation of drug/device combination product in the European Union or/and United States.
2. The person must have at least four years' experience dealing with the EU and/or US drug/device combination regulatory frameworks.

#### **4.3.6 Data Management (NVivo 10)**

The researcher transcribed all interviews verbatim and uploaded them into the NVivo 10 qualitative software to facilitate data management and analysis. Scholars generally recognise NVivo as a highly reputable tool for managing and supporting qualitative analytical work (Bryman, 2012, Bazeley and Jackson, 2013). Using NVivo to process the data provided

efficiency, thoroughness, and transparency (Bazeley and Jackson, 2013). NVivo facilitated a methodical examination of possibilities of investigation that time constraints would have prevented in a manual system. In addition, NVivo made possible the automation of several administrative tasks connected with the qualitative data analysis, permitting the researcher additional time to consider on the interpretive facets of the data. By ensuring a clear audit trail, the program guards against random, subjective analysis. All coding stages were documented in a way that would best enable an objective and meticulous approach to the data analysis.

#### **4.3.7 Data Analysis (Thematic Analysis)**

While programs such as NVivo enable systematic analysis, technology can never fully replace the development of an understanding of the data in order to build theory (Gibbs, 2002, Roberts and Wilson, 2002, Basit, 2003, Jones, 2007). In light of this, the researcher employed thematic analysis, a form of qualitative analysis utilised to examine classifications and present themes (patterns) that are correlated to the data (Jones, 2007, Boyatzis, 1998). It provides a systematic element to data analysis and allows the researcher to associate an analysis of the frequency of a theme with one of the whole content. This confers precision and sophistication and enhances the research's meaning.

##### **4.3.7.1 Reasons for choosing Thematic Analysis:**

Good qualitative research must draw interpretations consistent with collected data (Boyatzis, 1998, Denzin and Lincoln, 2005, Patton, 1990). Thematic analysis can detect and identify, e.g. factors or variables that influence any issue described by the participants (Boyatzis, 1998, Braun and Clarke, 2006). It makes participants' interpretations noteworthy in terms of giving the most suitable explanations for their behaviours, actions, and thoughts (Creswell, 2008, Vaismoradi et al., 2013). The flexibility of thematic analysis allows researchers to use it in both inductive and deductive methodologies (Dixon-Woods et al., 2005).

Thematic analysis enables the researcher to code and categorise data into themes (Vaismoradi et al., 2013, Boyatzis, 1998, Ezzy, 2013). In the case of the current research, the ways in which issues influence the perceptions of participants constitute a theme. Thematic analysis supports the display and classification of processed data according to its similarities and differences (Boyatzis, 1998, Ezzy, 2013, Vaismoradi et al., 2013). Achieving the above requires coding, categorisation, and noting patterns, which also facilitates the comprehension of an association between the variables and factors in order to make a logical chain of evidence (Creswell, 2008, Braun and Clarke, 2006, Miles and Huberman, 1994).

#### **4.3.7.2 The Thematic Analysis Decisions taken for this study:**

The first concept that needs to be clarified is what counts as a theme (Onwuegbuzie and Teddlie, 2003, Ryan and Bernard, 2003, Vaismoradi et al., 2013, Boyatzis, 1998). Braun and Clarke (2006) classify a theme as follows:

“Thematic analysis is a method for identifying, analysing, and reporting patterns (themes) within data. It minimally organises and describes your data set in (rich) detail... [Themes] capture something important about the data in relation to the research question, and represents some level of patterned response or meaning within the data.” (Braun and Clarke 2006, p.82)

Braun and Clarke (2006) note that quantifiable prevalence does not determine the “keyness” (Braun and Clarke 2006, p.82) of a theme. This suggests the researcher should contemplate this importance compared to that of other themes, and its relevance to the research question.

Braun and Clarke (2006) identify a second question a researcher must answer in undertaking thematic analysis: whether the analysis will be rich description of the entire data set or a detailed account of one particular aspect of the data. Braun and Clarke’s (2006) suggestion to focus on a rich description of the content of the entire dataset guided the research, in light of the fact that regulatory approval processes are an under researched area and few researchers have obtained access to individuals with firsthand knowledge of them.

Braun and Clarke (2006) also describe it as important to decide whether the researcher will code from an inductive or deductive point of view. This study followed an inductive approach, as the identified themes were closely linked to the actual data; as opposed to attempting a fit between the data and a pre-existing thematic coding framework of the interpreter's misconceptions (Boyatzis, 1998, Onwuegbuzie and Teddlie, 2003).

Finally, the choice between the levels of analysis must be made. There are two possible levels of analysis; firstly there is the semantic or explicit level and secondly, the latent or interpretive level (Boyatzis, 1998, Braun and Clarke, 2006, Rubin and Rubin, 2011). Semantic themes are surface meanings of the data, not going further than what a participant has said, but offering some interpretation in order to give meaning to the patterns and their significance (Braun & Clarke, 2006). Latent themes, however, investigate the underlying assumptions, ideas, and conceptualisations that are theorised as informing the content of the data (Braun & Clarke, 2006). This study aimed to work with themes only on a semantic level, identifying themes within the explicit meanings described by the respondents in their responses instead of looking for assumptions beyond that (Vaismoradi et al., 2013). A semantic level of analysis was considered to be fitting for the present study as it concentrates on what the participant has said with interpretations made based on patterns within the data. In contrast latent themes are interpreted based on underlying theory and is associated with a constructionist approach. The present study therefore employed thematic analysis within a realist perspective to explore participant's experience of drug/device regulation.

Three separate cycles of coding were undertaken, following the recommendations of Braun and Clarke (2006). Table 4 describes the five phases this thesis undertook, describing the processes in detail.

Table 4 Phases of Thematic Analysis (adapted from Braun and Clarke, 2006)

<b>Phase</b>	<b>Description of the Process</b>
1. Familiarising with your data	Transcribing data reading and rereading the data, recording noting preliminary ideas.
2. Generating initial codes	Coding worthy features of the data in a systematic fashion across the complete dataset, collating data applicable to each code.
3. Searching for themes	Collating codes into potential themes, gathering all data applicable to each potential theme.
4. Reviewing themes	Scrutinising the themes' functioning in relation to the coded extracts (Level 1) and the entire data set (Level 2), generating a thematic 'map' of the analysis.
5. Defining and naming themes	Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells; creating clear definitions and names for each theme.
6. Producing the report	The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis.

The researcher conducted initial thematic analysis. To establish the consistency of the conclusions of the coders and to determine inter-rater reliability the codes for the themes and subthemes were collaborated by a second independent analyst who had experience with qualitative methods and analysis (Hruschka et al., 2004, Patton, 1990). This verification process ensured the transcript, or paragraphs, reflected the themes and categories coded by the researcher (Denzin and Lincoln, 2005). The second analyst applied the themes to a subset of the data which was a random selection of 25% (n=5) of the interviews. The percent agreement between the two coders was 92%. The second coder also suggested the reorganization and addition of three subthemes and two main themes. Agreement was decided after discussion (e.g., examining relevant literature). The additions of these themes were discussed between the two coders and it was decided that they should be included in the analysis. Secondly, where possible, member checking was undertaken (Miles and Huberman, 1994). Although limited, this involved contacting four participants and requesting them to validate the researcher's understanding and interpretation of their transcripts to ensure authenticity.

### **Phase 1: Gaining Familiarity with the Text**

All interviews were transcribed verbatim, a process that aided obtaining familiarity with the data and therefore aiding in understanding it (McLellan et al., 2003, Davidson, 2009, Boyatzis, 1998). The transcripts were read and re-read in order to get familiar with the depth and breadth of the material. The recorded interviews were listened to 3 times in their entirety and frequently relistened to segments of the recording during phase 1 of the coding process. This process ensured that full immersion in the data. Notes of any interesting topic that appeared during the transcription process were made. An initial list of ideas about the content of the data emerged from phase 1.

### **Phase 2: Generating Initial Codes**

Generating initial codes from the data began with open coding, in which the researcher examined and labelled individual phrases and paragraphs with potential descriptive codes. A code is a word or a short phrase that can descriptively and interpretively grasp an idea that evokes meanings in data (Saldaña, 2012, Braun and Clarke, 2006, Boyatzis, 1998). Two criteria for identifying codes was used: identifying recurring meanings even when different words are used, and focusing on repeated and consistent patterns of actions through words, phrases, or sentences (Bazeley, 2007, Owen, 1984, Saldaña, 2012). Nodes<sup>1</sup> were created to code, store, and group conceptually relevant data with similar data from different sources (Boyatzis, 1998). This coding of relevant passages or texts (a sentence or paragraph) into nodes allowed the analysis to move from a superficial to a close engagement with the text. Using NVivo, the researcher created open/free/emergent nodes and tree nodes that could act as codes. Figure 2 is a screenshot from NVivo that shows the NVivo interface as well as an example of open codes.

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<sup>1</sup> A node is a term used in NVivo to describe the assembly of references concerning a particular theme. The references are collected by 'coding' sources such as interviews



Figure 2 NVivo 10 Screenshot of Open Codes

The screenshot displays the NVivo 10 software interface. The top menu bar includes File, Home, Create, External Data, Analyze, Query, Explore, Layout, and View. The left sidebar shows a tree view of Nodes, with 'Phase 1 - Open Coding' selected. The main window shows a table of open codes for 'Phase 1 - Open Coding'.

Name	Sources	References
Clashing of cultures (cultural differences)	11	28
Classification uncertainty	7	17
Classify the product in a way the suits them rather than the way that is right	2	2
Classifying the combination product as a combination product	4	5
Classifying the combination product as a medical device	7	12
Collaborating	11	95
Collaborating to generate sustainable relationships	4	21
Collaboration with regulators	2	8

Below the table, a specific open code is selected: 'Clashing of cultures (cultural di...'. The associated text shows a quotation from an interview: 'a big cultural battle in trying to make ourselves get taken seriously'. The quotation is circled in orange, and an arrow points from a callout box to it.

Annotations on the left side of the screenshot include:

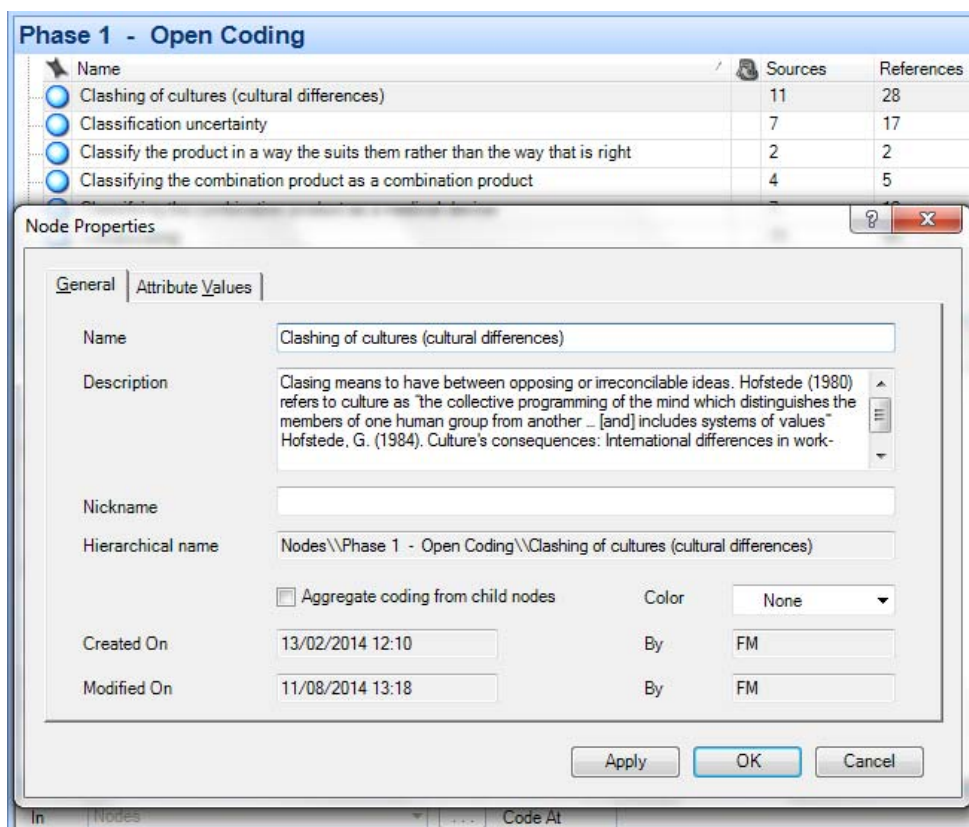
- Transcribed interviews saved into folder labelled cases
- Phase 1 Open Coding
- Phase 2 Categorisation of Codes
- Phase 3 Data Reduction

An annotation on the right side of the screenshot states: 'Example of Open codes, with title "Clashing of Cultures" highlighted'.

Another annotation on the right side of the screenshot states: 'Quotation from interview that is coded to this open code titled "Clashing of Cultures"'. An arrow points from this box to the circled quotation.

The ability to create, refine, add, or remove nodes during the analysis process as the researchers understanding evolved during the course of the analysis produced confidence and transparency (Hilal and Alabri, 2013). Coding is a formal foundation of thematic analysis, which ultimately represents an evidential linking of a category and a theme (Boyatzis, 1998, Rossman and Rallis, 2011). Thus, the researcher considered two methods of confirming that codes contained appropriate texts. The first was a detailed description of a code, which NVivo made possible (see Figure 3 below for an illustration). By making sure that descriptions fitted any new text, the researcher used inductive analysis in order to ensure a strong link between the codes and the data (Joffe and Yardley, 2004).

Figure 3 NVivo 10 Screenshot of the Code Description for Clashing of Cultures



The process generated 154 open codes. For example the following data were coded as

Clashing of cultures (cultural differences):

...a big cultural battle in trying to make ourselves get taken seriously.  
(Participant 09)

Throughout the analysis process, the researcher made sure that sentences from transcriptions extracted and coded were directly relevant to the phenomenon under investigation and answered the research questions (Owen, 1984, Braun and Clarke, 2006). Some passages could be coded under different nodes. The same strategies guided the analysis of each interview.

### **Phase 3 Searching for Themes**

This third phase of thematic analysis involved organising and combining the 154 codes into potential themes (Bryman, 2012, Braun and Clarke, 2006). To identify patterns in the datasets which constituted themes, the researcher collated all the relevant coded data extracts into meaningful groups and arranged them under a hierarchical structure of overarching themes and sub-themes (Boyatzis, 1998). NVivo provides a hierarchical structure that contains parent and child nodes. Rich accounts of nodes emerged and working with nodes, rather than transcripts, made it possible to derive themes. Thus, the process of creating a child node or a parent node involved analysing nodes for conceptual and mutual relationships. Figure 4 below shows a screenshot of tree codes.

Figure 4 NVivo Screenshot of Tree Codes

Name	Sources	Referen
Category - Acknowledgement an organisations culture can impact bringing a combination product to market	18	143
Subcategory - Bringing Cultures Together	12	40
Subcategory - Organisational Culture Clashes	15	44
Clashing of cultures (cultural differences)	11	28
Different mindset	9	12
Reconciling pharma and medical device mindsets	2	4
Subcategory - Startup	16	59
Category - Acknowledging the complexities in bringing a combination product to market	16	135
Acknowledging the complexities in bringing a combination product to market	11	71
Acknowledging the complexity of adding drug to medical device	10	19
Building on experience from previous regulatory submissions	6	14
Clashing of cultures (cultural differences)	11	28
Pharma and medical device regulators retrenched	1	1
Presubmission meetings with regulators	1	2
Category - Choosing the right commercialisation strategy to bring a combination product to market	12	93
Category - Choosing which Regulator in EU to hire	5	8
Category - Combination product technology considerations	16	146
Category - Communicating with regulators	13	306
Category - Cost of adhering to Regulatory Requirements	3	5
Category - Determining the Best Regulations for Combinations Products	15	108
Category - Determining the regulatory classification of a combination product	10	43
Category - Differences between Pharma and Medical Device Compaines	15	64
Clashing of cultures (cultural differences)	11	28
Manufacturing a medical device	4	6

Three key themes emerged in this process.

#### Phase 4 Reviewing Themes

Phase 4 involved the refinement of the 3 themes identified in Phase 3. Certain ideas, notions, patterns, and clusters of meaning emerged as recurrent in the interviews, and new themes emerged (Boyatzis, 1998). The researcher reviewed all extracts coded under each theme, reviewed the entire dataset to ensure that all relevant data in the dataset were coded under the relevant theme/s (which may have been missed in initial coding) and finally reviewed each theme to ensure that they “accurately reflect the meanings evident in the whole dataset”. Listening to the recordings of the interviews was also a part of this process. It revealed some themes identified earlier were not really themes, while other themes collapsed into each other.

### **Phase 5: Defining and naming themes**

Phase 5 involved defining and further refining the themes present in an analysis, and analysing the data within them. This process involved identifying the “essence” of each theme’s meaning as well as the significance of themes overall. The researcher chose quotes to illustrate and validate the categories, conducting and writing a detailed analysis for each individual theme.

### **Phase 6: Producing the Report**

This phase involved embedding extracts within an analytic narrative that conveys the story in a convincing way (Cavana et al., 2001, Boyatzis, 1998, Robson, 2002). The analytic narrative must go beyond description of the data, and make an argument in relation to the research question.

In spite of its strengths, the mixed methods approach has several disadvantages. These include the fact that using several methods incurs financial costs (Johnson and Onwuegbuzie, 2004) and takes time. In addition, the researcher needs to develop skills in more than one method (Denscombe, 2007). Further, findings from different methods might not corroborate one another. When findings from different methods do not support one another, the researcher may not have the tools to seek the larger meanings by this discrepancy (Denscombe, 2007).

#### **4.3.8 Development of Conceptual Model**

In a mixed methods study results merged and integrated to provide interpretation about the overall results of this study (Creswell & Plano Clark, 2011). A conceptual model provides a visual connection of how results are merged in a mixed methods study, and —represents how events unfold over time (Bernard and Ryan, 2009). A conceptual model was developed following the emergence of the themes (Figure 10). The graphical display maps out key findings of the study through merging results from all data sets (Bernard and Ryan, 2009).

### **4.3.9 Evaluating Qualitative Research**

Pickard (2013) outlined four concepts that quantitative researchers commonly use to determine the quality of the research findings: external validity, internal validity, objectivity, and reliability, (Pickard, 2013). Qualitative researchers commonly use trustworthiness and authenticity to determine and gauge the quality of the research in place of reliability and validity. The researcher applied these two criteria to determine the quality of the qualitative findings.

#### **Trustworthiness**

Trustworthiness of qualitative research means the merit of findings and their legitimacy (Silverman, 2013, Lincoln and Guba, 1985, Denzin and Lincoln, 2005). The concepts qualitative researchers most commonly use to establish trustworthiness of their research are credibility, transferability, dependability, and confirmability (Pickard, 2007).

#### **Credibility**

The objective here is to ensure that a research design will be both believable and meaningful (Bailey et al., 1999, Malterud, 2001, Silverman, 2013). The use of three pilot studies, as well as triangulation, ensured credibility. In the pilot studies, three experts reviewed the interview questions for ambiguity and for the likelihood of leading an interviewee or causing him or her adverse emotions or stress.

Bryman (2012) notes that triangulation, which requires using several research techniques and sources of data to investigate the same phenomenon (Bryman, 2012, Miles and Huberman, 1994), aids credibility. Employing several data collection techniques counteracts any limitations of individual techniques (Pickard, 2013). It further ensures accuracy of the study because the information is drawn from multiple sources of information. The researcher triangulated in the first phase by in the first phase comparing the data collected through the interviews with the contents of documents (including company profiles, press

releases etc.) collected and in the second phase by using the online questionnaires to support and qualify the issues raised in the interviews.

### **Transferability**

A rich and thorough description of the research case makes it possible to apply the findings to other contexts (Silverman, 2013). As Pickard (2013) notes, if sufficient similarities exist between two contexts, researchers may apply the research findings to a new context. In addition, a number of researchers have noted that using multiple cases helps to increase the transferability of qualitative findings (Silverman, 2013, Rossman and Rallis, 2011). The application of these concepts in this study should make transferability judgments possible (Lincoln and Guba, 1985). By providing detailed information about the experiences of 19 individuals who have sought regulatory approval for drug/device combination products and using the survey method, with a sample size of 158 in the second phase, this research created findings that should be transferable to other contexts.

### **Dependability**

Dependability means the likelihood of the findings being applicable to other cases with the same parameters. A clear account of the research process should reveal its dependability (Denzin and Lincoln, 2005, Baxter and Eyles, 1997). In order to provide such an account, the researcher must maintain complete records of the research process (Bailey et al., 1999, Bryman, 2006, Malterud, 2001). For this research the current chapter provides a clear account, and the researcher maintains complete records of all phases of the research processes.

### **Confirmability**

Confirmable research is not prejudiced by the personal values and prior beliefs of the researcher (Bryman, 2012, Malterud, 2001) but relies on the raw research data. This research uses the thematic analysis technique to show clearly the development of each theme or category from the raw data. It is detailed in section 4.3.7 how the researcher adhered to Braun and Clarke's (2006) guidelines for

conducting thematic analysis. Moreover, the researcher quoted the participants' perceptions and used them to reinforce all claims and conclusions. A complete audit trail, all of the recordings of the interviewees all interview transcripts, and all coding have been kept.

In summary, the criteria of trustworthiness and authenticity guided this research. They provided a healthy reference structure for the pursuit of quality.

### **Authenticity**

Authenticity relates to the coverage of each participant's experiences in a way that it preserves the context of the data and presents all perspectives equally so that the reader can come to an impartial decision (Malterud, 2001, Fossey et al., 2002, Bailey et al., 1999). To ensure authenticity the research needs to represent diverse viewpoints amongst members of the social setting, and therefore all the participants in the setting should have an equal chance to be included in the research (Whittemore et al., 2001, Baxter and Eyles, 1997). Two procedures ensured this research authenticity: the pilot studies and the participation of individuals from a variety of different organisations in interviews.

## **4.4 Quantitative Research Methodology (Phase Two)**

Phase two of this research used a survey as the quantitative methodology. The aim of this quantitative phase was to test and explore, in a larger sample, the identified facilitating factors in the interviews. The results of a web-based survey were used to establish if the results complemented, contradicted, or confirmed the findings of the research interviews.

The motivation for gathering qualitative data initially was that there were no existing instruments, nor a theoretic framework, for understanding the factors that facilitate obtaining regulatory approval of drug/device combination products in the EU and/or US. By basing the instrument's development on the themes generated



from the qualitative study, the purpose was to develop an instrument that more precisely measured the phenomenon than if it had been based on the limited amount of information currently available in the literature.

The survey designed in this phase is a descriptive survey. The research survey aimed to test and explore further, in a larger sample, the possible variation in perceptions between the informants. Descriptive surveys seek to describe a situation and look for trends and patterns within a sample group that can be generalised to the defined population of the study (Chambers and Skinner, 2003)). Explanatory surveys, on the other hand, aim to discover causal relationships between variables (Zikmund et al., 2012). In general, descriptive surveys have aims and objectives and explanatory surveys will state hypotheses (Robson, 2002). This research utilised the descriptive survey research approach because it has aims and objectives rather than theories and hypotheses to test.

In a mixed methods methodology, this phase represents the “mixing” or “integration” of the qualitative and quantitative phases, or the explicit relation of the qualitative and quantitative data (Creswell and Clark, 2007, Fetters and Freshwater, 2015). In instrument development design the data is not mixed in the literal sense, as the qualitative data analysis serves as the foundation for the quantitative data collection. However, the phases are connected through the process of transforming the qualitative themes into quantitative items. Because the transformation process has received relatively little attention in the literature, conceptualizing it as its own unique phase places an increased emphasis on the process of translating qualitative themes into quantitative items (O’Cathain et al., 2007, Greene et al., 1989, Bryman, 2007).

#### **4.4.1 Data Collection Technique (Web-based Survey)**

There are a variety of ways surveys can be administrated (e.g. mail, face to face, web-based) (Boyer et al., 2002, Sills and Song, 2002, Fowler, 2014, Fink, 2012). For this research, a web-based survey was conducted to gather data from respondents located in different countries.

Four reasons drove the choice of a web-based survey. Firstly, participants throughout the world who have internet access can respond to web-based surveys quickly and inexpensively (Sue and Ritter, 2012, Cavana et al., 2001, Rea and Parker, 2012). The participants in this research are located in different geographic locations and thus they needed to have easy access to the survey. Secondly, web-based surveys are an efficient method of collating data (Fink, 2012, Sue and Ritter, 2012). Survey return and data entry are fully automated through the web survey software. Reminders and clarification can be communicated efficiently. The completed surveys will not be lost in the process of mail delivery or manual data entry like in mail surveys. Thirdly, it is cost efficient, lacking a need for postage and paper (Blair et al., 2013, Fowler, 2014). Finally, online surveys provide confidentiality and security of information, a vital aspect of gaining the trust of participants from the medtech sector (Sue and Ritter, 2012, Rea and Parker, 2012).

Web-based surveys do have certain disadvantages. Firstly, respondents must be computer literate and have access to computers and the internet (Cavana et al., 2001, Sue and Ritter, 2012). This was not an issue for this research as the research sample consisted of persons from the Medtech sector that have access to computers and the internet. Secondly, web-based surveys do not permit an interviewer to explain an unclear question (Fink, 2012). To address this, the questions were tested for clarity during the pilot phase. In addition to this the survey provided the researcher's phone number and email address to the researcher at the outset for respondents who needed clarification (Appendix E). Finally, web-based surveys can be called impersonal; a researcher has limited ability to probe in-depth and participants may feel unmotivated to participate (Fink, 2012). In this study, the participant information sheet sought to provide

motivation by describing the expected value of the study in the participant information sheet, and the researcher promised the participants access to the best practice findings (Appendix E). Phase one mitigated the impact of the inability to probe in-depth.

### Survey Software Employed

A review of a number of survey software providers led to the selection of SurveyGizmo according to the following criteria:

That the survey software programs support different browsers: The literature (Manzo and Burke, 2012, Couper, 2000, Fan and Yan, 2010) indicates that it is vital that survey software programs are useable with browsers. Often, the same survey might look strikingly different to respondents in web browsers (Manzo and Burke, 2012, Simsek and Veiga, 2001). Because of these variations, some respondents may not be able to browse the surveys normally or submit their answers successfully. Annoying appearance or poor functionality might lead them to quit (Sue and Ritter, 2012). SurveyGizmo was compatible with all browsers. This was also verified in the pre-test phase.

Data Security: SurveyGizmo has anti-hacking measures, redundant firewalls, and continuous security scans. All of these features will aid the assurance of the confidentiality of all survey participants (Fan and Yan, 2010).

Inexpensive: As a student, the researcher could use SurveyGizmo with advanced features, supporting up to 1,000 responses per month and basic logic for 7 USD.

Appearance: The potential participants for the survey work in a high tech environment and the researcher believed that SurveyGizmo offered a format that would win their respect and affinity (Simsek and Veiga, 2001).

Tracking of Responses: SurveyGizmo provides an instant view of the current number of surveys completed and in process with a daily response. This feature allowed the researcher actively to monitor how many responses were being obtained and in real-time.

Privacy Features: SurveyGizmo offers a variety of privacy features including password protection, guaranteed data privacy, and Secure Sockets Layer (SSL) technology/advanced technology data centre security. All surveys were anonymous and required no identifying personal data. This was of paramount importance for the participants of the survey as the Medtech sector is highly secretive and participants had to know that their responses could not be tracked to their company, if they did not desire this. This feature was vital to a healthy response rate (Manzo and Burke, 2012, Fink, 2012).

Specific Features: SurveyGizmo had a “*save and continue later*” feature. Respondents can save their responses and review them at a later date as well as resume completion. Given this survey consisted of 8 number of pages, the researcher anticipated that participants might want to complete the survey in multiple sessions. This feature was deemed critical. SurveyGizmo also has measures in place that prevent respondents from completing multiple surveys. This feature was important to ensure the integrity of the survey results.

#### **4.4.2 Instrument Development**

The survey instrument was developed based on information from the interviews (phase one). The themes and factors from the interview analysis were used to develop a survey instrument that was constructed to address the research questions 4, 4a and 4b (Table 5). The interviewees' language was used to phrase some of the questions. The survey design followed the best practice guidelines suggested by Pickard (2013), Oppenheim (1992) and Cavana et al. (2001). It is a descriptive, rather than analytic, survey (Oppenheim, 1992). Descriptive studies describe how things are; they do not set out to test hypotheses. The important difference

between an analytical study and a descriptive study is that the latter is designed to test a hypothesis. Within survey research a distinction is made between analytical, descriptive and exploratory survey research. Exploratory research means to explore a new phenomenon in the early stages of the research process. Analytical research however (or theory testing) takes place when knowledge of phenomena has been articulated in a theoretical form using well-defined concepts, models and propositions (Forza, 2002). An analytical survey is appropriate for quantifiable data requiring statistical interpretation to gain its meaning (Cavana et al., 2001). A descriptive survey is aimed at understanding the relevance of a particular occurrence and describing the distribution of the result in a population (Forza 2002).

Table of Specifications.

The table of specifications (Table 5) links instrument items with research questions.

Table 5 Survey Instrument: Themes, Variables, Survey Items and Response Items

Facilitating Factor Id	Research Question	Variable	Survey item	Data Type	Data Analysis
	N/A	Position in organization	Q.1	Categorical (nominal)	Descriptive Statistics
	N/A	Length in current position	Q.2	Categorical (nominal)	Descriptive Statistics
	N/A	Years of experience with combination products	Q.3	Categorical (nominal)	Descriptive Statistics
	N/A	Organization type	Q.4	Categorical (nominal)	Descriptive Statistics
	N/A	Number of employees	Q.5	Categorical (nominal)	Descriptive Statistics
	N/A	Total Sales	Q.6	Categorical (nominal)	Descriptive Statistics
	N/A	Nature of combination product	Q.7	Categorical (nominal)	Descriptive Statistics
	N/A	Combination product market	Q.8	Categorical (nominal)	Descriptive Statistics
	N/A	Development Stage of Combination Product	Q.9	Categorical (nominal)	Descriptive Statistics
A	Is there a relation between combining components with regulatory approval into a combination product and obtaining regulatory approval?	Combining products with existing regulatory approval	Q. 10 Q.11	Categorical (ordinal)	Descriptive Statistics
B	Is there a relation between knowledge and obtaining Regulatory Approval	Knowledge of regulations	Q.12	Categorical (ordinal)	Descriptive Statistics
C	Is there a relation between experience of bringing a combination product to market and obtaining regulatory approval?	Experience of combination products	Q.13	Categorical (ordinal)	Descriptive Statistics
	N/A	Experience of EU regulations	Q.14	Categorical (nominal)	Descriptive Statistics
	N/A	Classification of combination product in EU	Q.15	Categorical (nominal)	Descriptive Statistics

Facilitating Factor Id	Research Question	Variable	Survey item	Data Type	Data Analysis
D	Is there a relation between choice of an experienced Notified Body and obtaining regulatory approval?	Notified Body's experience with combination products	Q.16	Categorical (ordinal)	Descriptive Statistics
E	Is there a relation between Notified Body combination product expertise and obtaining regulatory approval?	Employees with prior Experience	Q.16	Categorical (ordinal)	Descriptive Statistics
F	Is there a relation between engaging early with Notified Body and obtaining regulatory approval?	Early engagement with regulatory authorities	Q.17	Categorical (ordinal)	Descriptive Statistics
	What is the most critical facilitating factor associated with obtaining regulatory approval of drug/device combination products in the EU?	Most critical factor for EU approval and why	Q.18 Q.19	Categorical (ordinal)	Descriptive Statistics
	N/A	Experience of US regulations	Q.20	Categorical (nominal)	Descriptive Statistics
	What is the most critical facilitating factor associated with obtaining regulatory approval of drug/device combination products in the US?	Classification of combination product in US	Q.21	Categorical (nominal)	Descriptive Statistics
G	Is there a relationship between engaging early with Office of Combination Products and obtaining regulatory approval?	Engagement early with office of combination products	Q.22	Categorical (ordinal)	Descriptive Statistics
	N/A	Most critical facilitating factor for US approval and why	Q.23/24	Categorical (ordinal)	Descriptive Statistics
H	Is there a relationship between working in a partnership and obtaining regulatory approval?	Partnerships	Q.25 Q.26 Q.27	Categorical (ordinal) Categorical (ordinal) Categorical (nominal)	Descriptive Statistics
I	Is there a relationship between cultural differences between industries and obtaining regulatory approval?	Cultural differences	Q.28	Categorical (ordinal)	Descriptive Statistics

<b>Facilitating Factor Id</b>	<b>Research Question</b>	<b>Variable</b>	<b>Survey item</b>	<b>Data Type</b>	<b>Data Analysis</b>
J	Is there a relationship between working with a partner organization of different size and obtaining regulatory approval?	Partners size	Q.28	Categorical (ordinal)	Descriptive Statistics
K	Is there a relationship between a partner's pace of work and obtaining regulatory approval	Partners pace of work	Q.28	Categorical (ordinal)	Descriptive Statistics
L	Is there a relationship between a partner's attitude towards risk and obtaining regulatory approval	Partner's attitude towards risk	Q.28		
	What is the most critical facilitating factor associated with obtaining regulatory approval of drug/device combination products in the EU?	Most critical facilitating factor for successful partnership and why?	Q.29/Q.30	Categorical (nominal)	
	Not Applicable	Additional comments	Q.31	Categorical (nominal)	



Considerations that were incorporated into the instrument design were:

Length of survey: The length of a survey has a negative linear relation with response rates (Bryman, 2012). The researcher checked the completion time of the survey in the pre-test phase and deterred it would take approximately 10 minutes to complete, a length that appeared on the survey's cover page and in notifications recruiting survey participants.

The presentation of the web-based surveys: Couper (2000), discusses how that the presentation of web surveys directly affects the measurement error (Couper, 2000). Likewise, the presentation of a survey on the website can directly or indirectly affect the response rate. Question wording and ordering were therefore important factors considered in the development of the instrument.

Question Wording:

Lohr's checklist was used to avoid further biases or guided questions when phrasing the survey questions (Lohr, 1999);

1. Use simple, familiar words (avoid technical terms, jargon, and slang);
2. Use simple syntax;
3. Avoid words with ambiguous meanings, i.e., aim for wording that all respondents will interpret in the same way;
4. Strive for wording that is specific and concrete (as opposed to general and abstract); Make response options exhaustive and mutually exclusive;
5. Avoid leading or loaded questions that push respondents toward an answer;
6. Ask about one thing at a time (avoid double-barreled questions);
7. Avoid questions with single or double negations

Question Ordering:

Substantial ordering effects respondents' answer to traditional surveys in that the preceding questions can affect how potential respondents consider and evaluate a question. The following recommendations were considered in developing the

survey instrument (Tourangeau et al., 2000, Tourangeau et al., 2004, Couper et al., 2007):

1. Early questions should be easy and pleasant to answer, and should build rapport between the respondent and the researcher.
2. Questions at the very beginning of a questionnaire should explicitly address the topic of the survey, as it was described to the respondent prior to the interview.
3. Questions on the same topic should be grouped together.
4. Questions on the same topic should proceed from general to specific.
5. Questions on sensitive topics that might make respondents uncomfortable should be placed at the end of the questionnaire.
6. Filter questions should be included to avoid asking respondents questions that do not apply to them.

Type of Questions: The questionnaire used in this study contained four types of questions: open, closed, Likert Scale, and tick all that apply questions (see Appendix E).

Open-ended questions have no predefined options or categories included. Open-ended questions are exploratory in nature. Open ended questions were used in this survey as the research is exploratory in nature and this form of questions provides rich qualitative data.

For instance, question 18 simple asked respondents for their opinion:

*Q.18. What do you think is the most critical factor for obtaining prompt regulatory approval of a combination product in the EU?*

In contrast to open-ended questions, closed-ended questions constrain the answers of the respondents to response options given on the questionnaire. The advantage of closed-ended questions is that they are straightforward to standardise, and data gathered from them lend themselves to statistical analysis (Fink, 1995). The survey included this question 2:

*Q.2 How long have you been in this current position?*

- *Less than 4 years*
- *5-10 years*
- *11-15 years*
- *Greater than 15 years*

The questionnaire also used the Likert scale, a ratings question. Likert type scales provide an idea of how strongly a participant feels about something, giving more detail than a simple yes no answer. A series of 7-point Likert scale questions asked respondents to rate the importance of a number of factors (ranging from not at all important (1) to extremely important (7)).

Question 12 was part of the series:

*Q.12 How important is it to have knowledge of the regulatory requirements for combination products when attempting to bring them to market?*

<i>Not at all important</i>	<i>Low importance</i>	<i>Slightly unimportant</i>	<i>Neutral</i>	<i>Very important</i>	<i>Moderately important</i>	<i>Extremely important</i>

The fourth and final type of question employed in the survey is tick-all-that-apply (multi-response) questions. The tick-all-that-apply question format presents respondents with several response options to a single question. An example of this type of question in the survey is question 25.

*25) How was the combination product developed? (tick all that apply)*

*[ ] Through internal development*

*[ ] Acquisition (acquired a company that manufactured it)*

*In-licensed the technology for the combination product*

*Out-licensed the technology for the combination product to another company*

*Through a joint venture*

*Other (please specify): \_\_\_\_\_*

Contact delivery modes, pre-notifications and reminders: Respondents received three types of contacts for the purpose of informing respondents of the upcoming arrival of a survey or reminding respondents to complete the survey.

The first contact was an email requesting participation with a link to the online survey (Appendix F). This email included the participant information sheet (Appendix A) as an attachment. The participant information sheet contained information about the purpose and use of the survey, an estimation of the time completing the survey would take, and researcher contact information. The researcher followed up with a reminder email message with these individuals 7 days later (Appendix G).

The researcher employed social media to make three additional types of contacts. The first type of contact (Appendix H) was a notice posted in LinkedIn Groups that contained people who had expertise in the area of drug/device combination products. The second type of contact was InMails sent to individuals on LinkedIn (Appendix I). Sending these InMails had a cost but the researcher felt it was worth paying a fee in order to get access to high calibre survey participants. The researcher employed a more formal style in these InMails, determining it a more effective means of attracting attention. Another type of contact was direct messaging on the social networking site Twitter (Appendix J). This was again a less formal notification to catch people's attention.

#### **4.4.3 The Final Instrument**

Appendix E contains the final survey. This section describes the contents, which included 31 questions. The researcher developed the questions based on the literature and the themes identified by the semi-structured interviews.

##### Cover Page:

The first page of the web site presented the participant information sheet Appendix E).

##### Section One

Each section started with a description of what the section was designed to reveal.

##### Background and Demographic Information

Sections 1 and 2 of the survey were intended to make the respondent comfortable by using very straight forward questions. The intent was to build the respondents' confidence and trust in the questionnaire to improve overall response rates (Oppenheim, 1992). Questions sought information about the type of professionals participating in this survey and the organisations in which they work. In measured organisation size in terms of annual revenues, number of employees, and market share; organisation type; job title; length of time in current position; and length of experience with combination products.

##### Drug/device Combination Product Information

The beginning of this section states that for the remaining questions the participants should focus on one drug/device combination product with which they had the most experience.

Questions elicited the category of the drug/device combination product, in which territory the participant sought approval, and its stage of development. Answers provided context to the survey answers and the ability to compare the experiences relating to different types of product groups.

### Description of individual components that make up the Drug/Device Combination Product

This section sought to gain information about the product's components. The purpose was to measure patterns of participation in specific product sectors. These questions were based on the themes the qualitative phase of the research had revealed.

This section used a Likert scale (Figure 5) to seek participants' opinion as to the importance of three characteristics:

- prior regulatory approval for the components of the combination product;
- having knowledge of regulatory requirements prior to seeking approval; and
- experience bringing a combination product to market.

Figure 5 Screenshot of Likert Scale Questions

---

11. How important is having regulatory approval for the components of the combination product prior to their inclusion in the overall product?

Not at all important    Low importance    Slightly unimportant    Neutral    Moderately important    Very important    Extremely important

---

12. How important is it to have knowledge of the regulatory requirements for combination products when attempting to bring them to market?

Not at all important    Low importance    Slightly unimportant    Neutral    Moderately important    Very important    Extremely important

---

13. How important is it for employees to have prior experience of bringing combination products to market?

Not at all important    Low importance    Slightly unimportant    Neutral    Moderately important    Very important    Extremely important

---

### EU Regulatory Framework Experience

This section opened with a question asking if the respondent had experience of the EU regulatory framework for combination products. A no answer automatically brought the respondent to the next section. A yes answer led to questions relating specifically to the EU regulatory framework for drug/device combination products.

The first question sought the classification of their product in the EU. The objective was to discern any patterns in responses relating to products of certain product classifications.

The second two questions provided Likert Scales to determine the advantage of the Notified Body having experience with drug/device combination products and staff with relevant expertise (Figure 6).

Figure 6 Screenshot of Question Number 16

16. How important are the following attributes of the Notified Body you engage with when planning to develop a combination product in the EU?

	Not at all important	Low importance	Slightly unimportant	Neutral	Moderately important	Very important	Extremely important
Have prior experience with combination products	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Have staff with combination product expertise	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

The question (Figure 7) in this section provided a Likert scale in relation to the question of engaging with EU regulatory bodies early in the development process.

Figure 7 Screenshot of Question Number 17

17. How important is it to engage early with EU regulatory authorities when developing a combination product?

Not at all important    Low importance    Slightly unimportant    Neutral    Moderately important    Very important    Extremely important

These questions were testing the themes that were found in the interview phase.

This section concluded with two open questions, asking for the most critical factor for obtaining prompt regulatory approval of a drug/device combination product in the EU and why participants thought this.

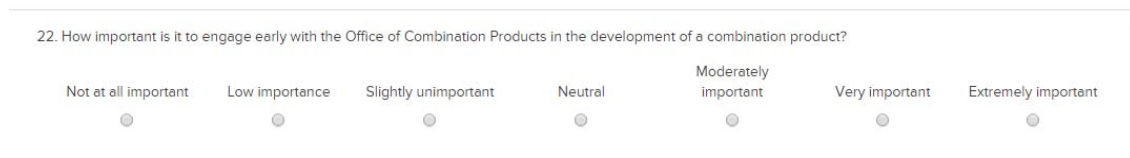
### US Regulatory Framework Experience

Like the prior question, this section opened with a question asking if the respondent had experience of the regulatory framework for combination products and diverted participants without such experience to the following section.

The first question asked for the classification of the product, seeking to identify any patterns in responses related to product classifications.

The next question related to timing in relation to engaging with the Office of Combination Products (Figure 8).

Figure 8 Screenshot of Survey Question Number 22



This section concluded with two open questions that allowed participants to describe the most critical factor for obtaining prompt regulatory approval of a drug/device combination product in the US and why?

### Partnerships in Developing Combination Products

This section investigated the theme of partnerships that emerged in the analysis of the interviews. The first question asked how whether the combination product was developed through internal development, acquisition, in-licensing, in-licensing, joint venture, or other.



The next question sought to determine why the company would have sought a partnership, providing a list of options and an open other field. Then a Likert scale question asked about the importance of partnerships. Four other Likert scale questions that tried to determine the importance of certain factors in a successful partnership followed. These factors were:

- Cultural differences between the medical device/pharmaceutical/biotechnology companies
- Working with a partner of a greater or smaller size than the participants' own organisations
- The pace at which a partner works
- The alignment of attitudes towards risk

This section concluded with an open question about the most critical factor for ensuring a successful partnership; the next question, also open, asked why?

#### Concluding Section

The survey concluded with a dialogue box allowing for participants to supply further details and/or their email addresses, which would allow them to receive the final results of the survey. It also included a note of gratitude and the researcher's email address.

#### **4.4.4 PreTesting and Pilot Testing of Survey Instrument**

No matter how closely a questionnaire follows recommendations based on best practices, it is likely to benefit from pretesting and piloting testing (Robson, 2002, Draugalis et al., 2008, Sills and Song, 2002, Alreck and Settle, 1995).

### Pretesting:

As Alreck and Settle (1995) point out, pretesting should “ensure... effectiveness and clarity” (p. 35) of a survey; Zikmund (2000) emphasize that Likert scale items should be clear and unambiguous. In the first pretesting stage, a faculty member who had experience in questionnaire development reviewed the survey and the participant information sheet. In the second stage two personnel from medical technology companies commented on the relevance of the questions.

Pretesting helped to eliminate measurement errors caused by poorly worded or ambiguous questions and instructions (Sills and Song, 2002). The results suggested the modification of five items in the questionnaire and alteration of instructions and scales in order to make the questionnaire clearer. Once the amendments were made the questionnaire was ready for pilot testing.

### Pilot Test

A pilot study conducted involved eight respondents: five from drug/device combination product manufacturing companies, two quantitative researchers, and one academic. The respondents were e-mailed the link to the online questionnaire and asked to complete it on different devices to verify its format on as many of these platforms as possible: smart phone, desktop, laptop, and iPad. Following this process, respondents described:

- The time needed to complete the questionnaire;
- Whether the instructions were understandable;
- Whether the questions were understandable;
- Whether they experienced any problems in comprehending the type of answers that were expected;
- Whether the proposed administration procedure would be successful;
- How the survey appeared on each platform; and
- Any other suggestions to improve the questionnaire.

After the pilot test, the researcher made a number of changes and additions to the instrument. These included:

- Refining of some of the questions to increase clarity and remove ambiguities;
- Adding additional items to achieve greater integrity;
- Contacting SurveyGizmo regarding a problem viewing questions that contained a lot of text on an iPhone screen; they rectified the problem by changing some of the survey online settings.

The average time participants described it took them to complete the survey was 10 minutes. Thus, the researcher stated in the invitation letters that it would take 10 minutes to complete the questionnaire.

#### **4.4.5 Sampling Strategy – Non-Probability**

A non-probability mixed purposeful sampling strategy, utilizing opportunistic and snowball sampling was employed (Miles and Huberman, 1994, Denzin and Lincoln, 2005). The main rationale for this choice is because of the diverse range of drug/device combination products, that fall into a wide category of products, across a variety of industries. It therefore be impossible for the researcher to identify all members of the population. Furthermore, many of the organisation involved with combination products are not easily accessible. They normally do not wish to divulge information relating to their products, as this information is seen as highly proprietary in the highly competitive landscape of the life sciences sector. Therefore it was found suitable to adopt the convenience sampling method for the purpose of this study.

The goal in choosing the non-probability mixed purposeful sampling strategy was to identify participants that Patton (1990) described as “information rich”, as was the case in phase one of the research for the qualitative study. Non-probability sampling means the probability of each potential respondent being included in the sample cannot be known (Easterby-Smith et al., 1991).

Respondents were contacted through:

- a) Email addresses obtained from company websites

- b) Networking with professional acquaintances
- c) Email addresses obtained from LinkedIn searches for individuals involved with obtaining regulatory approval of drug/device combination products in the EU and/or US
- d) InMails on LinkedIn
- e) Postings on Twitter to the researcher followers. The researcher had set up a Twitter account with the handle @CombinationProd.
- f) Postings in LinkedIn groups dedicated to drug/device combination products (Appendix K lists the LinkedIn groups through which the researcher sought participants)

#### **4.4.6 Survey Administration**

The survey was launched online using [www.surveygizmo.com](http://www.surveygizmo.com) on April 28th, 2014 and remained open until September 30th, 2014.

#### **4.4.7 Data Analysis**

Data from the survey was exported from SurveyGizmo™ and downloaded into Microsoft Excel. The survey data was cleaned in Excel. Data cleaning involved looking for and correcting any errors in the data set (Van den Broeck et al., 2005, Babbie, 2015). Subsequently the nominal and ordinal data was coded. Data coding involved converting the nominal and ordinal scale data in such a way that the statistical package to be used can handle the survey data correctly (Bazeley, 2013, De Vaus, 2013).

The cleaned and coded data was next manually entered into the software package Statistical Packages for Social Sciences (SPSS) v.21 (Pallant, 2013). The

researcher manually entered the data into SPSS, this process was time consuming, however, it was beneficial to be immersed with the data set (Pallant, 2013). The data were again cleaned to ensure that atypical data was not entered due to input errors by the researcher or participants. Data cleaning in SPSS was accomplished by running preliminary descriptive statistics (frequencies and percentages) on the data set. The frequency and percentage procedure was done to check the number of missing values in each variable. This allowed for the identification of atypical data. Data cleaning step is an important that ensures the quality of the data set (Cavana et al., 2001). This detailed examination of the data enabled the researcher to have a proper understanding of the data collected.

Descriptive statistics (frequencies, percentages, skewness, kurtosis, histograms and cross tabulations) was run on the categorical variables. This analysis was done in order to describe the sample profile and to determine what type of statistical tests were most appropriate to use on the data. Frequencies, percentages were displayed in tables. Bar charts were produced to visually display some data. The distribution of the items was assessed for normality by their skewness and kurtosis values.

Next multivariate analysis was done by using cross-tabulations in SPSS. Cross tabulations were done to examine the relationship between categorical variables in greater detail than frequencies for individual variables. Cross tabulation enabled the researchers to find correlations between responses to different questions.

The Fisher exact test was used to answer research question 4. Due to the fact the sampling method was non probability this reduced the amount of statistical tests that could be done on the data (Bryman and Cramer, 1994, Lohr, 1999). In addition, following a detailed examination of the data other statistical tests were determined not to be appropriate as assumptions for tests were not met (Bethlehem, 2009). The Fisher exact test was deemed suitable as the data set met the requirements for this test. When one or more of the cells has an expected frequency of five or less that Fisher's exact test is used (Lohr, 1999). If the cells

did not have an expected frequency of five or less the chi-square test can be used (Lohr, 1999). The chi-square test assumes that each cell has an expected frequency of five or more, but the Fisher's exact test has no such assumption and can be employed in spite of how small the expected frequency is. In this case, a better approximation was obtained by utilizing the Fisher's Exact Probability Test, which reduces the absolute value of each difference between observed and expected frequencies by 0.5 before squaring. In addition, the Fisher's Exact Probability Test is appropriate for use with 2 x 2 tables that violate the assumption of minimum expected cell count.

Open-ended survey responses were transcribed and entered into an NVivo 10 software program. The responses to the open-ended questions from the questionnaires were exported to NVivo 10 for analysis. These were coded to categories and counts of these answers were given in the results. Quotations were also provided in the results (Cooper et al., 2006). Responses to open-ended questions were categorised and coded as frequency counts.

#### **4.4.8 Evaluating Quantitative Research**

Reliability and validity are normal criteria used in quantitative research to determine and gauge the quality of the research (Bryman, 2012, Golafshani, 2003, Morse et al., 2008, Nunnally, 1978).

##### **Validity**

Validity in quantitative research focuses mainly on the validity of the instrument, in this case, the online questionnaire (Golafshani, 2003, Sandelowski, 1986, Cooper et al., 2006). A valid instrument contains questions that measure the concepts the researcher intends instead of something else (Creswell and Miller, 2000, Greene et al., 1989). To ensure validity, the pilot study tested whether respondents could understand the items presented on the questionnaire.

Researchers using mixed methods often use participants from the initial phase of the study as participants in the second phase of the study (Greene et al., 1989, Brewer and Hunter, 2006, Bryman, 2006). However, Creswell (2007) states that exploratory designs have a different procedure, because the two stages typically have mutually exclusive respondent groups. Because the purpose of the quantitative stage, stage 2 uses different and more participants than stage 1. Consequently, this study did not include the participants from the qualitative phase in the quantitative phase.

### **Reliability**

Reliability is the precision or accuracy of a measurement instrument (Blair et al., 2013, Sandelowski, 1986, Krefting, 1991). As Nunnally (1978) notes, without an assessment for reliability the interpretation of results may not be reliable. Reliability analysis determines an instrument's dependability, consistency, predictability, accuracy, and stability (Rea and Parker, 2012, Morse et al., 2008, Golafshani, 2003, Chambers and Skinner, 2003). As Pallant (2001) describes, testing the internal consistency of each construct by using Cronbach's coefficient alpha can ensure reliability.

However, the objective of the survey method in this research was to validate the qualitative findings gathered in the first phase. Thus, the researcher employed a descriptive survey method for the second phase. Pickard (2007) describes how descriptive surveys are not suitable for sophisticated statistical analysis. Questions were not arranged under distinct constructs, and the surveys objective was not to test a research framework. Therefore, it was not appropriate to conduct sophisticated reliability tests.

Chapter six discusses the results of this second quantitative phase as well as the qualitative phase.

#### **4.5 Integration of qualitative and quantitative data**

Following the separate analysis of all qualitative (Chapter 5) and quantitative (Chapter 6) research data instruments, in a mixed methods study, the results are then merged and integrated provide interpretation about the overall results of this study (Creswell & Plano Clark, 2011). Conceptual models can be utilised to integrate qualitative and quantitative results (Creswell & Plano Clark, 2011). This is what was done for the integration process of the methods for this research.

Following analysis of the quantitative data in phase two the initial conceptual model was revised (Figure 42) in order to reflect the integration of the survey data. Conceptual models allow the identification of interconnections between quantitative and qualitative results at a conceptual level. The graphical display maps out key findings of the study through merging results from all data sets (Bernard & Ryan, 2010).

#### **4.6 Ethical Considerations**

Ethical considerations relate to the proper conduct of the research process and should be a part of any research design (Bryman, 2012, Creswell, 2008, Robson, 2002) to ensure accuracy and honest representation and to protect the confidentiality of research participants (Zikmund et al., 2012) to protect participating organisations and individuals from any adverse consequences of their participation (Zikmund et al., 2012, Robson, 2002).

The researcher took ethical issues into consideration throughout both the interview and survey phases of this research. The measures to ensure ethical standards included ensuring confidentiality by disguising the names of the participating respondents (with pseudonyms, 01, 02 etc.) and organisations in all public presentations of the research, careful protection of the relevant documentation (in secure files on the researcher's computer), and not discussing confidential information with anyone.



#### **4.6.1 Mixed Method Research Disadvantages**

In spite of its strengths, the mixed method approach has several disadvantages. These include the fact that using several methods incurs financial costs and takes time. In addition, the researcher needs to develop skills in more than one method (Denscombe, 2007). Further, findings from different methods might not corroborate one another. When findings from different methods do not corroborate one another, the researcher may not have the tools to seek the larger meanings by this discrepancy (Denscombe, 2007).

For this research, design, data collection, and data analysis took a good deal of time, and conducting nineteen face-to-face interviews was expensive. However, the use of an online questionnaire to collect quantitative data reduced costs. Further, the findings of the research survey are mostly consistent with the findings of the interviews, which simplifies the analysis process.

#### **4.6.2 Challenges in Using Sequential Exploratory Design**

##### ***Strengths of the Exploratory Design.***

The exploratory design has a number of strengths (Bryman, 2006, Bryman, 2008, Erzberger and Kelle, 2003). These include:

- The addition of a quantitative component can make the qualitative method more tolerable to quantitative-biased audiences.
- Exploratory design can be applicable to research projects that involve a number of studies as well as single studies.
- The distinct phases make it relatively straightforward to describe, implement, and report.

##### ***Challenges in Using the Exploratory Design.***

As with all research designs, exploratory design has a number of challenges:

- Implementing the two-phase approach can be time consuming to design and execute.

- Researchers should reflect on whether the same individuals will serve as participants in both the qualitative and quantitative phases. This was not done in the case of this research; the interview participants were not sent the survey.

The rest of this section will describe how this research approached the complications of a mixed methods research method design.

### **Improving Accuracy through Research Method Design**

Triangulation permits the researcher to cross check the findings from one method to the findings from a different method (Bryman, 2006, Denscombe, 2010) and to develop a research instruments specifically appropriate for the research questions. For this research, the gathering of qualitative data initially through interviews was useful as a way of shaping the type of questions that were used in the subsequent quantitative survey. The findings therefore of the survey assisted to corroborate the results of the face-to-face interviews.

### **Balancing Strengths and Weaknesses of Mixed Methods Research Design**

In keeping with the use of mixed methods to offset inherent weakness or bias in a particular method, Denscombe (2007) suggests that researchers who choose to use semi-structured interviews as the main data collection method might also choose to supplement this method with the use of a closed-answer questionnaire. For this research, semi-structured interviews in the first phase provided an in-depth understanding of the factors that might facilitative drug/device combination approval in the EU and US. In the second phase the online survey was used to supplement the interviews form phase one and provide an in-depth understanding of the factors that might facilitative drug/device combination approval in the EU and US. The use of interviews allowed the researcher to investigate the opinions, and logic of the key informants. However, the limited number of interviewees (19 participants), leaves the data open to criticism as not being representative. The survey hence played a key role in supplying data from a larger sample to supplement the interview findings.

## **4.7 Conclusion**

This chapter established the research methodology. It discussed selection and justification of the interview and survey methodologies and presented the detailed research design. It described the two methodologies employed and described the reasons for using a mixed methodology to seek insight into the factors that may influence successfully obtaining drug/device combination products in the EU and the US. It described the collection of the data in each phase, qualitative and quantitative. It described the development and administration of the online questionnaire and the data analysis techniques used in each phase. The following chapter analyses and discusses the interview findings.

## **5 Analysis of the Interview Findings**

*This chapter reports on the analysis of the exploratory, first phase of the research, the semi-structured interviews. The analysis undertaken here answers research question number three; what are the facilitating factors for obtaining regulatory approval in the EU and/or US?*

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### **5.1 Sample Demographics**

Table 6 presents a summary profile of the participants in the study, along with an identifying number (01-19) to facilitate the presentation of results and the discussion that follows, as well as to protect the confidentiality of the participants. The participants included senior professionals within contract research organisations, regulators, medical device, and pharmaceutical companies.

Table 6 Interviewee Demographics

<b>Number</b>	<b>Job Title</b>	<b>Experience with Combination Products (years)</b>	<b>Firm Type</b>	<b>*Firm Size</b>	<b>Product Type</b>	<b>Parts of the Combination Products Manufactured by the Firm</b>	<b>Stage of Product in Development (if not for sale yet)</b>	<b>On sale in EU and/or US Market</b>	<b>Plan to sell into EU and/or US Market</b>
01	Head of Business Development	15 years	Medical Device Company	Large	Prefilled Syringe	Medical device	On Market	E.U. & U.S.	Non-Applicable
02	Vice President of Product Development	8 years	Device/Biologic Manufacturer	Medium	Prefilled Syringe	Medical device	In development	No	EU & US
03	Chief Executive Officer	13 years	Device/Drug Manufacturer	Medium	Drug Eluting beads	Medical device and drug	On market	EU	US
04	Head of Business Development	5 years	Device/Drug Manufacturer	Large	Prefilled Syringe	The drug	On market	EU	Non-Applicable
05	Head of Business Development	11 years	Device/Drug Manufacturer	Large	Prefilled Syringe	The drug	On market	EU	Non-Applicable
06	Director of Regulatory	19 years	United States Regulator	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Non-Applicable
07	Head of Clinical Research (ex European Regulator )	10 years	Contract Research Organisation	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
08	Director of Business Development and Marketing (ex Pharmaceutical industry)	20 years	Contract Research Organisation	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Non-Applicable
09	Head of Regulatory Affairs	20 years	European Regulator	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Non-Applicable

<b>Participant Number</b>	<b>Participant Job Title</b>	<b>Number of years Experience with Combination Products</b>	<b>Firm Type</b>	<b>*Firm Size</b>	<b>Combination Product Type</b>	<b>Parts of the Combination Products Manufactured by the Firm</b>	<b>Stage of Product in Development (if not for sale yet)</b>	<b>On sale in E.U. and/or U.S. Market selling</b>	<b>Plan to sell into E.U. and/or U.S. market</b>
10	Regulatory Affairs Specialist	6 years	Device/Drug Manufacturer	Medium	Antimicrobial coated wound	Medical device	On Market	E.U. & U.S.	Not Applicable
11	Chief Executive Officer	7 years	Device/Drug Manufacturer	Small	Drug Eluting Patch	Medical device	In development	No	E.U. & U.S.
12	Clinical Assessment Manager	5 years	European Regulator	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
13	Vice President of Quality Systems	14 years	Device/Drug Manufacturer	Large	Drug Eluting Stent	Medical Device and drug	On Market	E.U. & U.S.	Not Applicable
14	Certification Officer	6 years	European Regulator	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
15	Quality and Regulatory Director	10 years	Device/Biologic Manufacturer	Large	Drug Eluting Stent	Medical device and Drug	On Market	E.U. & U.S.	Not Applicable
16	Regulatory Affairs Specialist	7 years	Device/Drug Manufacturer	Large	Drug Eluting Stent	Medical device and Drug	On Market	E.U. & U.S.	Not Applicable
17	Senior R&D Manager	9 years	Device/Drug Manufacturer	Large	Drug Eluting Stent	Medical device and drug	On Market	E.U. & U.S.	Not Applicable
18	Quality and Regulatory Director	8 years	Device/Drug Manufacturer	Small	Aerosol drug delivery	Medical device	On Market	E.U. & U.S.	Not Applicable
19	Consultant (ex U.S. Regulator)	13 years	US Regulator	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

\*Large (greater than 251 employees)

Medium (51-250 employees)

Small (11-50 employees)

Micro-entities (up to 10 employees)

## **5.2 Research question number 3: *What are the facilitating factors for obtaining regulatory approval in the EU and/or US?***

This section answers the research question 3; what are the facilitating factors for obtaining regulatory approval in the EU and/or US?

### *Themes*

Participants offered a rich description of their experiences seeking to achieve approval for drug/device combination products under EU and US regulations. Four themes and seven subthemes, called facilitating factors in this dissertation, emerged from the data, encapsulating the factors that facilitate obtaining regulatory approval of a drug/device combination product in the US and/or EU (Figure 9 and table 7). Appendix L gives an example of the coding process that was undertaken in NVivo 10 for one of the facilitating factors that was identified; managing regulatory authority relationships.

Participants described them as beneficial to navigating the EU and US regulatory approval process for drug/device combination products. These themes were: effectively collaborating with partners involved with obtaining regulatory approval, managing regulatory authority relationships, the impact that the type of drug-drug has on obtaining regulatory approval and the substantial advantage of having experience of previously obtaining regulatory approval for a drug/device combination products.

Figure 9 Conceptual Model of the Interview Themes

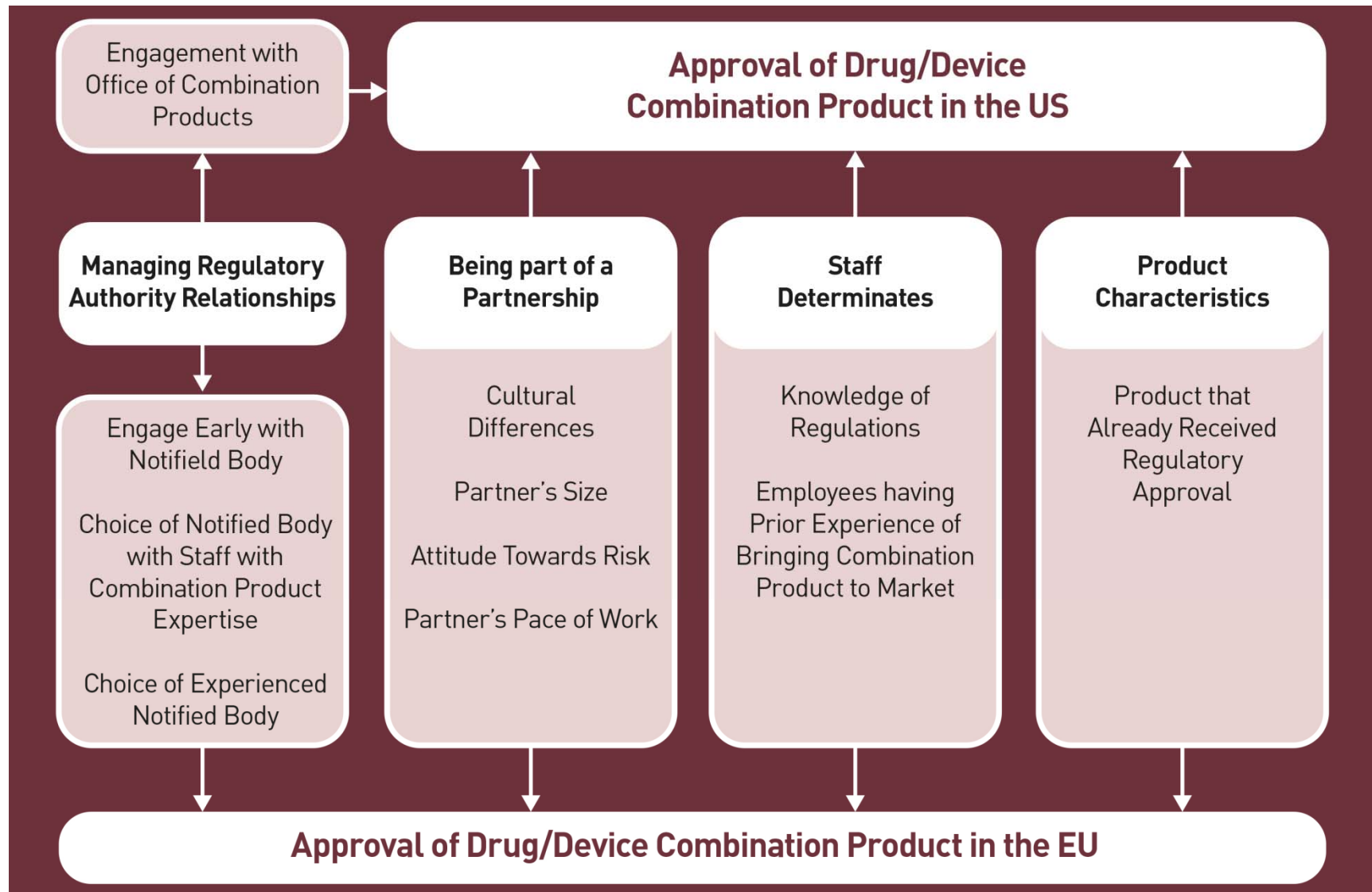




Table 7 Table of Conceptual Model Interview Themes

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<b>Interview Themes</b>	
<b>T<sub>1</sub></b>	Obtaining regulatory approval is influenced by the management of regulatory authorities relationships in both the US and EU contexts
<b>T<sub>1.1</sub></b>	The management of regulatory authorities in the US relates to early engagement with the Office of Combination products
<b>T<sub>1.2</sub></b>	The management of regulatory authorities in the EU relates to early engagement with Notified Bodies
<b>T<sub>1.3</sub></b>	The management of regulatory authorities in the EU relates to the choice of a Notified Body with staff with Combination product expertise
<b>T<sub>1.4</sub></b>	The management of regulatory authorities in the EU relates to the choice of an experienced Notified Body
<b>T<sub>2</sub></b>	Obtaining regulatory approval is influenced by being part of a partnership
<b>T<sub>2.1</sub></b>	Being part of a successful partnership relates to the partners cultural differences
<b>T<sub>2.2</sub></b>	Being part of a successful partnership relates to the sizes of the partner's organisation
<b>T<sub>2.3</sub></b>	Being part of a successful partnership relates to the partners attitude towards risk management
<b>T<sub>2.4</sub></b>	Being part of a successful partnership relates to the pace of work
<b>T<sub>3</sub></b>	Obtaining regulatory approval is influenced by the characteristics of the companies staff
<b>T<sub>3.1</sub></b>	Staff that are successful in working on a combination product relates to their knowledge of combination product regulations
<b>T<sub>3.2</sub></b>	Staff that are successful in working on a combination product relates to their experience of bringing combination products to market
<b>T<sub>4</sub></b>	Obtaining regulatory approval is influenced by the characteristics of the product
<b>T<sub>4.1</sub></b>	Having a product that has components that already received regulatory approval relates to product characteristics

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The quotations below describe each enabling factor.

**T<sub>1</sub> Obtaining regulatory approval is influenced by the management of regulatory authorities relationships in both the US and EU contexts**

In the US the FDA manages the regulatory process for drug/device combination products. As described in Chapter Three, in the EU, a Notified Body, Competent Authority, or the European Medicine Agency, depending on the drug/device product classification directs the process. Interviewees emphasized the importance of managing regulatory relationships. The next sections will discuss the two sub-themes that emerged from this theme.

**T<sub>1.1</sub> The management of regulatory authorities in the US relates to early engagement with the Office of Combination products**

**T<sub>1.2</sub> The management of regulatory authorities in the EU relates to early engagement with Notified Bodies**

Interviewees emphasized the importance of establishing a relationship early with the regulatory authority that will be involved in approving the drug/device combination product. Participant 17, a senior R&D manager at a drug eluting stent company noted that as a federal agency, the FDA requires certain processes of communication. A European regulator commented that companies should engage with Notified Bodies early in the product planning process in order to avoid problems if the Notified Body does not agree with the company's regulatory strategy. The European regulator said:

Put down the expectations at the beginning, everyone will be like; that is a very high bar you put on there, but it is better if you know what it is going to be like in the beginning rather than it coming at you later. (Participant 14)

She also said:

The most important thing is earlier consultation. Consult with us about their early product development plan (Participant 14)

Participant 06, a U.S. regulator, agreed, saying that early discussions, even in the earliest stages of development, allow regulators to identify challenges, “the principal mode of

action,” and “who should review it or what the regulatory pathway may be.”

He also commented:

I think it is important that they seek early consultation to identify the regulatory pathway. Is the product going to be a medical product or a medical device?  
(Participant 06)

Participants that have attained approval for combination products in the United States commented on the importance on engaging early with the Office of Combination Products. One European regulator observed that:

The Office of Combination Products seems to be a very sensible idea. In that we have a huge struggle at a European level to try and determine what regulatory regime is best applied to borderline line products, when it is not terribly clear whether the product falls into the medicinal products directive, [or] medical devices directive.... The Office of Combination Products seems a very good model.... (Participant 09)

A vice president of a drug eluting stent manufacturer also spoke highly of the merits of the Office of Combination Products:

I think the Office of Combination product is good.... it is particularly good at interacting with industry.... So I think that the Office of Combination Product’s role in general has been a very successful one for FDA and for companies alike (Participant 13)

### **T<sub>1.3</sub> The management of regulatory authorities in the EU relates to the choice of a Notified Body with staff with combination product expertise**

### **T<sub>1.4</sub> The management of regulatory authorities in the EU relates to the choice of an experienced Notified Body**

The majority of participants with experience with the EU regulatory process mentioned that the selection of a Notified Body that is suitable to a company’s requirements is important in Europe. For example, a vice president of a medical device company who has been involved with the commercialisation of a number of drug eluting stents (including one of the first approved in the EU and the US) was asked what advice he would give to a new start-up company entering the area of drug/device combination products in the EU. He said:

The first bit of advice for a start up company is to choose the right Notified Body. I think that partnership is crucial. They will have to certify it; through them you will be reaching out to the drug authority. (Participant 15)

A European regulator also emphasised the importance of choosing the correct Notified Body and competent authority:

Remember you are there for a long term relationship with your competent Authority and Notified Body (Participant 14)

Another European regulator shared this view, saying that the first big regulatory decision is Picking your Notified Body...based on competence.... [D]oes your Notified Body know about combination products? Do they have other people in their stable [that do] the same sort of thing? Have they dealt with combination products before? (Participant 09)

A senior regulatory affairs specialist at a large drug eluting stent manufacturer also emphasised the importance of the Notified Body interface with the Competent Authority :

[I]f you work closely with your Notified Body; work out strategies with them; it will help you in the long run. I think if the Notified Body has a good relationship with the Competent Authority , that helps as well; it facilitates the approval process. (Participant 16)

In conclusion the successful management of regulatory relationships can be achieved by being aware of choosing the most suitable Notified Body to work with and engaging early with regulatory authorities when developing a regulatory strategy.

## **T<sub>2</sub> - Obtaining Regulatory Approval is Influenced by being part of a Partnership**

More than one company often works together to bring a single drug/device combination product to market. A number of the interviewees mentioned the importance of effective collaboration. Participant 08 had worked for a number of years in a number of pharmaceutical companies involved with developing drugs and devices for the respiratory market. He said:

This is one of the inherent problems actually today and in the future, in trying to get drug/device combination products coordinated and successfully managed and developed and on time, during the patent life, onto the market, you know. In that you have the complication of more than one company involved. These interactions between the two companies are one of the biggest challenges in trying to develop these drug/device combinations products. [Participant 08]

The sections below describe subthemes related to collaboration with partners.

Asked about the influence of these partnerships on the regulatory approval process, a number of participants mentioned the importance of building partnerships with organisations established in the market. Participant 08 remarked on the importance of this from the point of view of sustainability:

It is very critical that companies that have a new formulation for a drug that they pick the correct nebuliser; the one that is going to be on the market and available. They might pick the cheapest nebuliser, because they have a certain price strategy and two year after they market they go out of business and they are no longer producing that nebuliser. That is an example of a poor commercial strategy. [Participant 08]

A clinical assessment manager who works for a European competent authority corroborated this view, emphasising that established suppliers have strong data to back their products:

The nature of the relationship that they (the device manufacturer) have with their supplier, the pharmaceutical company is very critical, to make sure they are partnering with a reliable source of the medicinal substance, that there is likely to be a good dataset behind the medicinal substance and that will in event ease their regulatory interface. [Participant 12]

### **T<sub>2.1</sub> Being part of a successful partnership relates to the partners cultural differences**

Interviewees highlighted the importance of reconciling the pharmaceutical and medical device mindsets, and consequently the different philosophies behind the drug and device regulations. Participant 01, for example, said that partners working at pharmaceutical companies have trouble adjusting to the medical device criteria and that he has actually hired consultants to explain the different expectations in each area.

Participant 09 reported similar experiences, saying that the different mindset that dictates the different regulations “might well go back to the differences between the scientists and engineering perspective.”

Another interviewee highlighted the importance of the reconciliation of these different mindsets:

There were different cultures; traditionally pharmaceutical culture and device culture; which went through simple things like how many devices do we have to test to show that a certain attribute is appropriate. There were vastly different expectations and then there is a narrower range of actual manufacturing processes used in the pharmaceutical industry than there is in the medical devices industry in terms of in pharmaceutical tabulating, formulation, and packaging.... (I) think the biggest challenges were bring those two teams together and getting them working through the same development process. [Participant 15]

Participant 16 described resolving the problem with the mindset problem. He noted that devices approval processes offer more flexibility than pharmaceutical processes, and said that in seeking approval for a drug eluting stent, his company hired a woman with a strong pharmaceutical background for her expertise.

In conclusion being an effective collaborator is deemed as critical by the majority of the participants of the interviews. With the emergence of the three subthemes relating to effective collaboration it is a factor that those consider entering the drug/device combination product area must be aware of.

## **T<sub>2.2</sub> Being part of a successful partnership relates to the sizes of the partner's organisation**

Dyer, Kale et al. (2001) describe how in a partnership between companies, each company often has a different role. In the case of drug/device combination product partnerships, typically one partner is a pharmaceutical company while the other is a medical device company. They bring different skills, knowledge, and resources to the task (Karim and Mitchell, 2004). Clear communication between partners is crucial for obtaining regulatory approval of their products (Dyer et al., 2001). The literature on partnership concurs with this view (Duncan and Moriarty, 1998, Mohr and Spekman, 1994). One participant who was involved in developing a drug/device combination product with a company that was based in India and her company was based in Europe, pointed out how communication problems caused a delay in obtaining regulatory approval for the product:

One project, the drug company was in India. The project was lead by a team ... (w)ho were also based in India... (A)ll project communications were done by phone, whereas the pharmaceutical company were able to meet the project Directors on the face to face level, cause they were both in the same country, in India, not too far apart...(w)hereas we were in Ireland. ...(T)hey extended the project beyond their estimated project timelines, due to the geographic distance and the language barriers.  
[Participant 10]

A component of clear communication, clear division of ownership in the partnership was also identified as an important factor in seeking regulatory approval. Frequently the interviewees described that in drug/device combination partnerships the medical device partner has ultimate control of the medical device component of the product and the pharmaceutical company will have control of the drug element. This can have an impact on how they manage the process of obtaining regulatory approval for the component parts of the product and the final combined product. A certification officer employed by a European Notified Body, had this to say about the division of ownership in partnerships:

I would have experience of one company, who subcontracted out a lot of their sub processes including one of their druggly bit. While the product appeared to be fine I was concerned with the arms length approach that was taken.

This could have potentially have happened with any subcontractor, but it was noticeable that it was one of the key druggy steps. Yes it was all covered by intellectual property and confidentiality but for that again I felt that the legal manufacturing should have more ownership and have his finger more on the pulse. [Participant 14]

Interviewees highlighted for consideration is that when working with a partner to seek regulatory approval for their product, the size of the companies forming the partnerships has an impact. Frequently, interviewees said that in the case of drug/device combination product partnerships one partner usually is significantly larger than the other partner. Participants described the problems these different types of partnerships can cause if not managed properly.

Interviewees mentioned partners' different industries as a source of conflict. A head of regulatory affairs of a European Notified Body, who has worked in this area for 20 years, observed that companies that come together to develop drug/device combination have very different characteristics:

I see a lot of difference in the caution they have (the medical device versus the pharmaceutical company). If you look at some of the larger pharmaceutical companies that are moving back into the device area, after having sold of their device parts 10-15 years ago. With the pharmaceutical mindset there is more time to go through the whole process, there is more time to conceptualise the process. There is a need to get constant confirmation that they are on the right track, in terms of pre audits in starting small, getting to know the system etc. Etc. [Participant 09]

Participant 09 felt these factors can have a significant impact on the success of the partnerships and ultimately the success of getting regulatory approval for their product. Asked if there was a difference in how a medical device company and a pharmaceutical company approach entering the market of drug/device combination products, he observed:

There is a difference, but the similarity is in that it is very hard if you are from the device (medical device world) to understand the differences with drug regulations and vice versa, that is the same. It is a different mindset that is the basis of the regulations



and that might well go back to the differences between the scientists and engineering perspective. [Participant 09]

A European regulator working at a competent authority described the differences he saw in the way companies of different sizes interact with his employer. He observed that large, multi-national companies communicate less because they have more experience, and that a request for more information may meet more resistance from a large company than a smaller company.

Smaller companies can be more open, maybe engage with us early, work through the process. Smaller companies also tend to have more resource constraints, more financial constraints... (Which can cause problems. [Participant 12]

A serial entrepreneur who has been involved in numerous start-ups in the aerosol industry said that being a big company can have its own problems, saying that they can pool

A lot of resources but it is hard to get a decision made. There is a lot of *toing and froing*...they have the resources to put it altogether at the end; it is still hard to get a decision out of them as to what way they are going submit something. They can over-analyse the questions that come back from FDA and we have to come back with the ultimate answer...(I) found that in a small company you go with what makes sense and you go with your knowledge and this is the reason and this is how we will defend them and here it is. [Participant 18]

He also acknowledged an advantage of being in a larger company, with more knowledge on which to draw.

Interviewees' comments concur with the literature about relationships one dominant partner – such partnerships make the small partner vulnerable (Todeva and Knoke, 2005, Cravens et al., 2000, Kauser and Shaw, 2004, Killing, 1978). Participants say that the pharmaceutical player, typically the larger company, often manages the whole process of obtaining regulatory approval. The head of business development at a syringe manufacture who partners with dominant pharmaceutical companies on a regulator basis commented as follows:

They (the pharmaceutical company) manage the whole process (of obtaining regulatory approval), we will deliver the information they use to populate their device dossier into their regulation file. [Participant 1]

Participant 8 described the relationship with dominant partners with some humour:

You out licence to a large company, and for your company that is the baby, that is the whole meat, and mash potatoes, and the gravy and the Guinness, on the size, for everyone in your little company with 300 people. Then it goes to a company with 50,000 people and they have dozens of project and now it has a priority that is not number one. Then it is about the internal politics, it is competing for resources and that is one of the things that affect this. [Participant 1]

#### **T<sub>2.4</sub> Being part of a successful partnership relates to the pace of work**

A chief executive officer at a drug eluting stent manufacturer who has had experience of working with pharmaceutical companies on the drug element of the drug eluting stent said that these differences can cause frustration in the partnership, particularly their attitudes towards pace of work:

They (pharmaceutical personnel) work about four times slower than medical devices. Drugs take ten years to get to market. The type of devices we make take two years to get to market. There is a difference in pace, which can be infuriating, but that is something that we are getting used to. [Participant 11]

#### **T<sub>3</sub> Obtaining regulatory approval is influenced by the characteristics of the companies' staff**

A number of participants said that people who have first-hand experience of working with combination products working on the development of a combination product have an advantage in obtaining approval. One participant, an experienced project manager involved in

developing and bringing a next generation of drug eluting stents to the market in the European Union and United States identified the need for experienced people to be involved in the process:

[T]hey would have to be very experienced people...each person was chosen by previous experience.... [W]e knew each person had to be senior. These were not just people who were starting off; they were all A players. (Participant 17)

He further outlined his team's practical regulatory experience of the US regulatory system:

[T]he Research & Development, Design Assurance, regulatory and operations, and Product Development core team members had all been through that process once before or even twice. Some of them had been through Premarket approval written process and Premarket approval submission process. Two of them had been through the *investigational device exemption* process for clinical before and would understand what was required. And the operations person knew what would be required have to be built for clinical trials, roughly even though it is different for every clinical trial. Definitely we were on the experienced path in that respect. (Participant 17)

Some participants described knowing the pathway for gaining regulatory approval for a combination product at the beginning of the product development process as critically important.

#### **T<sub>4</sub> Obtaining regulatory approval is influenced by the characteristics of the product**

A number of participants noted that the classification of the combination product is an important strategic decision. They described having a biologic-drug/device combination classified as primarily mechanical and secondarily medicinal as advantageous. The medical device regulatory pathway is less cumbersome than the medicinal route in both the EU and the US. Two sub-themes emerged in this area.

#### **T4.1 Having a product that has components that already received regulatory approval relates to product characteristics**

The Chief Executive Officer of a drug eluting beads company said the company designed the product specifically to obtain classification as mainly mechanical. While a preloaded bead would be convenient for the practitioner, their device requires the healthcare practitioner user to load the drug onto the bead before use. He refers here to 510(k), a premarket submission made to the FDA to show that the device to be marketed is at least as safe and effective, that is, substantially equivalent, as a legally marketed device that is not subject to premarket approval:

It was very important that we knew that we would get a 510(k) and having a device that was loaded by the hospital was crucial. To be honest we have not made much progress with the preloaded device from a regulatory point of view...at the outset [we] could have done what we didn't want to do; the regulators told us what they wanted [for] a Premarket Approval.... [I]t was too expensive for the rate of return and I think that was the right decision, but I think some companies...given what the product might be, may not have the freedom to be able to have a product that loads in the hospital.  
[Participant 03]

The product was classified as a medical device in the European Union and as a combination product in the United States, where the agency deemed its primary mode of action to be mechanical.

Most of the participants described leveraging an existing technology that has already achieved regulatory approval as a smart strategy when entering the combination product area. Technologies the regulatory agencies deem proven, participants feel, receive quicker regulatory approval when incorporated in a combination product. A regulator commented that bringing a combination product for a new drug is a very difficult task, especially for a small manufacturer:

If you look at the energy it takes, the time, the extraordinary amount of clinical data and the overall budget needed to accomplish this (bringing a combination product to market that consists of components that are new to the market). I am not confident that any small manufacture would be able to do that. If there is a possibility to lean on

existing product files and have a biosimilar to [an] existing registered product, there might be the opportunity (Participant 09)

A nebuliser manufacturer, Participant 11, also alluded to this strategy when he said that for regulators, pumps are a “quite well understood entity.” Participant 12, a European regulator said that the simplest way to regulatory approval is to use “A pharmaceutical that is already approved.”

In conclusion it is clear from the analysis of the interviews and the number of participants highlighted the importance of what type of combination of products makes up the final product.

### **5.3 Conclusion**

This chapter presented an analysis of 19 semi-structured interviews undertaken in the first phase of this thesis. The interviews are analysed to determine the factors participants identified as facilitating regulatory approval of a drug/device combination product in the United States and/or the European Union. Four themes and seven subthemes emerged from the data. Strategic regulatory management is seen as critical when developing a innovative biomedical technology. Researchers have acknowledged that having knowledge on how to determine the appropriate combination product path for regulation would be advantageous to organisations (Gibbs, 2006). The participants in this study highlighted a number of key areas companies should consider when developing their regulatory management strategy.

Participants described effective collaboration with partners who they are involved with in obtaining regulatory approval as crucial. This finding agrees what the views of some scholars (Bidault and Cummings, 1994). Frequently participants commented that medical device manufacturers often do not have the resources to bring a complete drug/device combination product to market on their own but must partner with the supplier of the drug, which is usually a large pharmaceutical company. Participations agreed that successful collaboration with this partner is key to obtaining regulatory approval and that the role each company has

in the partnership is important. A number of participants described the fact that these partnerships usually involve companies with different cultures as an obstacle.

Interviews also emphasized the importance of managing regulatory relationships. The majority of participants who have experience of the EU regulatory framework for drug/device combination products deemed the strategic selection of a Notified Body as critical. In Europe, the manufacturer has the discretion to choose a Notified Body with which to engage. The participants in this study described these agencies as having different levels of expertise. A key theme individuals who have developed a number of combination products emphasizes is that ensuring that the notified bodies you choose to engage with have combination product expertise in-house has a big impact. Participants described selecting the right Notified Body as a way of saving time and money, as well as increasing a company's chances for successful market entry into the combination product area.

Participants also referenced prompt engagement and communication with regulators as an important strategy. Early involvement of the selected Notified Body in the product development plan, for example, should help avoid costly problems that could occur if the Notified Body does not agree with the regulatory strategy. Early contact is important because the regulation of a combination product is complex, or the regulatory classification of a combination product is frequently not straightforward. Issues can occur because of poor regulatory knowledge in the product development process (Pangarkar et al., 2010). Larger companies with more resources have advantages. For companies without the well-staffed infrastructure to marshal their products through the regulatory labyrinth, this can prove challenging.

Likewise participants felt that companies wanting to enter into the US combination product market should engage early with the Office of Combination Products if they do not know the designation of their product, or engage early with the relevant FDA centre if they know the designation. The message clearly states the importance of engaging early and often with regulatory partners.

The research participants also highlighted the impact of the type of drug/device combination product on obtaining regulatory approval of the product. A subtheme that emerged was that

the strategic classification of a combination product was considered important when trying to overcome the challenging requirements for certain types of drug/device combination products. In the European Union, the medical regulations for a combination product that gets classified as a medical device are less burdensome than those that govern medicinal products. Likewise, in the United States, if the combination product's primary mode of action is the drug, a combination product faces a more costly and lengthy route to approval.

Smart leveraging of existing technology is also an important strategy to employ. The pharmaceutical industry has been criticised for not putting enough effort into developing new drugs rather than utilising their existing drug portfolios in different ways (Cuatrecasas, 2006, Martinez et al., 2007). When major pharmaceutical companies partner with medical device companies to use a drug that was already approved, combined with a device to develop a new product, this offers a new source of revenue without the added initial research and development expense of developing a new drug. When medical device companies leverage their existing technology with a new component, they open up whole new markets for their products. For example, a company can take an approved syringe medical device and pair it with additional drugs. Combining products that have already been on the market separately has proven to make approval processes less burdensome.

The theme that regulatory experience of this area is an advantage mirrors others' findings. The literature describes strategic regulatory management as critical when developing an innovative biomedical technology (Abraham and Davis, 2007). Researchers have acknowledged that having knowledge on how to determine the appropriate combination product path for regulation would be advantageous to organisations (Gibbs, 2006). Understanding the regulatory process for combination products as a result of previous experience will facilitate swift approval of the product. Regulatory requirements substantively impact the manner in which companies develop new biomedical technologies and bring them to market and, by impacting the time for product approval, largely determine when the product can be used on a patient. Pietzsch, Paté-Cornell et al. (2008) suggested that regulatory requirements play a substantive role in shaping activities and decisions in the process. Participants in this study concurred. Not all organisations has this type of experience, however, interviewees frequently mentioned having had to hire consultants who were knowledgeable of the drug/device combination product to plug this knowledge gap.

In conclusion, this section described the data gathered in phase one of the mixed method study and its analysis. The researcher used the results from this phase of research as input to develop a quantitative survey that seeks larger samples views of the factors that facilitate obtaining drug/device regulatory approval in the EU and US. The following section presents the results of the survey.



## **6 Analysis of the Survey Dataset**

*This chapter provides the reader with the results of phase two of the research (the survey). It gives the descriptive statistics of the survey sample; it answers research questions 4, 4a and 4b. The revised conceptual model, which reflects the findings from phase one of the research and findings from phase two of the research, is presented. This model reflects a visualization of the integrations of the qualitative and quantitative findings. A discussion on the survey findings follows.*

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### **6.1 Sample Demographics**

A total of 255 people accessed the survey via SurveyGizmo. Of the 255, 97 did not complete the survey. Thus 158 valid responses were received. The survey was conducted between April 2014 and September 2014. Table 8 shows a demographic breakdown of the sample across several variables, including respondents' professional title, years in the current position, years of experience with combination products, organization size, industry sector and sales.

Table 8 Frequencies and Percentages of Demographic Variable

<b>Variable</b>	<b>Frequency</b>	<b>Percentage (%)</b>
<b>Position in Organization</b>		
President/CEO	26	16.5
Vice President	29	18.4
Head of Business Development	1	.6
R&D Manager	16	10.1
Quality Manger	7	4.4
Director of Regulatory Affairs	26	16.5
Regulatory Manager	2	1.3
Regulatory Specialist	9	5.7
Process Development Manager	9	5.7
Project Manager	12	7.6
Consultant	21	13.3
<b>Years in Current Position</b>		
Less than 4 years	75	47.5
5-10 years	51	32.3
11-15 years	17	10.8
Greater than 15 years	15	9.5
<b>Years Experience with Combination Products</b>		
Less than 4 years	48	30.4
5-10 years	55	34.8
11-15 years	32	20.3
Greater than 15 years	23	14.6
<b>Organization Size</b>		
Micro-entities (0-10)	44	27.8
Small (11-50)	22	13.9
Medium (51-250)	11	7.0
Large (250 plus)	81	51.3
<b>Variable</b>		
	<b>Frequency</b>	<b>Percentage (%)</b>
<b>Industry Sector</b>		
Law Firm	2	1.3
Contract/Clinical Research Organization	5	3.2
Industry – Medical Device	66	41.8
Industry – Pharmaceutical	26	16.5
Industry - Biotechnology	9	5.7
Industry – Biopharmaceutical	16	10.1
Consultant	27	17.1
Other	7	4.4
<b>Annual Sales</b>		
Less than \$5 million	62	39.2
Between \$5 million - \$10 million	10	6.3
Between \$10 million - \$50 million	18	11.4
Over \$51 million	68	43.0

Of those who responded, a combined total of 34.9% of respondents were C-level executives, such as presidents, chief executive officers, and vice presidents, and the remainder consisted of senior management in areas such as quality management, project managers, research and development, and process development managers. Almost a quarter (23.5%) of the respondents worked in regulation. All of the respondents' primary job functions fell into the required survey target; these individuals have knowledge of the regulatory approval process that would be both deep and holistic. This suggests respondents were well-suited to the research questions.

In terms of the length of time in current position, a combined total of 52.6% of respondents indicated that they had been in their positions for greater than five years. Almost a third, 32.3% were in their positions 5–15 years, 20.3% were in their positions for 11-15 years and 9.5% greater than 15 years. Almost half (47%) of the respondents indicated that they had been in their positions for fewer than four years. A combined total of 69.7% of the respondents had greater than five years of experience with combination products, some of them across multiple positions. All respondents, in other words, have extensive knowledge of the research topic built over many years.

Participants' responses indicate that their employers include a range of different organisation sizes and industry sectors. Almost three quarters (74.4%) of respondents are employed directly by companies that seek regulatory approval of combination drug products. This was distributed across the four types of companies that are typically involved with drug/device combination products as follows: 41.8% worked for medical device companies, 16.5% for pharmaceutical companies, 6% for biotechnology companies, and 10.1% for biopharmaceutical. The researcher thus achieved the goal of gathering respondents from across these types of organisations. Most of the remaining respondents, 17.1%, were consultants. Many firms hire consultants to help them through the regulatory process, and consultants typically have worked for companies directly involved with combination products in the past. One respondent in the remaining 8.5%, who indicated "other," with respect to his or her employer, was employed by a company the respondent termed a drug/device combination product company.

This study measures organisation size by the number of employees. Table 9 shows the number of employees in the respondent's organisations, which reveals a range of different organization sizes and industry sectors represented in the sample. Approximately half (51.3%) of the respondents work in large companies and less than half were from smaller companies. A significant portion was from very small companies (27.8%). This is not surprising as the medical technology sector consists of companies of a variety of sizes and most consultants probably are employed by 1-2 person companies. Table 9 provides current annual sales, which is an indicator of enterprise performance as well as organisation size. Participant responses indicate 43% work for organizations with sales of over 51 million dollars, with 39.2% having sales of less than 5 million.

#### *Combination Product Type and Market*

The combination product industry consists of a variety of product types, as the survey results reflect. Table 9 reflects the data on the single combination product that respondents focused on for this part of the survey. The most common product type cited in the survey was drug eluting stents (17.7%), a very established product, followed by prefilled injector pens (15.8%), and biologic prefilled syringes (10.1%). The category designated "Others" (15.8%) includes novel products like UV Light activated drug, aerosolized antibiotic, and transcranial intratumoral injection devices for delivery of an anti-tumor replicating virus. This selection of products represents a diverse range of drug/device combination products.

The largest number of respondents cited drug delivery as the market (48.7%) for their products. Almost a quarter (22.2%) cited cardiology, followed by smaller numbers in the areas of ophthalmics (6.3%), wound management (5.7%), and orthopaedics (4.4%). The category designated "Others" included markets like diabetes, obesity, hemophilia treatment, intensive care unit, immunology, radiology, oncology and gene therapy. The sample therefore represented the diversity in the range of markets drug/device combination products serve.

The survey asked respondents to focus on a single product in answering questions. Their products are in the following stages of development; 51.9% in post-market, 23.4% in clinical, 14.6% in pre-market submission, 8.2% in pre-clinical and 1.9% in initial development. These

figures indicate that a combined total of 48.1% of the products have not yet reached the commercial stage and are still in the R&D stages of development (in clinical, pre-market submission, pre-clinical, and initial development).

Table 9 Combination Product Information

Variable	Frequency	Percentage (%)
<b>Nature of Combination Product</b>		
Drug Eluting Patch	4	2.5
Drug Eluting Stent	28	17.7
Drug Eluting Bead	1	.6
Drug Coated Balloon	5	3.2
Antimicrobial Catheter	2	1.3
Implantable Cardiovascular Devices	2	1.3
Antimicrobial Bone Cement	1	.6
Bone Fusion System	1	.6
Bone Graft with Peptide	1	.6
Bone Graft Implant	1	.6
Implantable Infusion Pump	2	1.3
Biologic Prefilled Syringe	16	10.1
Transdermal Patch	9	5.7
Prefilled Injector Pen	25	15.8
Dry Powder Inhaler	6	3.8
Wound Covering	4	2.5
Surgical Mesh with Antibiotic Coating	2	1.3
Fibrin Sealant	1	.6
Insulin Pump	3	1.9
Dermagraft	1	.6
Nebuliser	6	3.8
Metered Dose Inhaler	5	3.2
Intraocular Implant	7	4.4
Other	25	15.8
<b>Combination Product Area</b>		
Orthopaedics	7	4.4
Drug Delivery	77	48.7
Wound Management	9	5.7
Cardiology	35	22.2
Ophthalmic	10	6.3
Plastic Surgery	3	1.9
Dental	3	1.9
Oncology	4	2.5
Other	9	5.7

Variable	Frequency	Percentage (%)
<b>Stage of Development of the Combination Product</b>		
Initial Development	3	1.9
Pre-Clinical	13	8.2
Clinical	37	23.4
Pre-Market Submission	23	14.6
Post-Market	82	51.9

### *EU Regulatory Framework*

The next set of research questions refer to respondents' experience of the EU regulatory framework for combination products. Respondents were asked if they had experience of the EU regulatory framework of combination products. The data shown in table 10 shows that more than half of those responding to the survey (63%) had experience of the EU regulatory framework for combination product, while 37% reported no experience of this framework.

Respondents were also asked about the classification of their combination product in the European Union. The most common classification was Class III Medical Device (39%). Class III medical devices are the most high risk devices, known as active implantable devices. A classic example of a class III medical device is a cochlear implant; drug eluting stents are also class III. The next most common group are the medicinal products, which made up 27% of the products.

Table 10 EU Combination Product Information

<b>Variable</b>	<b>Frequency</b>	<b>Percentage (%)</b>
Experience of the EU Regulatory Framework		
Yes	100	63
No	59	37
Classification of Product in the EU		
Medicinal Product	27	27
Class I Basic Medical Device	0	0
Class I (sterile) Medical Device	2	2
Class I (with a measuring function) Medical Device	0	0
Class IIa Medical Device	13	13
Class IIb Medical Device	7	7
Class III Medical Device	39	39
Biologic	6	6
Not available in the EU	4	4
Don't know	2	2

### *Experience of US Regulatory Framework*

The next set of research questions refer to respondents' experience of the US regulatory framework for combination products. Respondents were asked if they had experience of the

US regulatory framework of combination products. The data shown in table 11 show that a majority of those responding to the survey (83%) indicated that they have experience of the US regulatory framework for combination products.

Respondents were also asked about the classification of their combination product in the United States. The most common classification was combination product (45%). The next most common was Class III medical devices. Fourteen percent of the respondents reported that their combination product was classified as a drug in the United States.

Table 11 US Combination Product Information

<b>Variable</b>	<b>Frequency</b>	<b>Percentage (%)</b>
<b>Experience of the US Regulatory Framework</b>		
<i>Yes</i>	130	83
No	27	17
<b>Classification of Product in the EU</b>		
Combination product	58	45
A drug	18	14
Class I Medical Device	0	0
Class II Medical Device	11	9
Class III Medical Device	29	22
Biologic	11	9
Not available in the United States	2	2
Don't Know	1	1

## **6.2 Research Question Number 4: Determine whether the factors identified in the interviews are agreed with in a larger sample?**

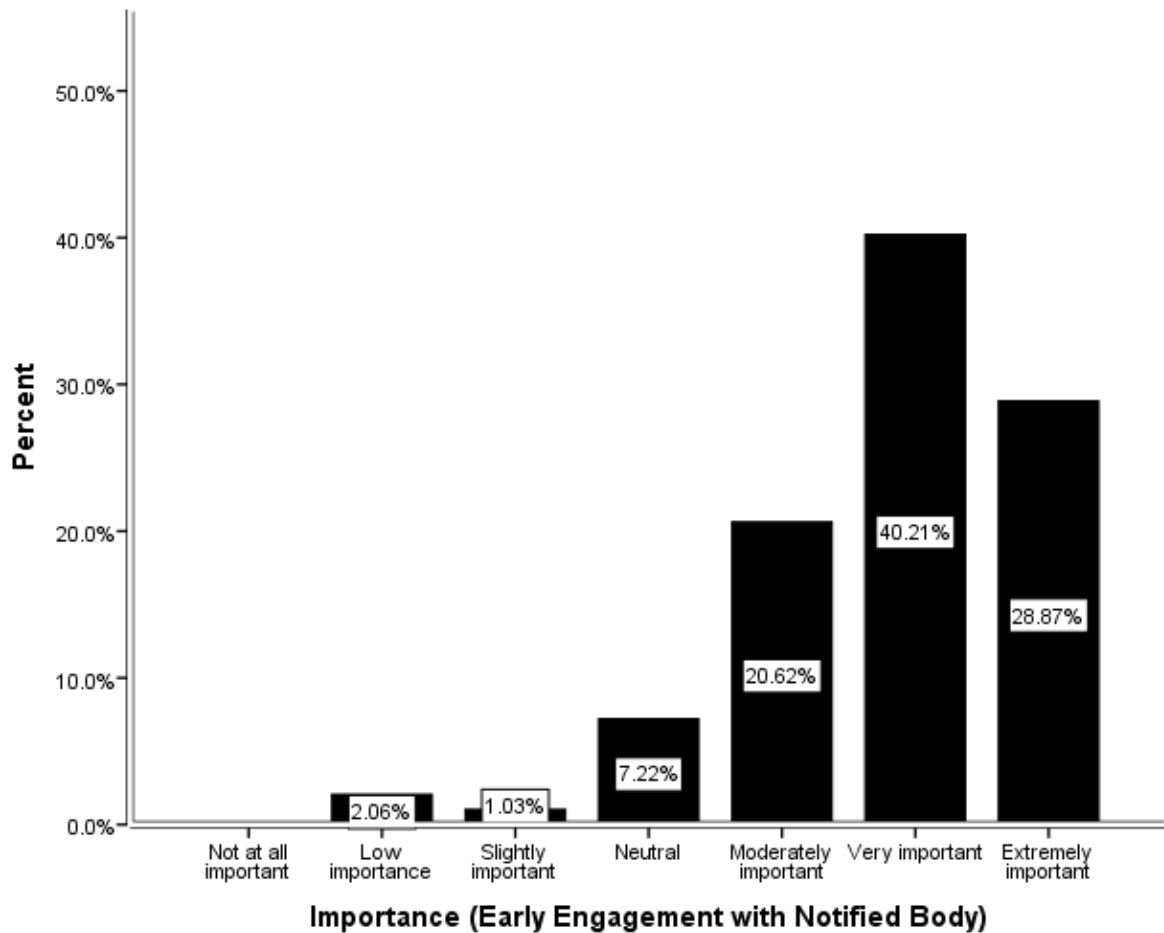
Relationship with Regulatory Authorities

*EU Regulatory Authority Relationships*

The majority of the respondents, 69.08%, indicated that engaging early with a Notified Body was extremely important or very important. This finding agreed with the views of interview

participants. Only 3.09% of the survey respondents indicated that engaging early with a Notified Body was not at all important or of low importance. Figure 10 shows these results.

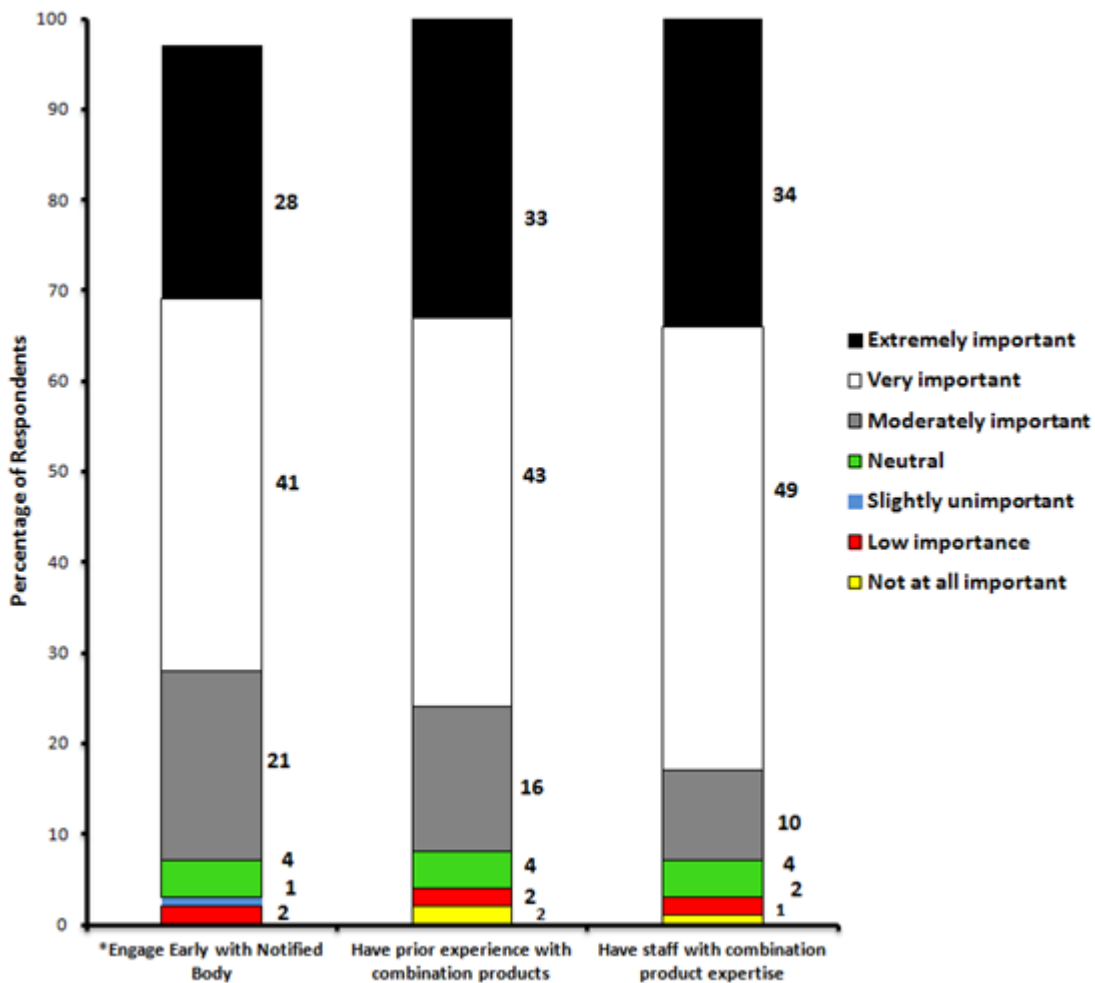
Figure 10 Importance (Early Engagement with Notified Body)



The next three questions in the survey addressed the Notified Bodies and the firms’ interactions with them. Figure 11 illustrates respondents’ answers to these three questions on this topic. The results are consistent across all three questions and corroborate the interview findings. A significant portion of the respondents believe that the importance of these factors are extremely important or very important: early engagement with notified bodies (68%); notified bodies having combination product experience (76%); and notified bodies having staff with combination product expertise (83%).



Figure 11 Interactions with Notified Bodies

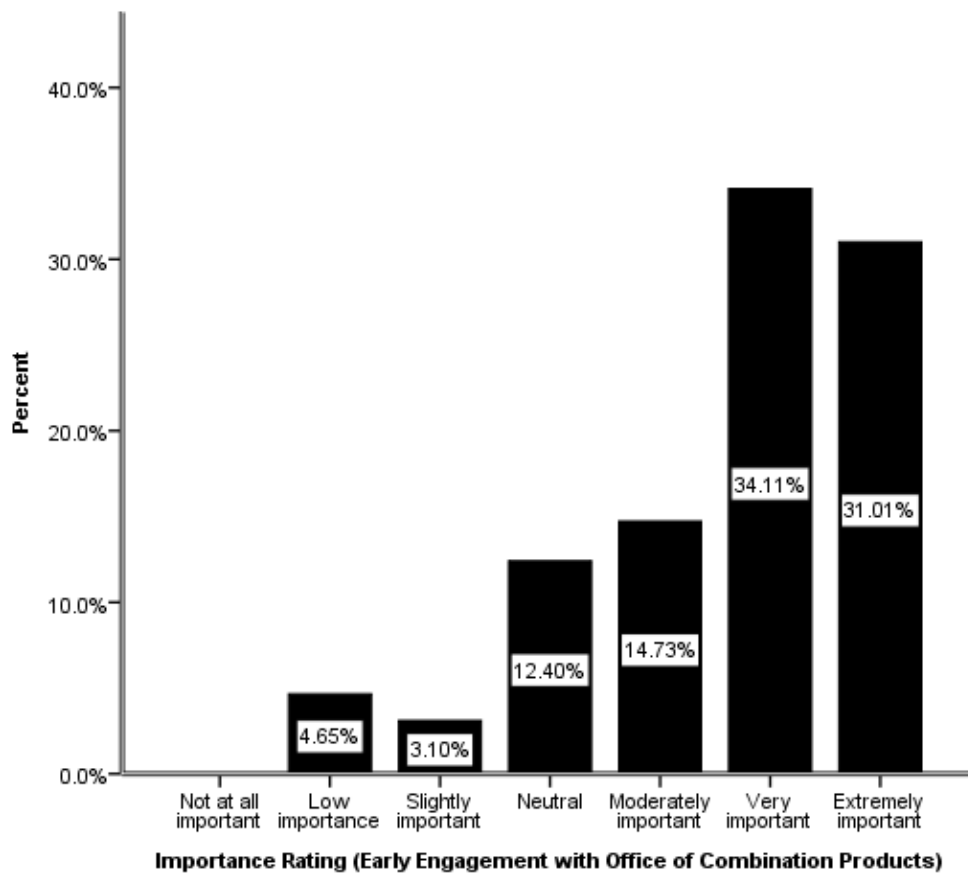


*\*NB some variable percentages do not round up to 100% due to missing cases*

### *Relationship with US Regulatory Authority*

The research questions here relate to the US regulatory authority with oversight over combination products—the FDA’s office of combination products. Survey participants were asked how important it was to engage early with the office of combination products when planning on seeking regulatory approval for the product. Figure 12 illustrates the responses to this question. Once again, as the question regarding the EU regulatory authorities suggests, a significant portion of the respondents (65.12%) stated that the importance of early engagement with notified bodies is extremely important or very important.

Figure 12 Importance of Engaging Early the Office of Combination Products



### 6.2.1 Partnerships

The next question addressed partnerships involved in the drug/device combination products on which the respondents based their answers. The theme of collaborating effectively with partners was seen as significant in the interview phase of the study. The answer to this section was surprising, as 57% of the respondents said that they developed their drug/device combination products through internal development (Figure 13). While a sizeable minority, 42.11%, formed a partnership (acquisition, in-licence a technology, out licence a technology or a joint venture) in order to develop their drug/device combination product, this finding nonetheless diverged from interviews, which might suggest that organisations would prefer to develop products in partnership.

Figure 13 Development Strategies for the Combination Product

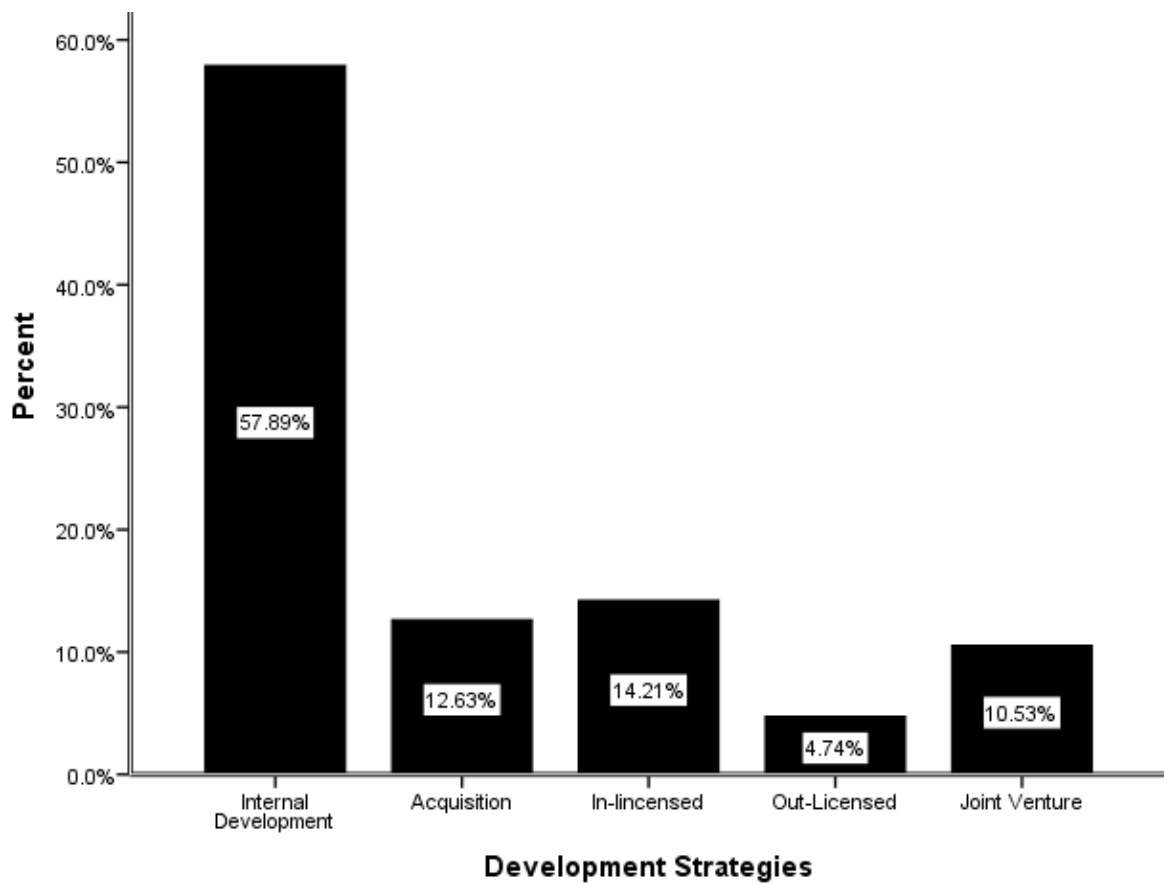
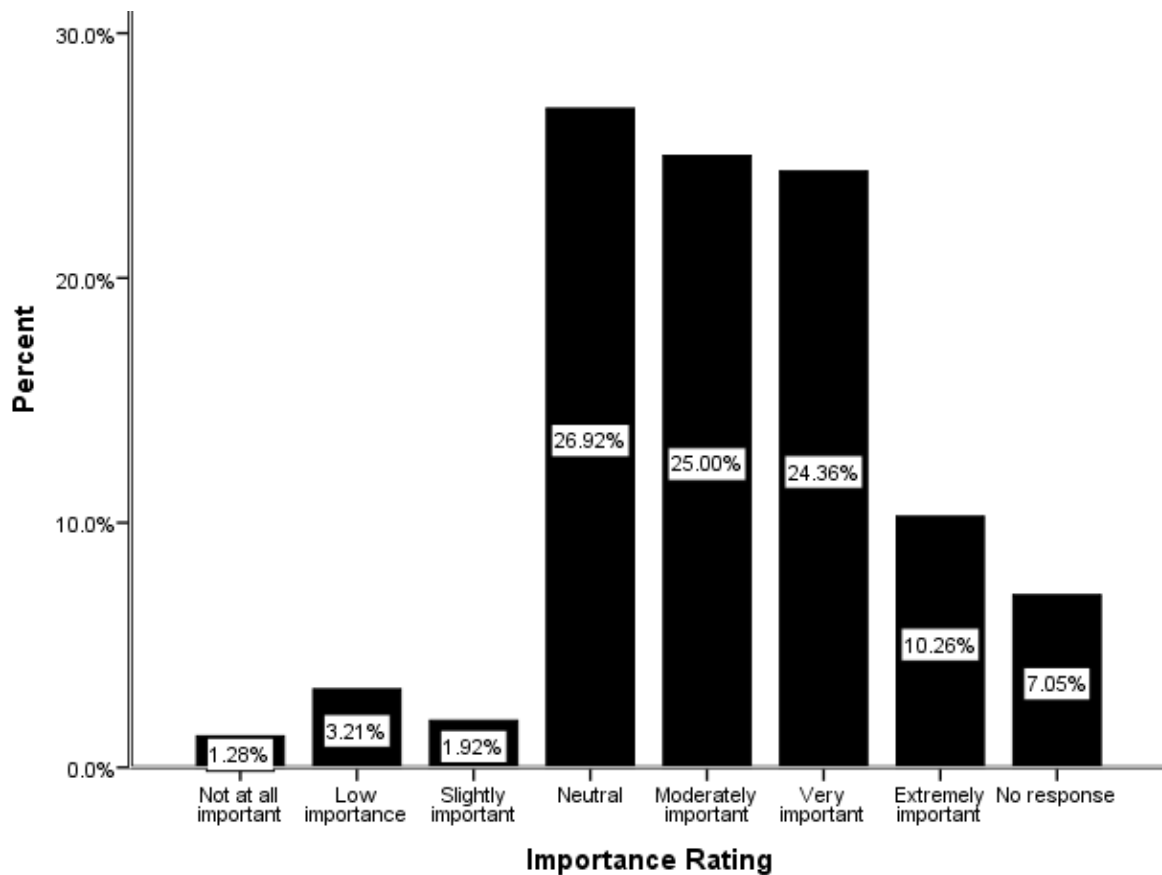


Figure 14 depicts the survey responses to the question regarding the importance of forming a partnership when bringing a combination product to the market. Only 10.26% of survey respondents felt partnerships were extremely important, but a combined total of 49.36% felt it was either moderately or very important to form a partnership in order to bring a combination product to the market. This result corroborated interview findings.

Figure 14 Importance of Forming Partnerships When Bringing a Combination Product Successfully to the Market



The next three questions addressed the factors that had an impact on the success of partnerships. These factors were the impact of cultural differences between partners (Figure 15), the importance of working with partners of difference sizes (Figure 16), the importance of the different partner’s attitudes towards risk (Figure 17), and the importance of the pace of work of the different partners (Figure 18). These themes relate to the success of a partnership. All four factors were deemed important: the impact of cultural differences between partners, a combined total of 51.28% for very important and extremely important; the impact of

working with partners of different sizes a combined total of 20.51% for very important and extremely important; the impact of the different partners' attitudes towards risk a combined total of 60.9% for very important and extremely important; and the pace of work of the different partners a combined total of 57.05% for very important and extremely important. Thus, these findings wholly or partially contradicted the interview findings which identified all of these factors as very important.

Figure 15 Importance of Cultural Differences between Partners

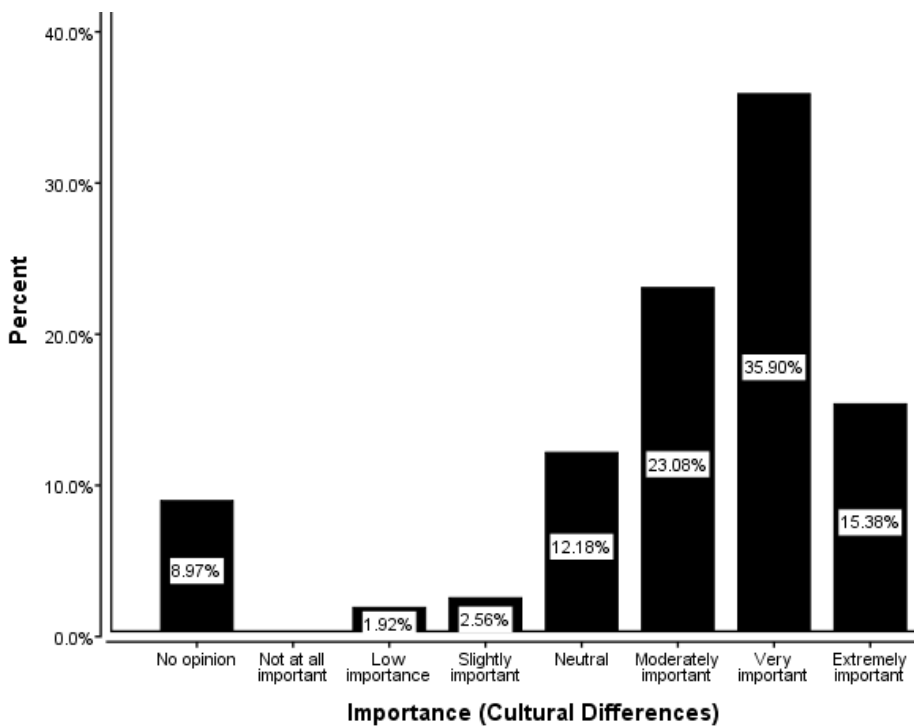


Figure 16 The Importance of the Difference Sizes of Organisations in a Partnership

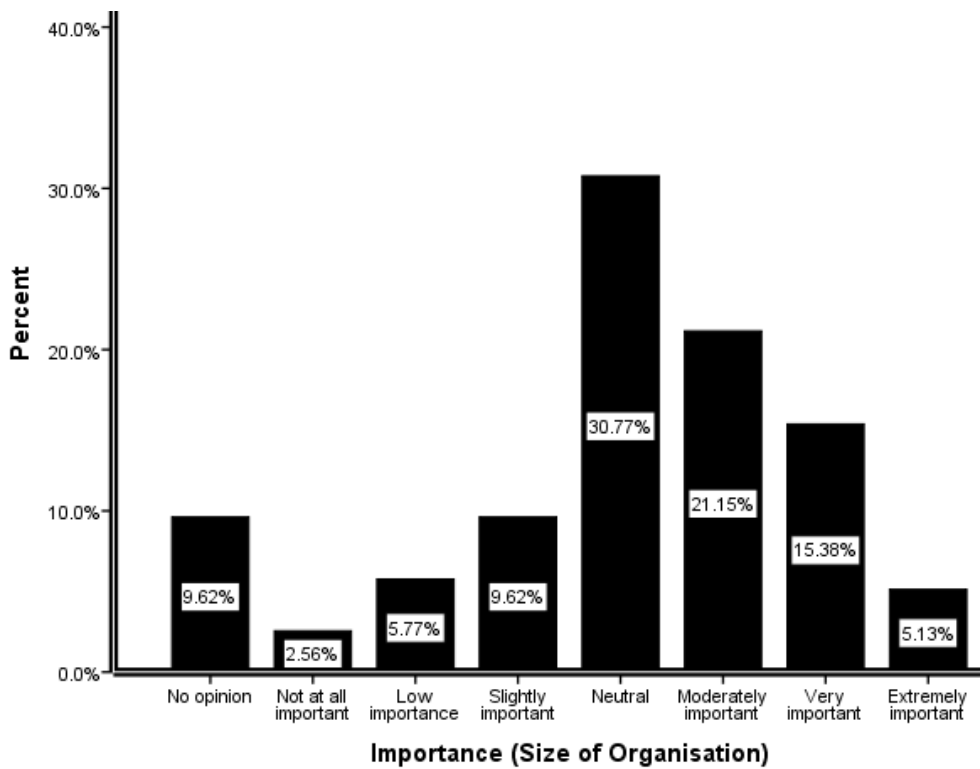


Figure 17 Importance of Partners' Attitude towards Risk

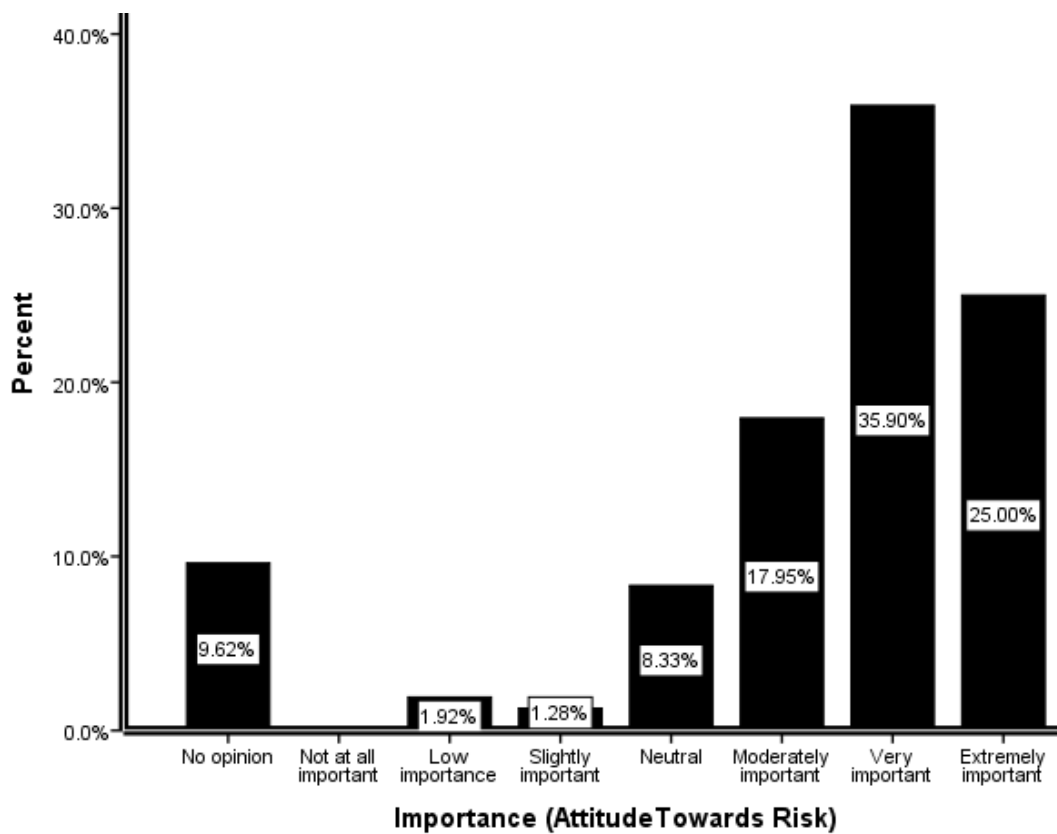
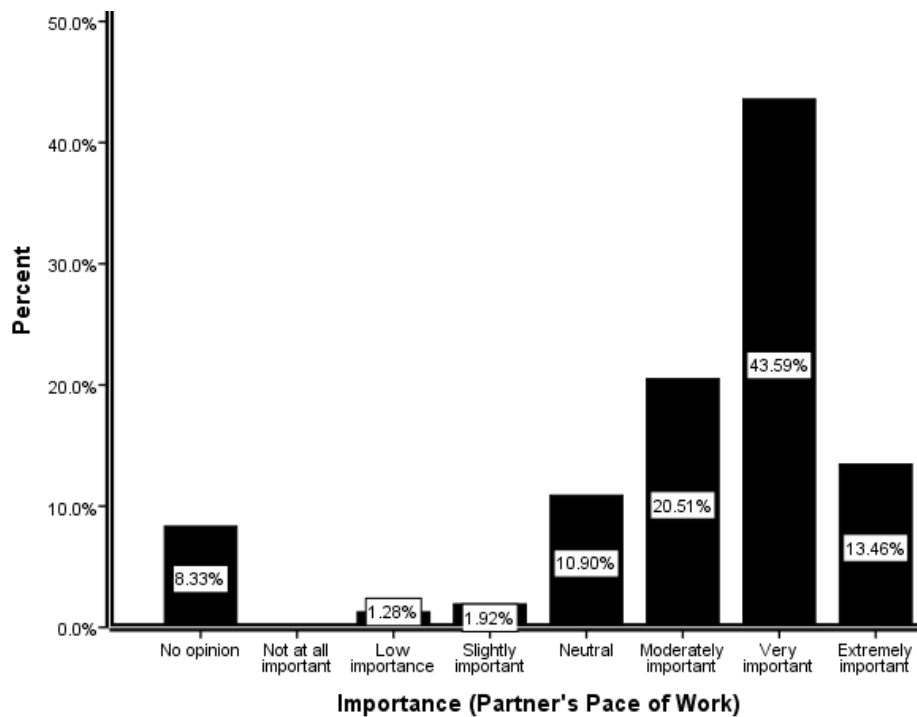


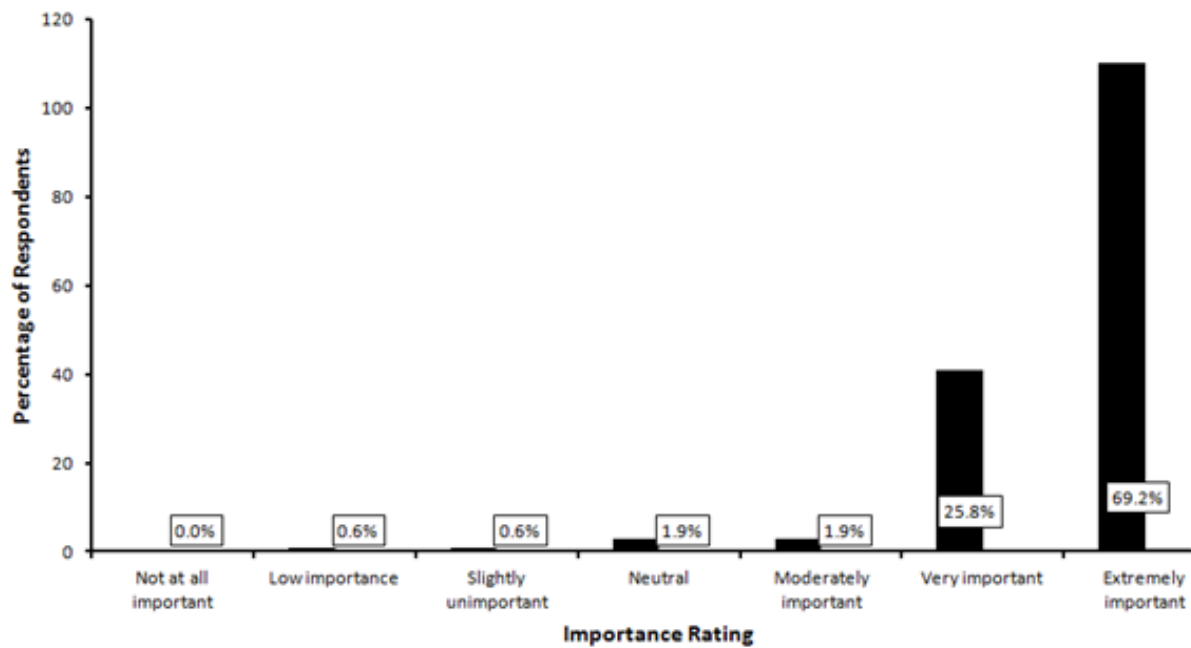
Figure 18 Importance of Partners' Pace of Work



## 6.2.2 Characteristics of the Organisations Staff

A number of the interviews in phase one of the research emphasised the substantial advantage of having experience of previously obtaining regulatory approval for a drug/device combination product. This theme was the basis for the second research question in the survey, which asked respondents to rate the importance of having regulatory knowledge when bringing a product to market. An overwhelming 95% of the respondents indicated that having regulatory knowledge when bringing a product to market was extremely important or very important (Figure 19). This finding corroborated strongly with the interview findings.

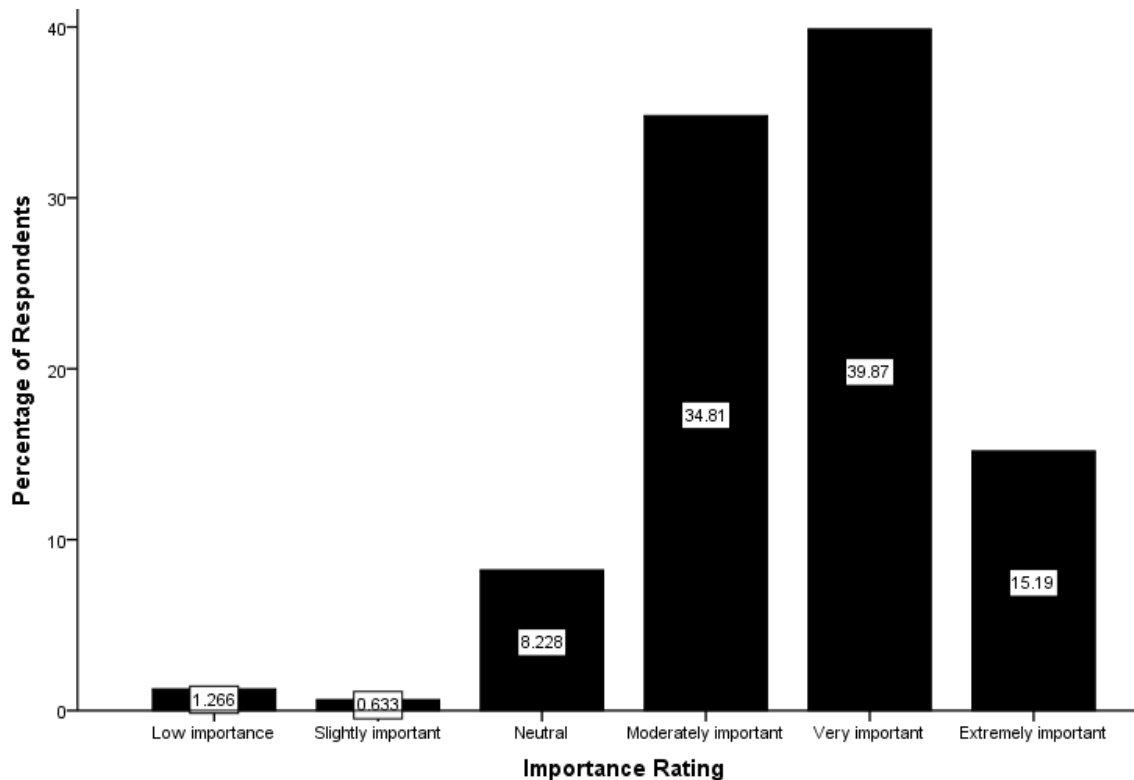
Figure 19 Importance of Regulatory Knowledge When Bringing Combination Products to Market



The next question addressed the importance of having experience of bringing a combination product to market (Figure 20). More than half (56%) indicated that this was extremely important or very important; a finding that diverges from interview results which suggested this is a very important factor.



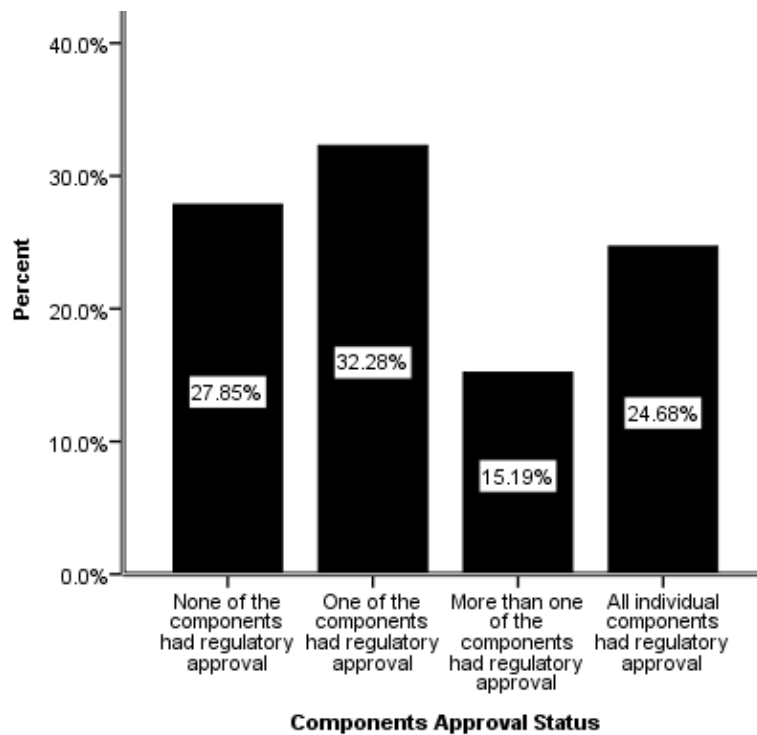
Figure 20 Importance of Employees Having Experience in Bringing a Combination Product to Market



### 6.2.3 Components with Regulatory Approval

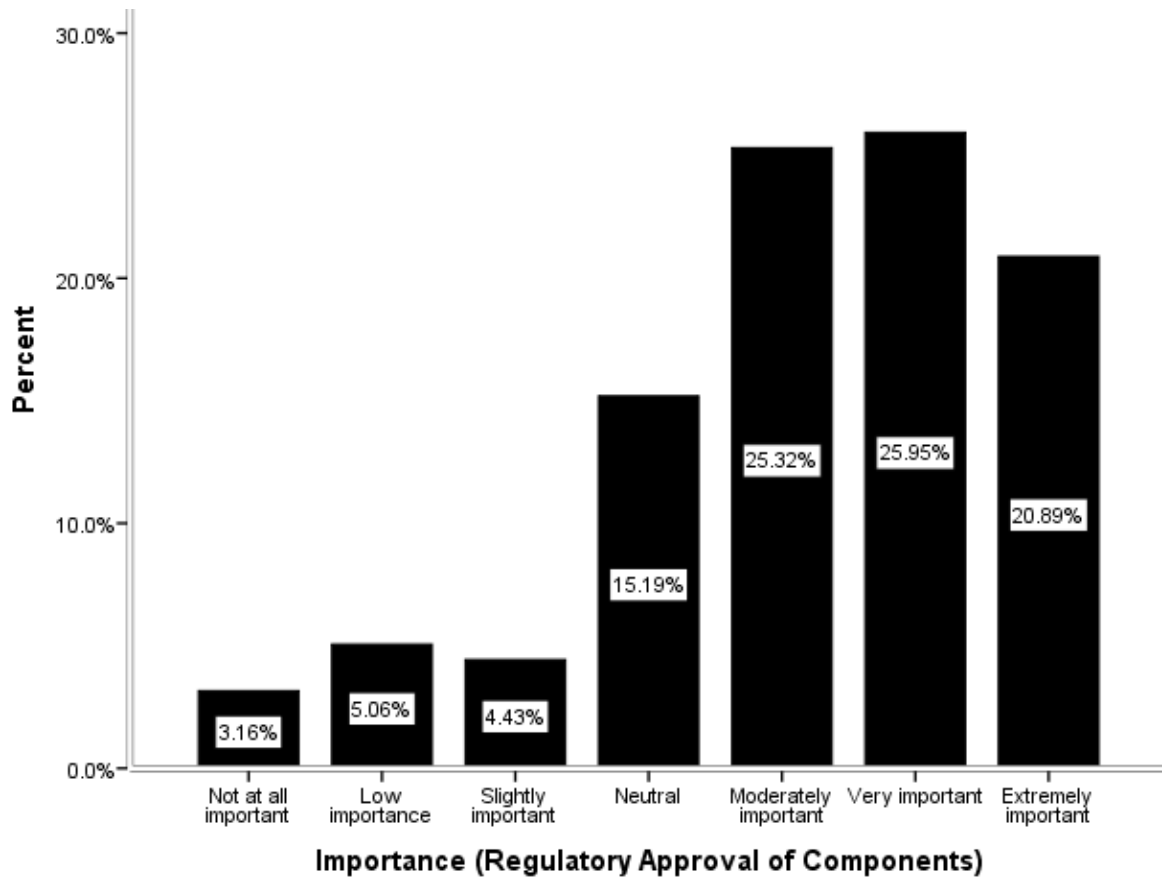
The next question addressed the perceived importance of having regulatory approval of the combination product components. This question was based on the subtheme in which interviewees stated that combining components that have already received regulatory approval together into a drug/device combination product confers an advantage. Before asking respondents whether they agree, the survey asked respondents whether none, one, more than one, or all components of their product already have regulatory approval applied. The results for this question are shown in Figure 21. Almost a third, 32.28% of the products had at least one component that had regulatory approval before it was combined, 15.19% had more than one of the components having regulatory approval before they were combined, and 24.68% had all individual components with regulatory approval before they were combined. More than a quarter (27.85%) of the products had no components with regulatory approval before they were combined. Overall, these findings show that the majority of products have at least one component previously approved suggest the interviews accurately identified a common means of boosting chances of regulatory approval for combination products.

Figure 21 Components with Regulatory Approval



The next question in this section asked respondents to rate the importance of having regulatory approval of components of combination products. The results for this question are shown in Figure 22. The majority of the respondents, 72.16%, indicated that having regulatory approval of components was at least moderately important. This finding agreed with the views held by the interview participants. Only 3.16% of the survey respondents indicated that having regulatory approval of components was not at all important.

Figure 22 Importance of Having Regulatory Approval of Components of Combination Products



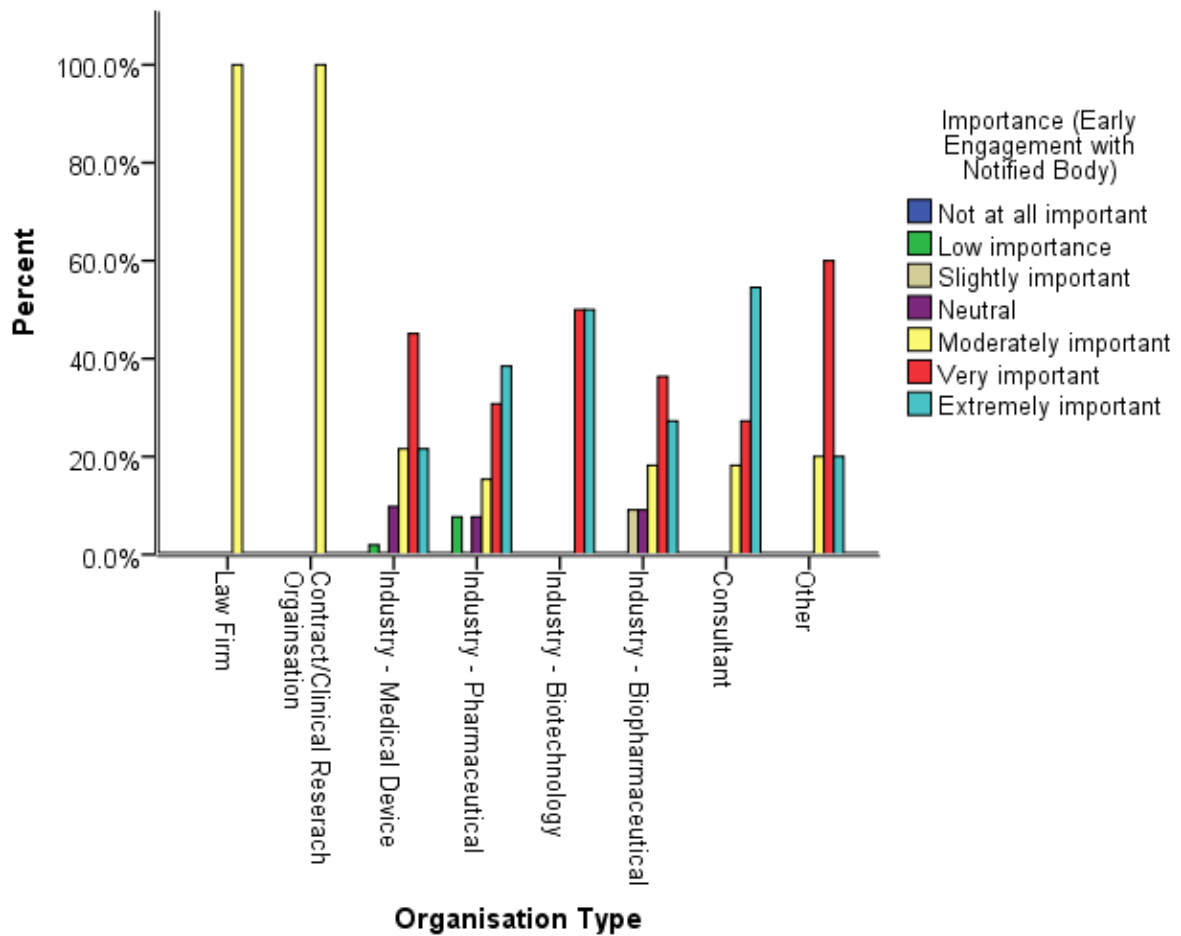
**6.3 Research Question 4a: Are there differing perceptions across organisations types, annual sales and number of employees regarding the different facilitating factors for obtaining regulatory approval in the EU and US?**

Relationship with Regulatory Authorities

*EU Authorities*

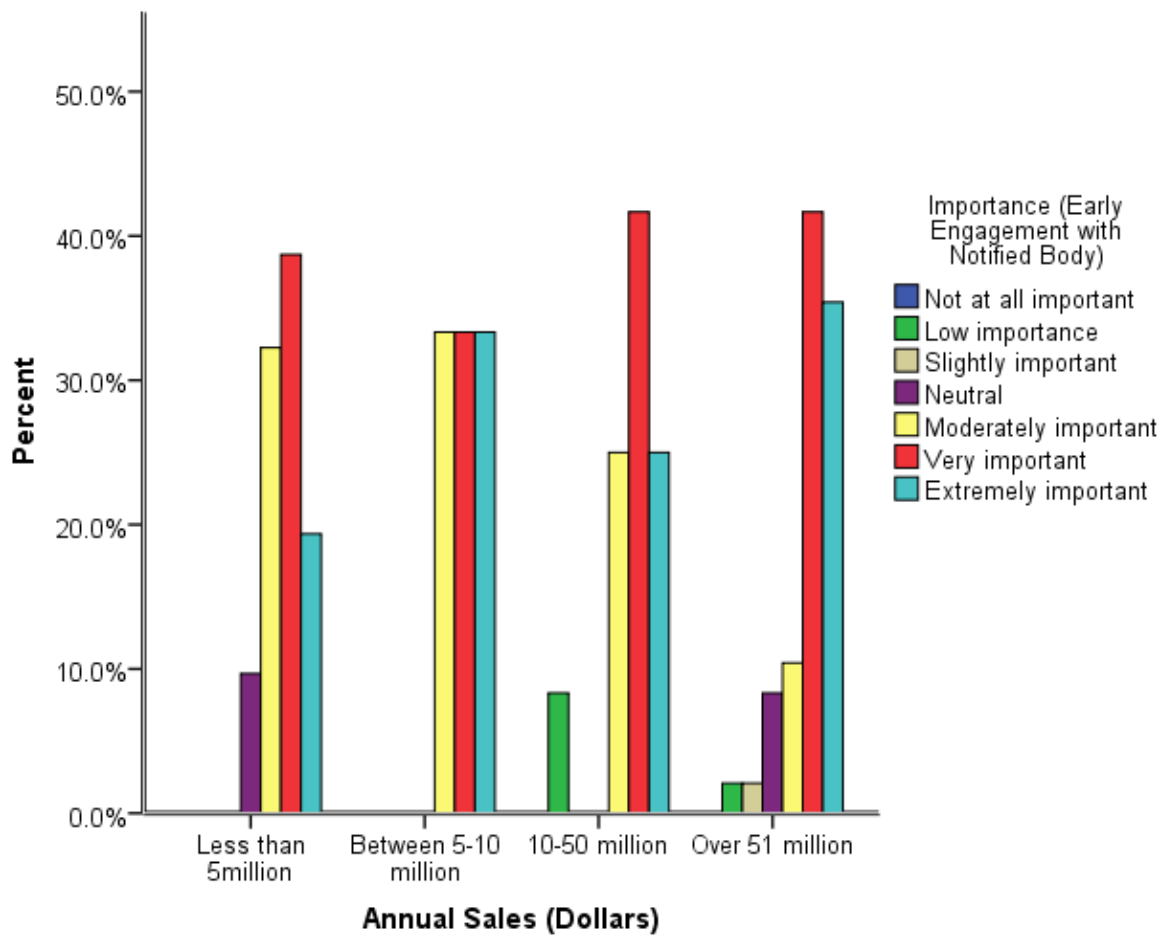
It was investigated if there were differing perceptions across organisation types regarding the importance of engaging early with notified bodies. A cross-tabulation comparing the two variables “Importance of Engaging Early with Notified Body” with “Organisation Type” was run and the results appear figure 23. Respondents across all organization types advocated early engagement most strongly.

Figure 23 Cross Tabulation of Organisation Type and Importance of Early Engagement with Notified Body



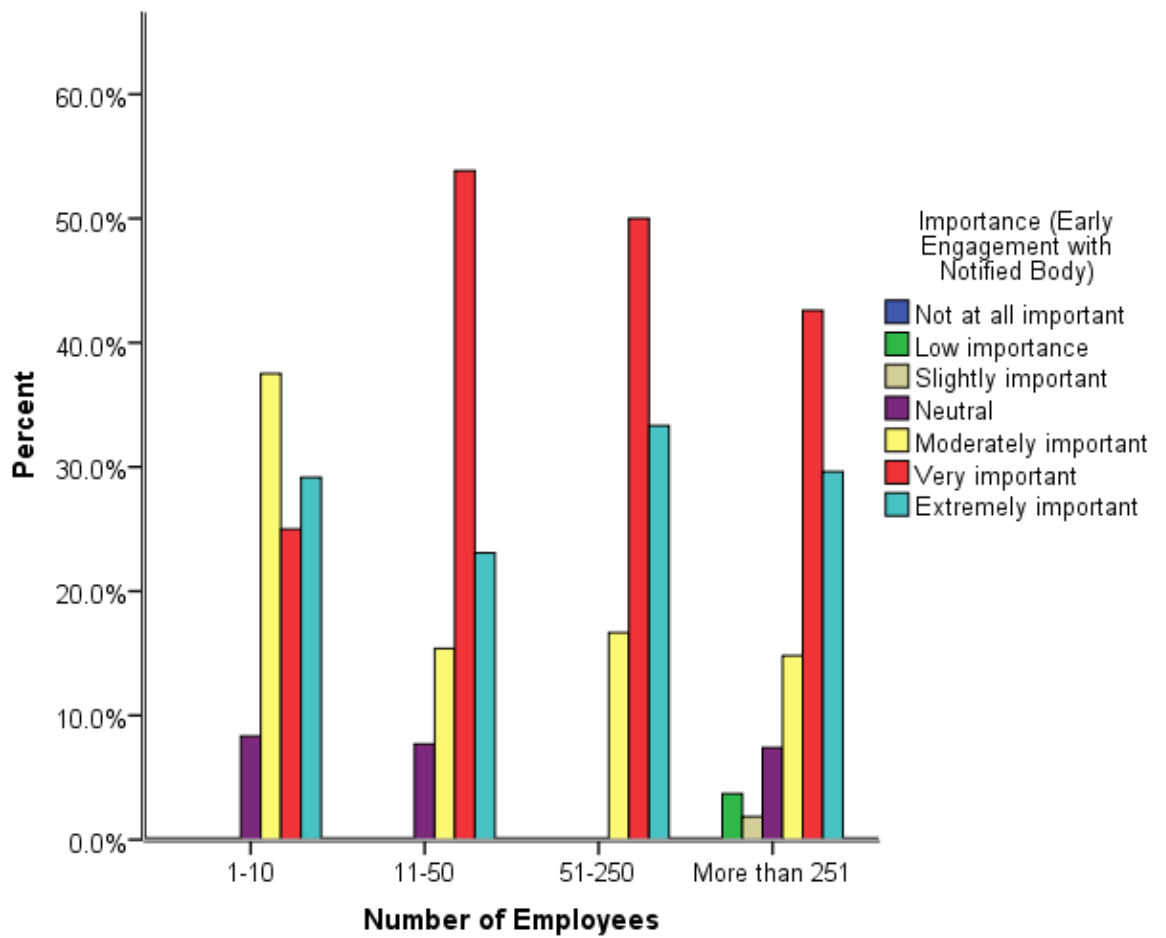
To further explore these relationships, differences among the sizes of the organisations’ perception of the importance rating of early engagement with notified bodies were examined through a cross tabulation comparing the two variables “Importance of Engaging Early with EU Notified Body” with “Sales/Number of Employees”. The results of this cross tabulation are seen in the clustered bar chart in Figure 24 and 25. This cross tabulation shows that all sizes of companies advocated early engagement.

Figure 24 Cross Tabulation of Annual Sales and Early Engagement with Notified Body



The cross tabulation illustrated in Figure 27 of the variables “Importance of Engaging Early with EU Regulatory Authority” and “Number of Employees” corroborates this finding.

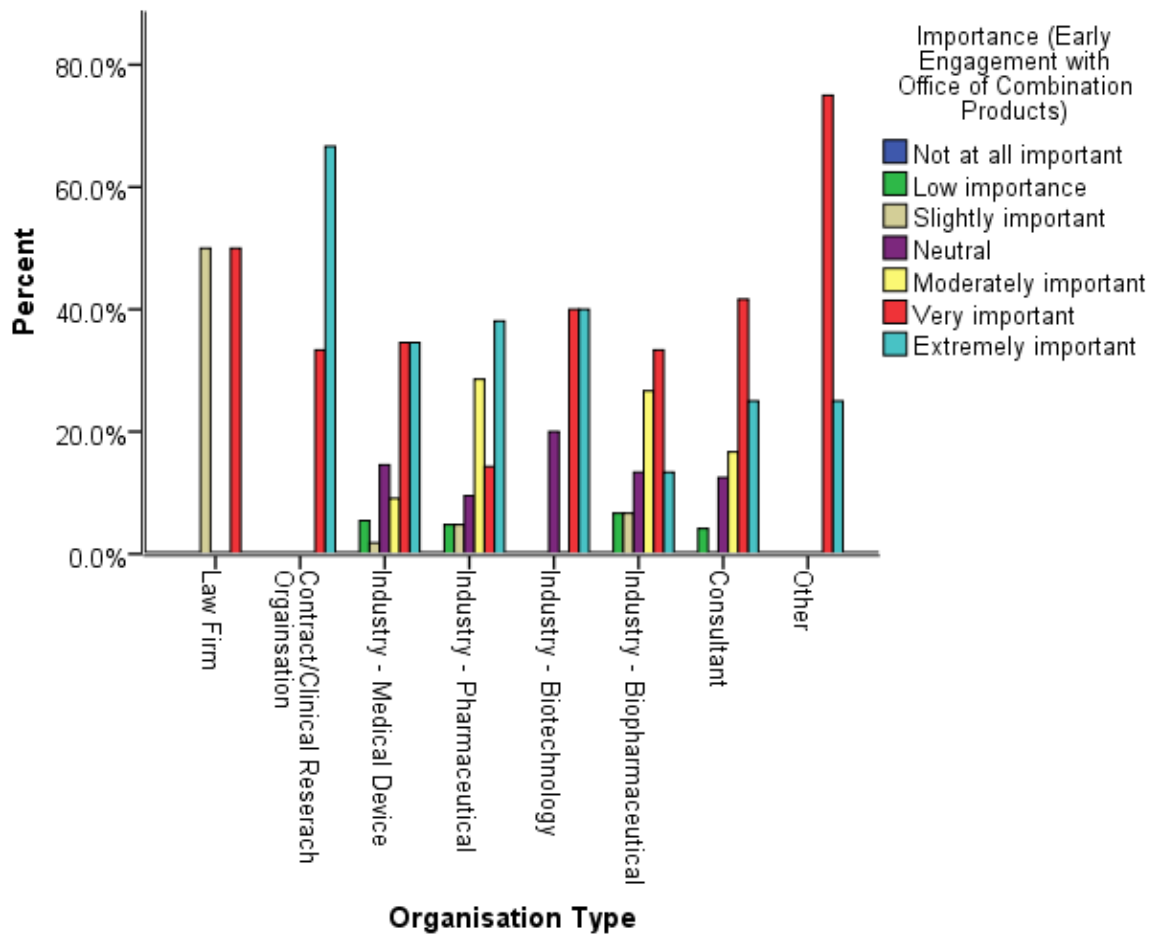
Figure 25 Cross Tabulation of Annual Sales and Early Engagement with Notified Body



*US Regulatory Authority*

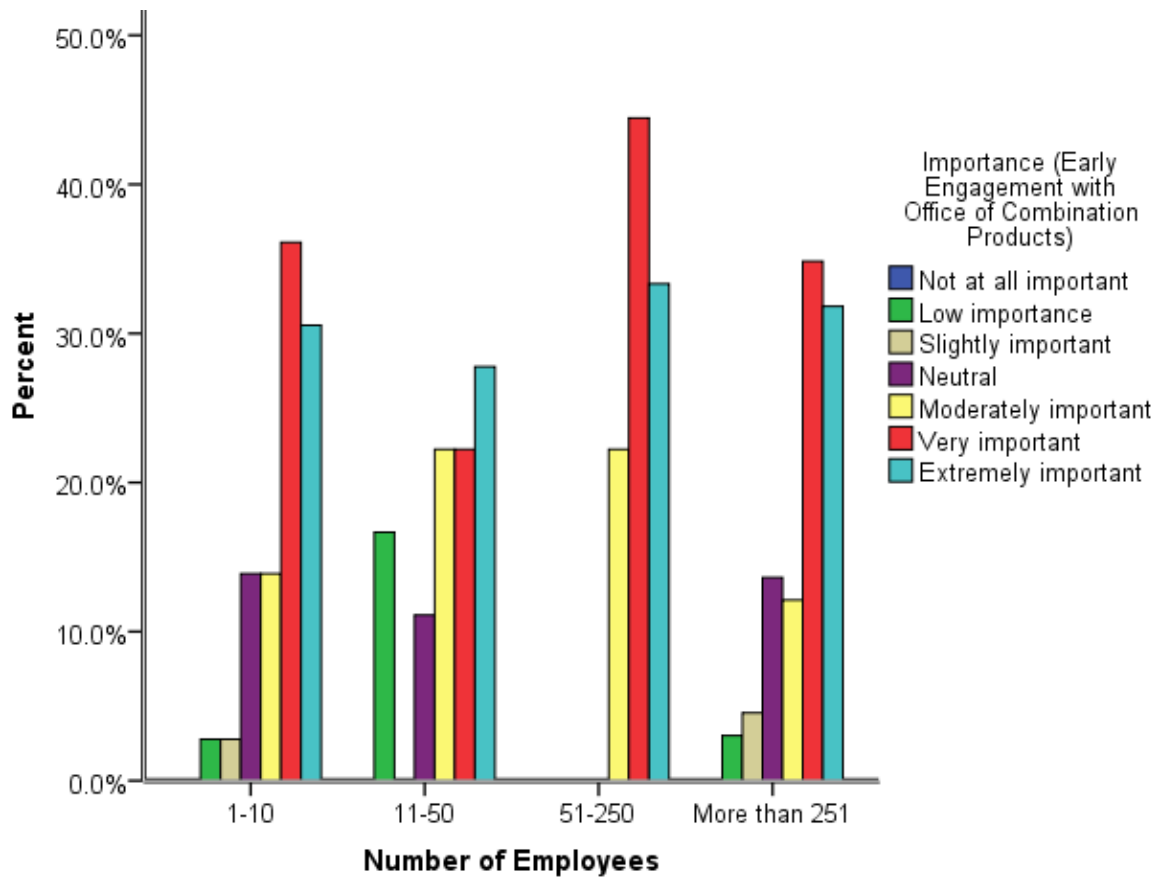
It was investigated if there were differing perceptions across organisation types regarding the importance to engage early with the office of combination products. A cross tab (Figure 26) of “Type of Organisation” and “Importance of Engaging Early with Office of Combination Products” reveals that contract/clinical research organisations are the group that most strongly advocate the importance of this early engagement, while biopharmaceuticals are the group that advocate this the least.

Figure 26 Cross Tabulation of Organisation Type and Early Engagement with Office of Combination Products



The cross tabulation of the variables “Importance of Engaging Early with US Regulatory Authority” and “Number of Employee” (Figure 27) corroborates this finding.

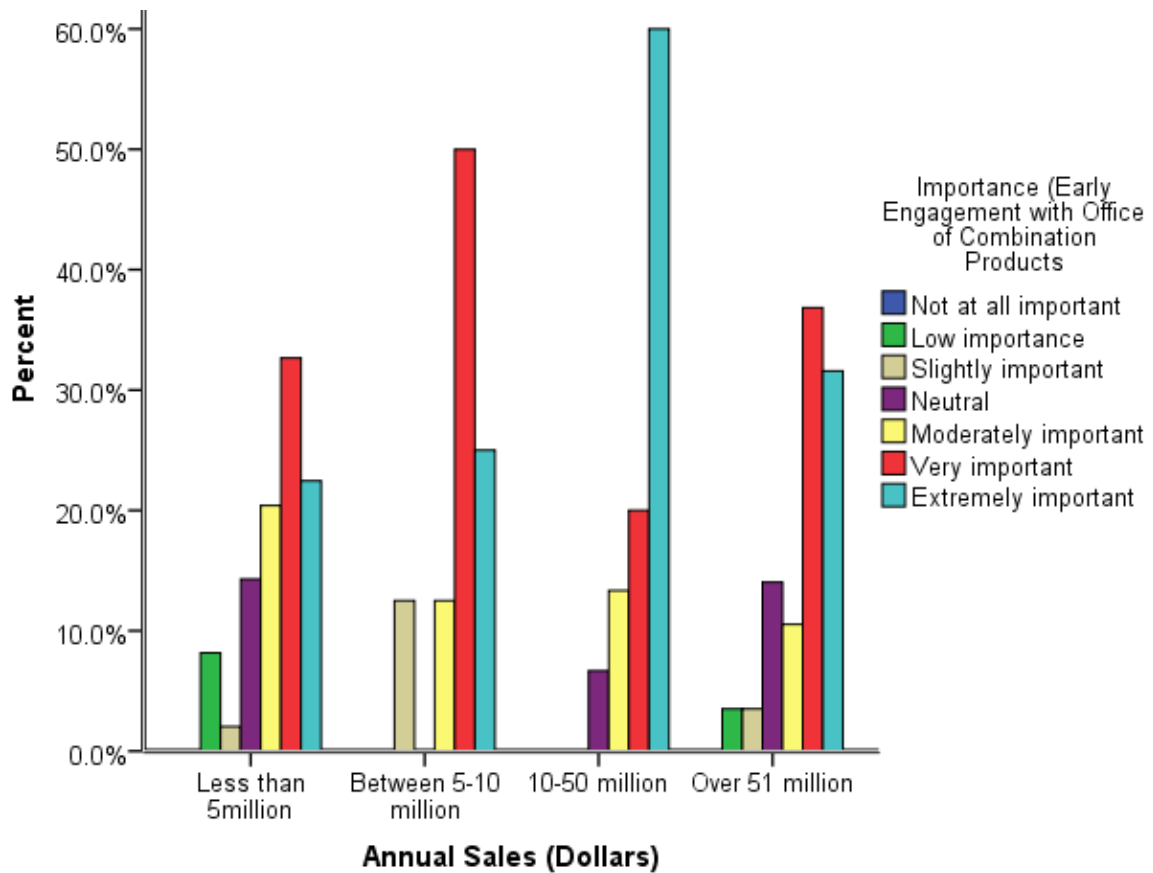
Figure 27 Cross Tabulation of Number of Employees and Early Engagement with Office of Combination Products



This finding is corroborated by the cross tabulation of the variables “Importance of Engaging Early with US Regulatory Authority” and “Annual Sales” (Figure 28).



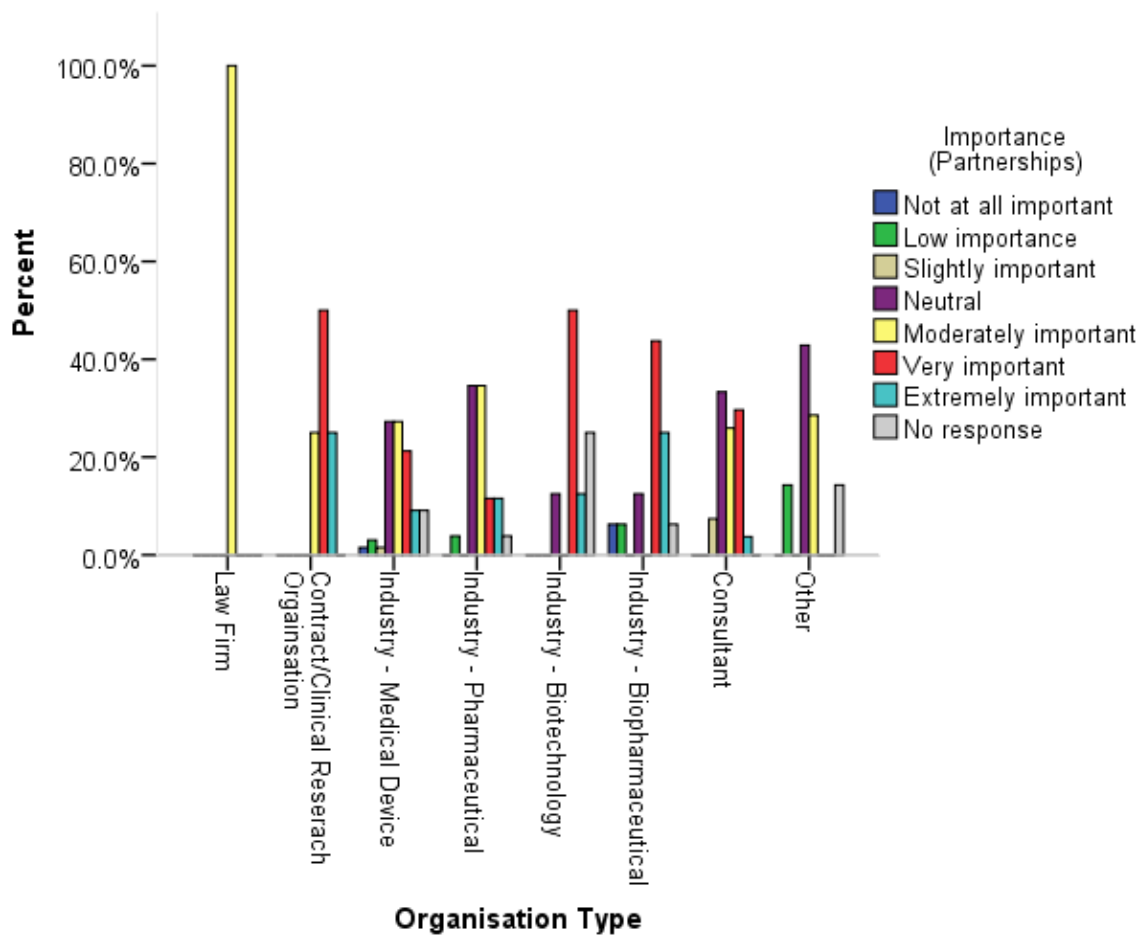
Figure 28 Cross Tabulation of Annual Sales and Early Engagement with Office of Combination Products



### 6.3.1 Partnerships

The researcher wanted to investigate if there were differing perceptions across organisation types regarding the importance of being part of a partnership. Figure 29 is a cross-tabulation table comparing the two variables “Importance of Partnerships” and “Organisation Type”. In most industries, a majority of respondents at least deemed partnerships moderately important, although respondents in the pharmaceutical and “other” categories differed.

Figure 29 Cross Tabulation of Importance of Partnerships and Organisation Type



To further explore these relationships, differences among the sizes of the organisations perception of the importance rating of partnerships were examined through a cross tabulation comparing the two variables “Importance of Partnerships” with “Sales/Number of Employees” is shown in Figure 30 and Figure 31. Employees of smaller companies were more likely to emphasize the importance of partnerships.

Figure 30 Cross Tabulation of Importance of Partnerships and Annual Sales

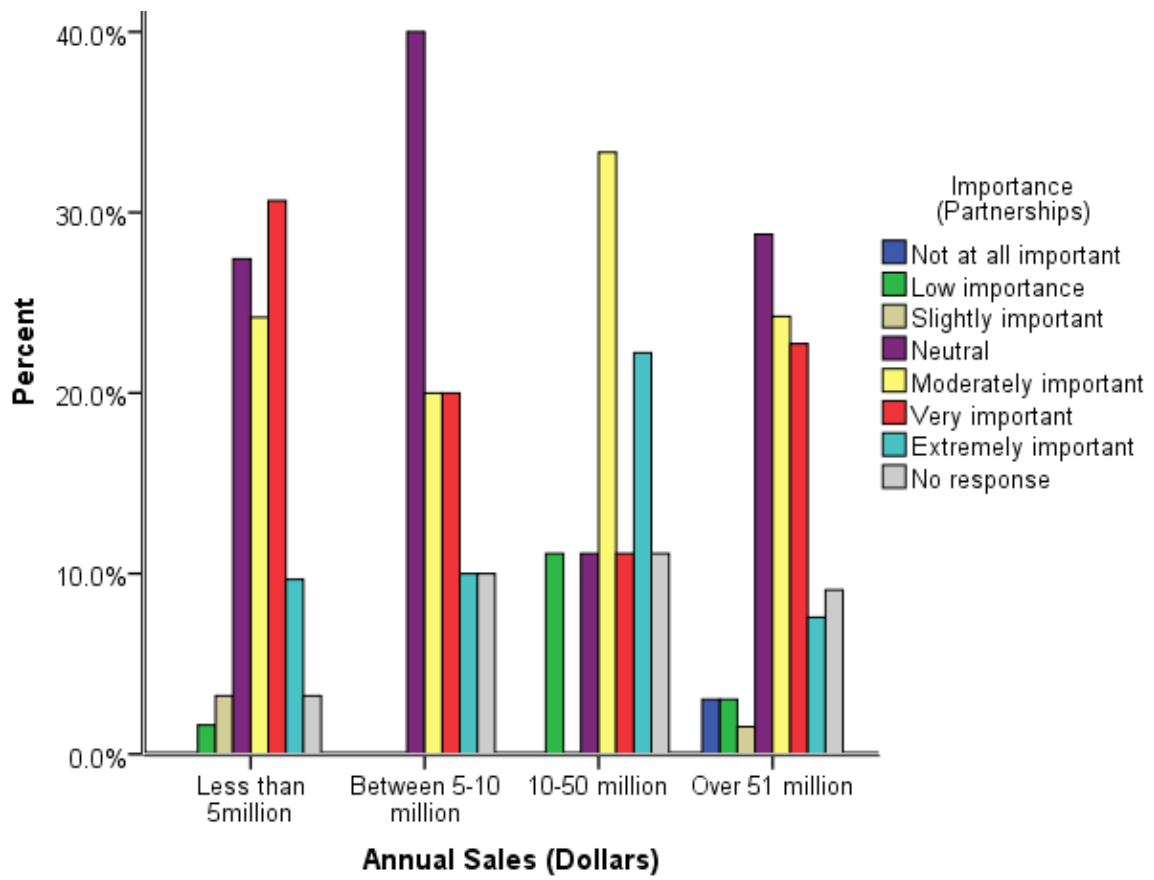
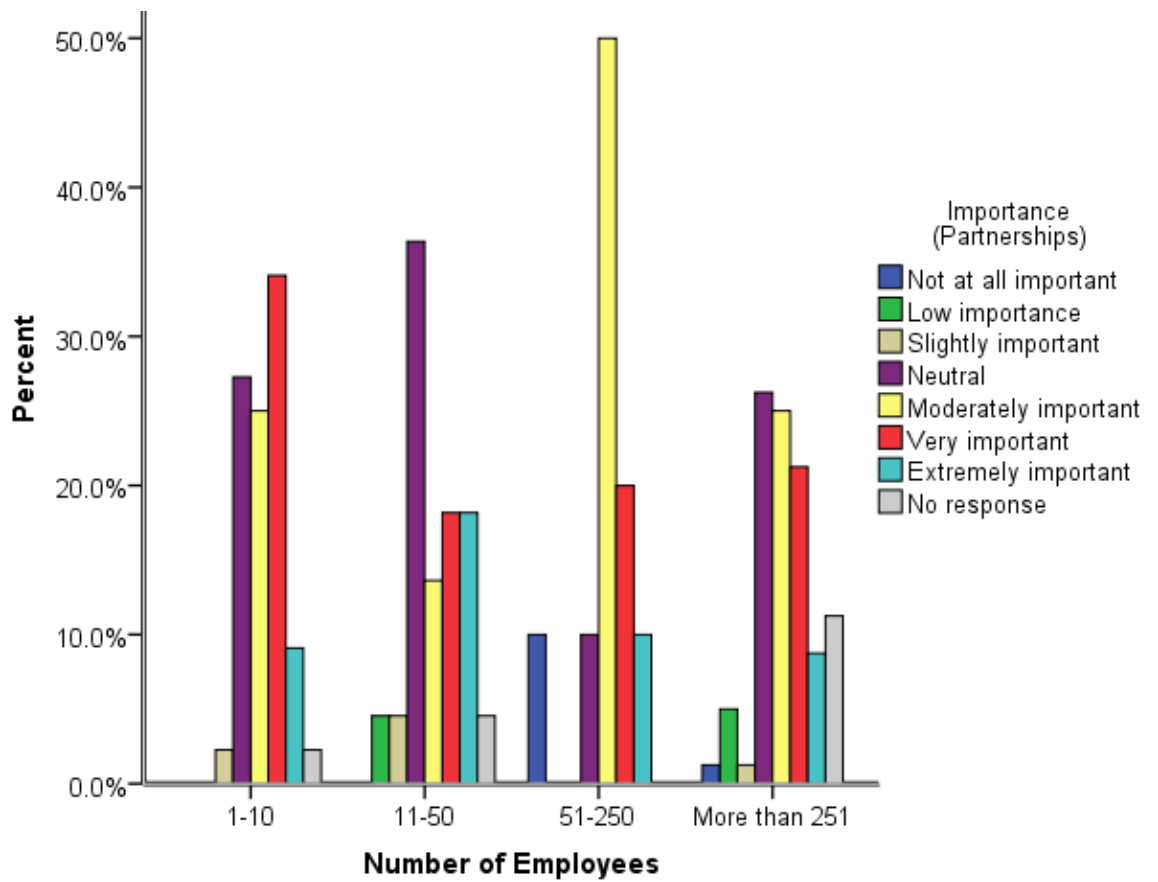
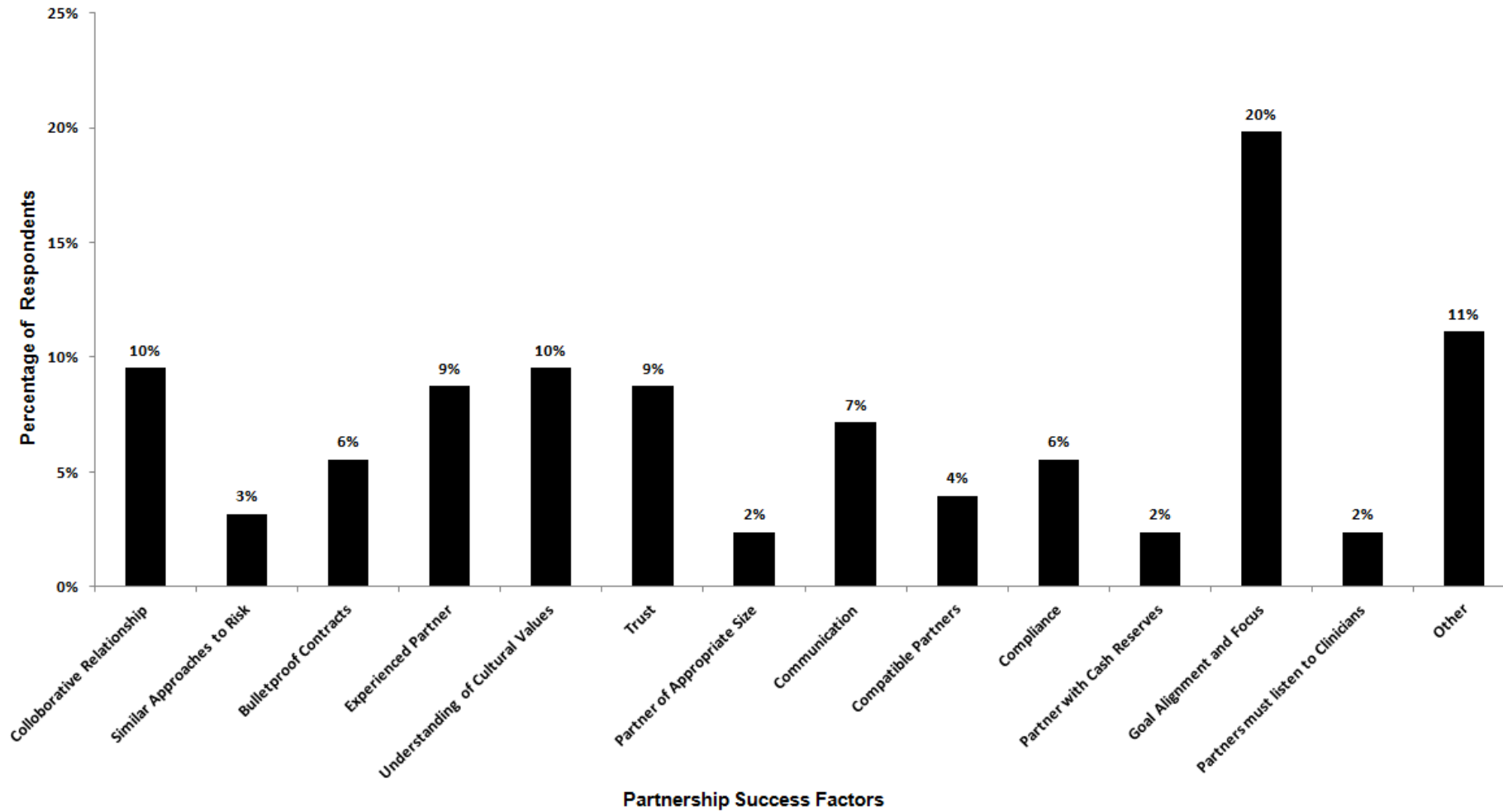


Figure 31 Cross Tabulation of Importance of Partnerships and Number of Employees



The next question in this section was open ended and did not provide respondents specific answers from which to choose. Respondents were asked to describe the most critical factor that enables successful partnerships involving companies bringing a drug/device combination product to market. The responses fell into 14 categories, shown in Figure 32.

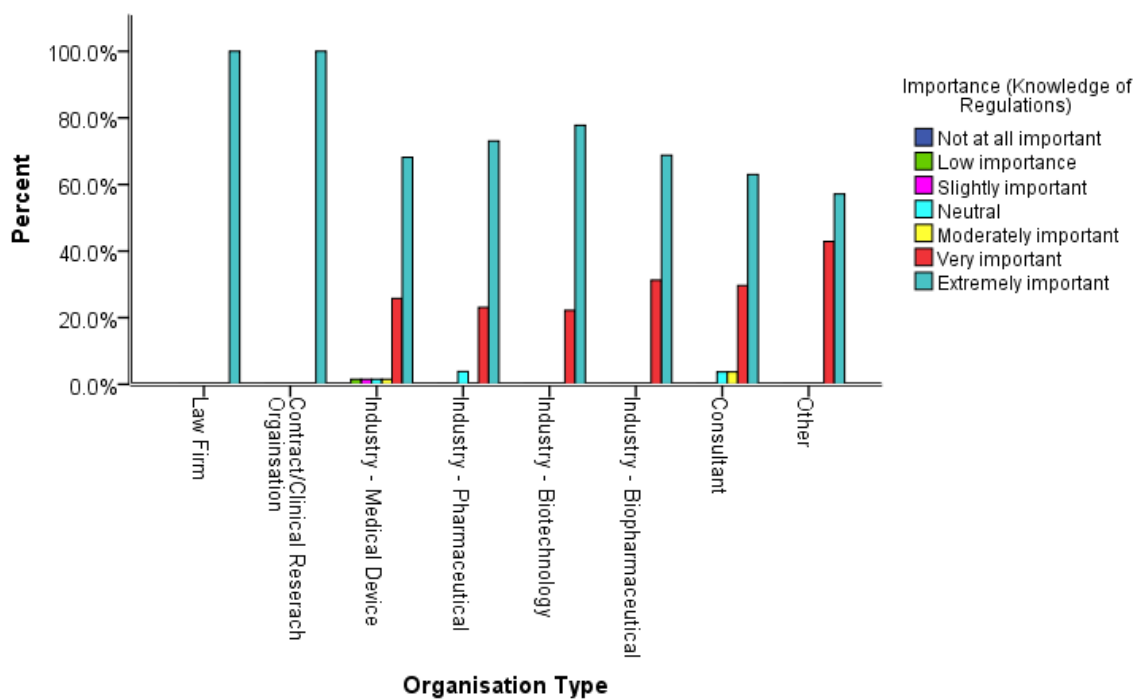
Figure 32 Factors for Successful Combination Product Partnerships



### 6.3.2 Characteristics of the Organisations' Staff

The researcher wanted to investigate if there were differing perceptions across organization types regarding the importance of employees having knowledge of combination product regulations. A cross-tabulation table comparing the two variables “Importance of Knowledge of Regulations” with “Organisation Type” is shown in figure 33. There is agreement across all organisation types that knowledge of regulations is important.

Figure 33 Cross Tabulation of Organisation Type and Importance of Knowledge of Regulations



To further explore these relationships, the sizes of the organisations perception of the importance rating of having knowledge of regulations were examined through a cross tabulation comparing the two variables “Importance of Knowledge of Regulations” with “Sales/Number of Employees”, as shown in Figure 34 and Figure 35. Results were consistent across all sizes of organisations that knowledge of regulations is important.

Figure 34 Cross Tabulation of Number of Employees and Importance of Knowledge of Regulations

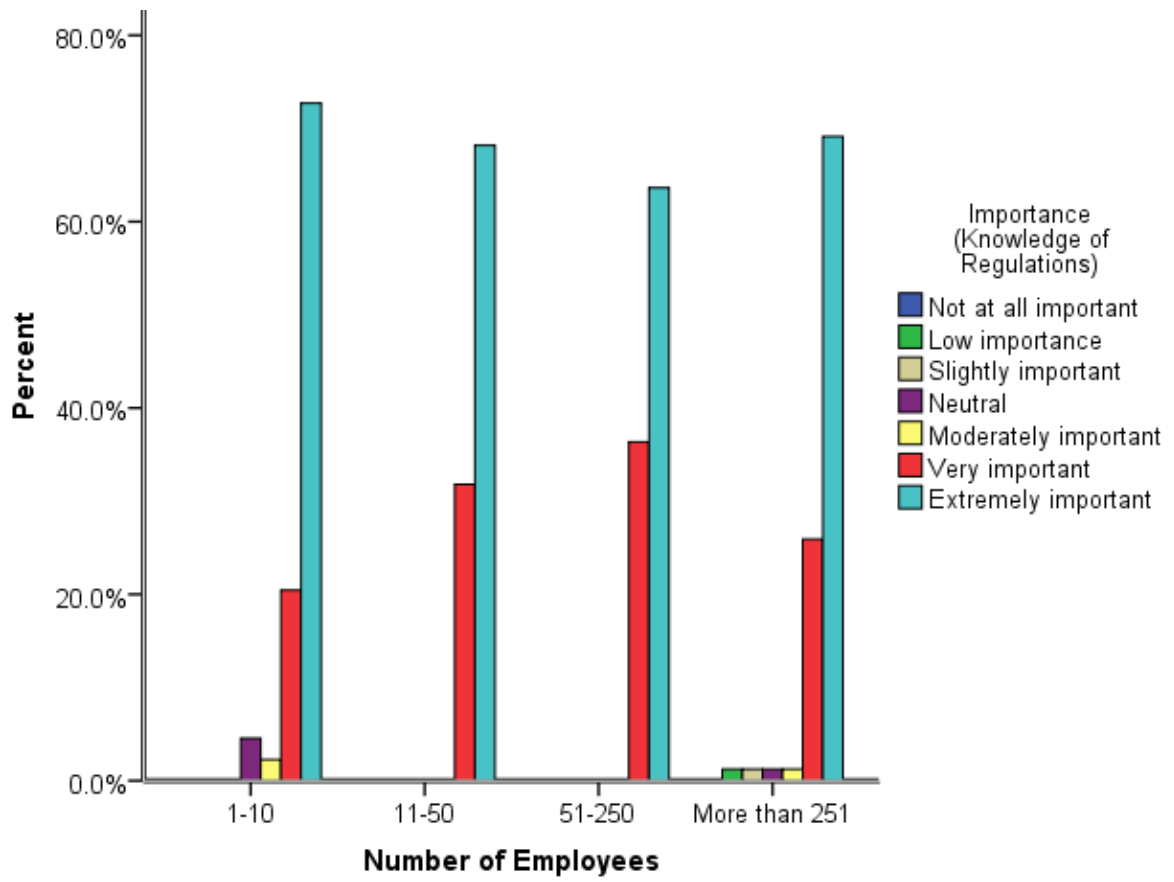
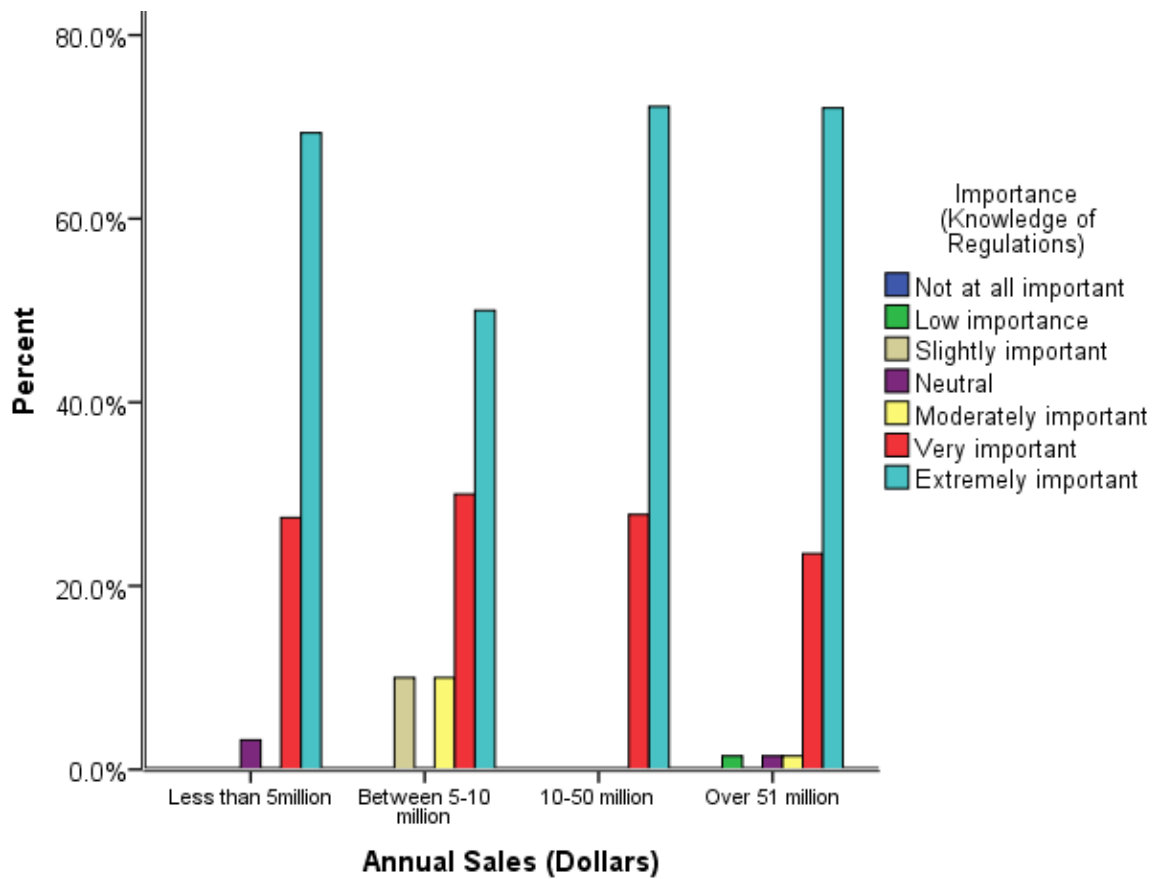


Figure 35 Cross Tabulation of Annual Sales and Importance of Knowledge of Regulations

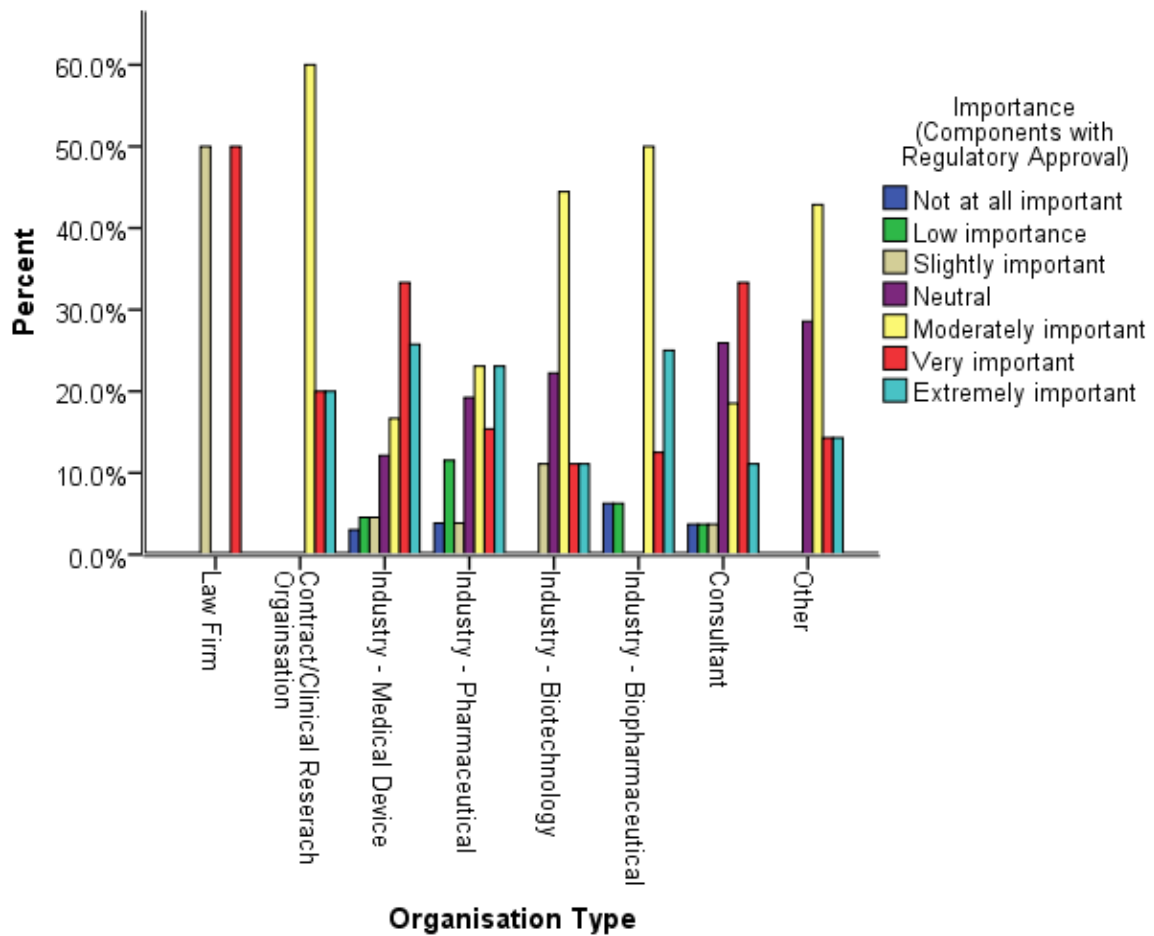


### 6.3.3 Components with Regulatory Approval

The researcher wanted to investigate if there were differing perceptions across organisation types regarding the importance of product components with regulatory approval. A cross-tabulation table comparing the two variables “Importance of Components with Regulatory Approval” with “Organisation Type” is shown in figure 36. There is agreement across all organisation types that knowledge of regulations is at least moderately important.



Figure 36 Cross Tabulation of Organisation Type and Importance of Components with Regulatory Approval



To further explore these relationships, differences among the sizes of the organisations’ perception of the importance rating of having knowledge of regulations were examined through a cross tabulation comparing the two variables “Importance of Components with Regulatory Approval” with “Sales/Number of Employees”, as shown in Figure 37 and Figure 38. Results were consistent across all sizes of organisations that knowledge of regulations is important.

Figure 37 Cross Tabulation of Annual Sales and Importance of Components with Regulatory Approval

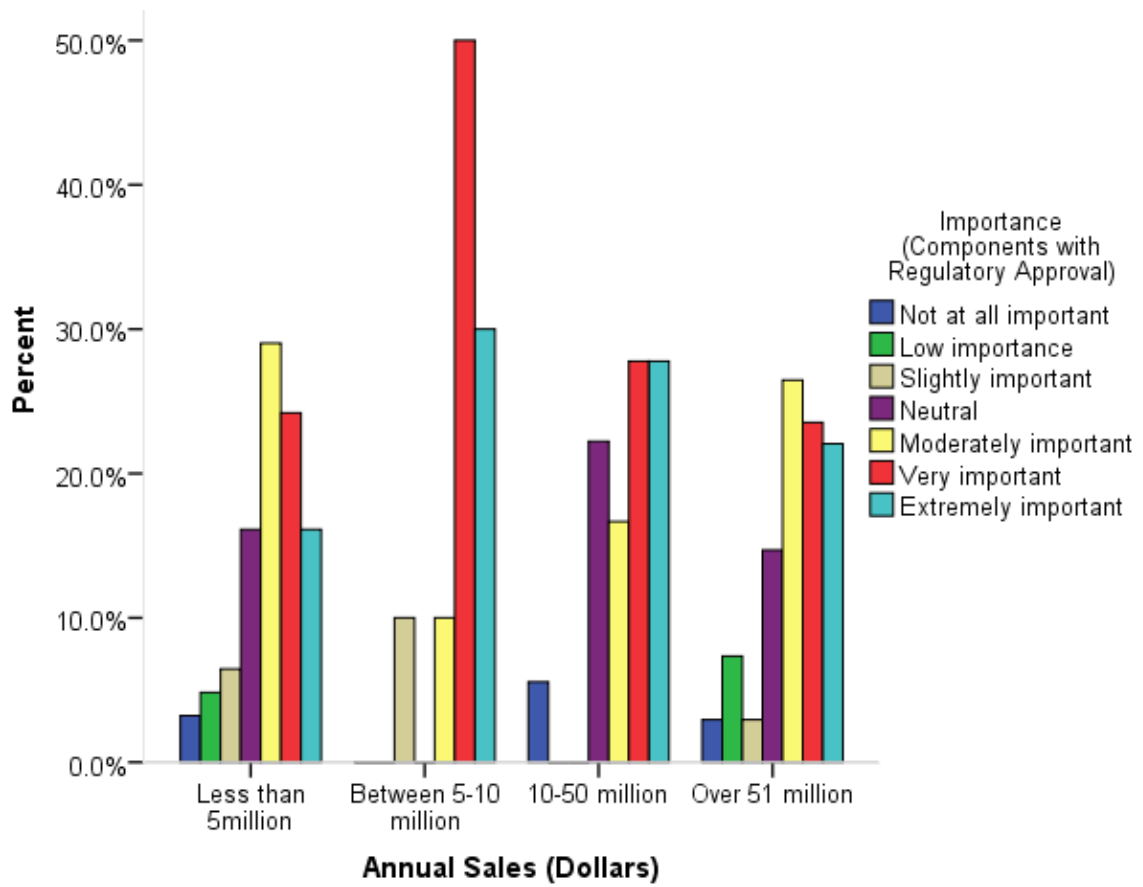
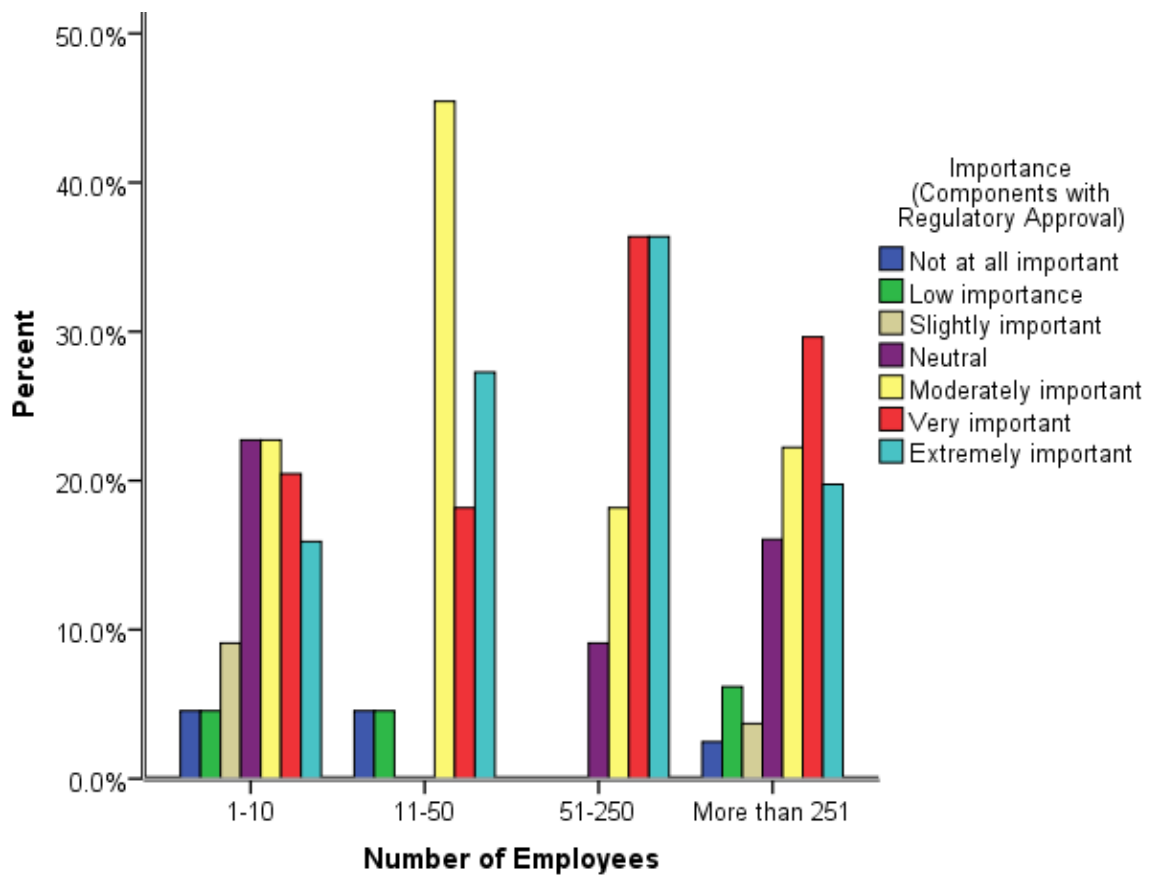


Figure 38 Cross Tabulation of Annual Sales and Importance of Components with Regulatory Approval



**6.4 Research Question 4b: Are there significant relationships between organisation types, sizes, product type, market and obtaining regulatory approval in the EU and US?**

Fisher’s exact test was used to determine if there was a significant relationship between organisations types, size of organisation, product type, and market and obtaining regulatory approval in either country. A P value of < .05 was considered to be statistically significant. The Fisher exact test was used because the frequency assumption was violated, with the sparseness of the cells not meeting the assumption of no more than 10% of the cells having the expected frequency below 5 (Portney & Watkins, 2009).

### 6.4.1 Organisation Type

To determine if there is a relationship between organisation type and obtaining regulatory approval a Fisher's exact test was run (Table 12). The following hypothesis (HO: the null hypothesis and HA: the alternative hypothesis) was explored:

HO1= Obtaining regulatory approval of combination product is not significantly associated with the type of business

HA1= Obtaining regulatory approval in the European Union and/or United States is significantly associated with the type of business

The result is P=.392, indicating that the null hypothesis can be accepted; there is no significant difference in obtaining regulatory approval and the organisation type.

Table 12 Significant Tests for the Relationship between Organisation Type and Obtaining Regulatory Approval

Chi-Square Tests					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.540 <sup>a</sup>	7	.375	.386	
Likelihood Ratio	8.493	7	.291	.368	
Fisher's Exact Test	7.293			.392	
Linear-by-Linear Association	1.945 <sup>b</sup>	1	.163	.169	.089
N of Valid Cases	158				

a. 8 cells (50.0%) have expected count less than 5. The minimum expected count is .96.

b. The standardized statistic is -1.395.

### 6.4.2 Organisation Size (number of employees and annual sales)

To determine if there is a relationship between the size of the organisation (sales/number of employees) and obtaining regulatory approvals a Fisher's exact test was run (Table 13 and Table 14).

*Number of Employees*

The following hypothesis (HO: The null hypothesis and HA: The alternative hypothesis) was explored for the number of employees using the Fisher’s exact test:

HO1= Obtaining regulatory approval of combination product is not significantly associated with the number of employees

HA1= Obtaining regulatory approval in the European Union and/or United States is significantly associated with the number of employees

Table 13 Significant Tests for Relationship between the Number of Employees and Obtaining Regulatory Approval

<b>Chi-Square Tests</b>					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.817 <sup>a</sup>	3	.282	.288	
Likelihood Ratio	3.847	3	.278	<sup>b</sup>	
Fisher's Exact Test	3.768			.288	
Linear-by-Linear Association	1.776 <sup>c</sup>	1	.183	.185	.102
N of Valid Cases	158				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.29.

b. Cannot be computed because unable to open temporary file.

c. The standardized statistic is 1.333.

The result is P=.288, indicating that the null hypothesis can be accepted; there is no significant difference in obtaining regulatory approval and the number of employees.

*Annual Sales (Table 14)*

The following hypothesis (HO: The null hypothesis and HA: The alternative hypothesis) was explored for the annual sales using the Fisher’s exact test:

HO1= Obtaining regulatory approval of combination product is not significantly associated with the annual sales

HA1= Obtaining regulatory approval in the European Union and/or United States is significantly associated with the annual sales

Table 14 Significant Tests for Relationship between the Annual Sales and Obtaining Regulatory Approval

Chi-Square Tests					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.493 <sup>a</sup>	3	.477	.482	
Likelihood Ratio	2.531	3	.470	.482	
Fisher's Exact Test	2.470			.484	
Linear-by-Linear Association	.368 <sup>b</sup>	1	.544	.564	.292
N of Valid Cases	158				

a. 1 cells (12.5%) have expected count less than 5. The minimum expected count is 4.81.

b. The standardized statistic is .607.

The result is  $P=.484$ , indicating that the null hypothesis can be accepted; there is no significant difference in obtaining regulatory approval and the annual sales.

### 6.4.3 Type of Product

To determine if there is a relationship between the type of product and obtaining regulatory approval a Fisher's exact test was run (Table 15). The following hypothesis (HO: The null hypothesis and HA: The alternative hypothesis) was explored for the type of product using the Fisher's exact test:

HO1= Obtaining regulatory approval of combination product is not significantly associated with the type of product

HA1= Obtaining regulatory approval in the European Union and/or United States is significantly associated with the type of product

Table 15 Significant Tests for Relationship between the Type of Product and Obtaining Regulatory Approval

<b>Chi-Square Tests</b>					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	33.314 <sup>a</sup>	23	.076	.031	
Likelihood Ratio	40.142	23	.015	.047	
Fisher's Exact Test	32.746			.022	
Linear-by-Linear Association	8.448 <sup>b</sup>	1	.004	.004	.002
N of Valid Cases	158				

a. 40 cells (83.3%) have expected count less than 5. The minimum expected count is .48.

b. The standardized statistic is -2.907.

The result is  $P=.022$ , indicating that the null hypothesis can be rejected; there is a significant difference in obtaining regulatory approval and the type of product.

#### 6.4.4 Market

To determine if there is a relationship between the market and obtaining regulatory approval a Fisher's exact test was run (Table 16). The following hypothesis (HO: The null hypothesis and HA: The alternative hypothesis) was explored for the type of product using the Fisher's exact test:

HO1= Obtaining regulatory approval of the combination product is not significantly associated with the market

HA1= Obtaining regulatory approval in the EU and/or US is significantly associated with the market

Table 16 Significant Tests for Relationship between Annual Sales and Obtaining Regulatory Approval

<b>Chi-Square Tests</b>					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	18.133 <sup>a</sup>	9	.034	.019	
Likelihood Ratio	20.150	9	.017	.032	
Fisher's Exact Test	17.534			.020	
Linear-by-Linear Association	.036 <sup>b</sup>	1	.850	.858	.440
N of Valid Cases	158				

a. 15 cells (75.0%) have expected count less than 5. The minimum expected count is .48.

b. The standardized statistic is .190.

The result is  $P=.020$ , indicating that the null hypothesis can be rejected; there is a significant difference in obtaining regulatory approval and the market.

## 6.5 Opened Ended Questions Responses

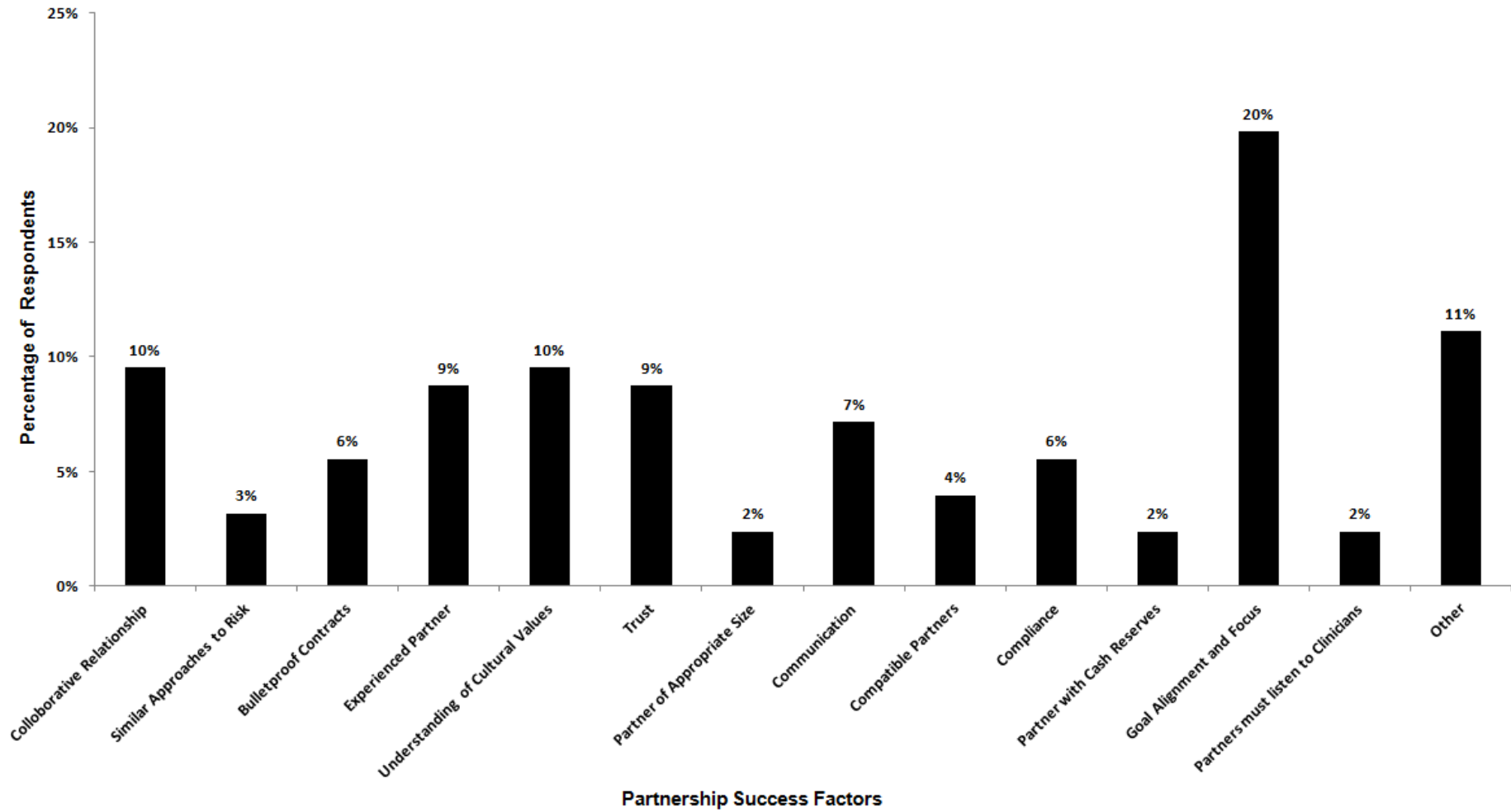
The following is a description of the findings for the qualitative data that were collected in the survey, much of it based on open-ended responses.

### 6.5.1 Opened-Ended Questions Responses—Partnerships

Respondents gave a number of rich responses to open-ended questions indicating Factors for Successful Combination Product Partnerships. The responses were grouped into categories. The total number of responses for each category were summed and displayed in Figure 39.



Figure 39 Factors for Successful Combination Product Partnerships



Examples of the statements grouped into some of the categories shown in Figure 41 include:

Theme	Sample Quotations
Good Collaborative Relationship	‘Ability to work together with candour and common objectives’, ‘Agree where to agree and disagree’
Similar approach to risk	‘Mutual respect, reward, and risk.’
Bulletproof contracts	‘Bulletproof contracts, both business and quality’, ‘Clear roles and contractual obligations’
Experienced Partner	‘Business and development experience of the partner’, ‘Each should have vast experience in their field’
Understanding Cultural Values	‘Clear understanding of skills set of both organization and the pace of work of both organisations’, ‘Same culture, Huge differences in perception of time and ability to withstand the differences’, ‘Understand each other coming from different product “worlds”’
Trust	‘Trust and mutual respect for each other’s capabilities’
Partner of Appropriate Size	‘Size of companies, Large partner would not care much about a smaller partner’ ‘The relative sizes of the partners and the importance of the product to each partner’
Close Communication	‘Close communication; shared engagement’
Compatible Partners	‘Common or shared goals’ ‘Compatible work ethic and ethics’
Compliance	‘Complies with regulatory & compliance requirement’, ‘A common understanding of the regulations’
Partners with Deep Pockets	‘Deep pockets of the strategic partner’, ‘Funding’
Aligned, goal focused	‘Amount of importance placed on the project.’, ‘Clear and agreed to milestones and timelines’

Partners must listen to  
Clinicians

‘many manufacturers will not listen to doctors!’ ‘partners must listen to clinicians, My experience is that clinicians and scientists are ignored by commercial organisations who think, wrongly, that they know best and need not work in partnership with clinicians’

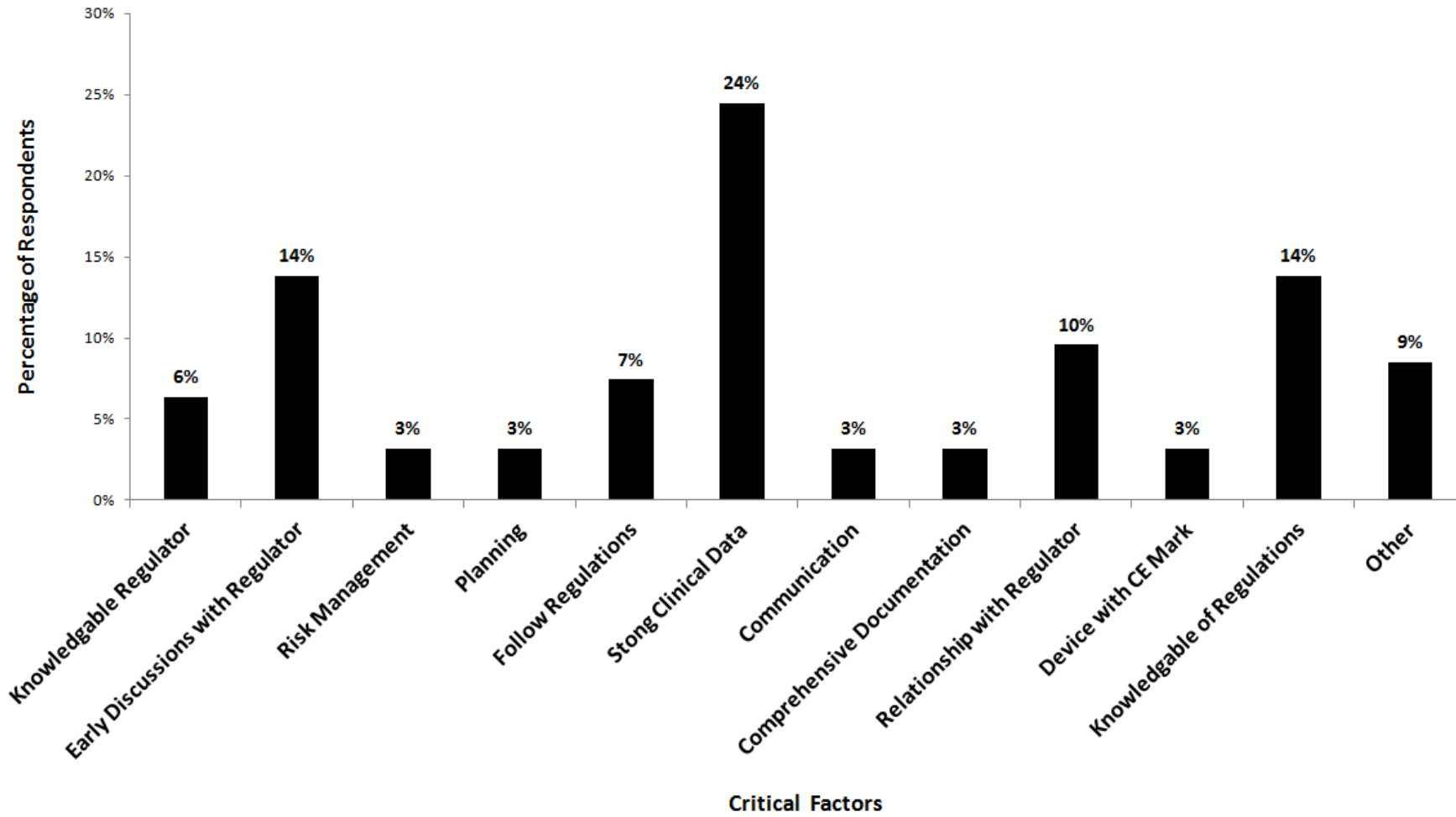
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### **6.5.2 Opened Ended Questions Responses—the Critical Factor for Obtaining Regulatory Approval in the European Union**

Respondents were asked to describe the most critical factor in obtaining prompt regulatory approval of combination products in the European Union. There were 94 responses and these were categorised into 12 categories, shown in Figure 40. Answers varied widely, with 23% indicating that having strong clinical data was important to prompt regulatory approval, 14% indicating having early discussions was important, another 14% referring to knowledge of regulations was important, and 10% referencing the importance of a good relationship with the regulator. The smaller categories were following the regulations (7%), having a knowledgeable regulator (6%), risk management (3%), planning (3%), communication with regulators (3%), comprehensive documentation (3%), and device with CE mark (3%). An ‘other’ category corresponded to 9% for responses that did not fall into the other categories.

The category of having strong clinical data did not appear in any of the interviews, but 24% of survey respondents mentioned it.

Figure 40 Critical Factors for Obtaining Regulatory Approval in the EU



Examples of the statements grouped into some of the categories shown in the table above are included below:

Theme	Sample Quotations
Strong clinical data	‘Clinical data demonstrating safety in efficacy in EU’, ‘Convincing clinical evidence of safety and efficacy that demonstrates an acceptable benefit/risk ratio for a patient’ ‘Solid data’ ‘high quality clinical data’
Having early discussions with regulator	‘Design product for approval by early discussion with regulatory authorities’, ‘Early discussion with regulatory authority to establish development path.’ ‘Scientific Advice from multiple health authorities very early in the process’ ‘It is important to have meetings (scientific advice, pre-IMPD / pre-IND ...) with the regulatory authorities to keep them informed on the project status, seek advice on specific topics where you are uncertain of what is necessary to be carried out and to share your approach for the development up front – it is better to be aware early if the authorities have questions or suggestions’
Knowledge of regulations was	‘follow the rules.’ ‘understanding the manufacturing process and specification expectations of the agency’ ‘Understanding and agreeing classification, understanding of the regulations surrounding both constituent parts’
Having a good relationship with the regulator	‘good collaboration with authorities’, ‘Good relationship between Manufacturer / Notified Body / Competent Authority’, ‘Choosing a Notified Body that has a good relationship with a Competent Authority who has experience in regulation of the drug component’
Follow the regulations	‘Following regulations, and appropriate documentation of this’, ‘Interpreting medical device regulations’
Knowledgeable regulator	‘A reviewer with a strong technical background’
Risk management	‘Addressing risk management appropriately’, ‘risk mitigation’

Planning	‘Appropriate planning’
Communication	‘Communication with health authorities’
Comprehensive documentation	‘Comprehensive and coherent documentation’
Device with CE mark	‘CE mark on purchased device components’

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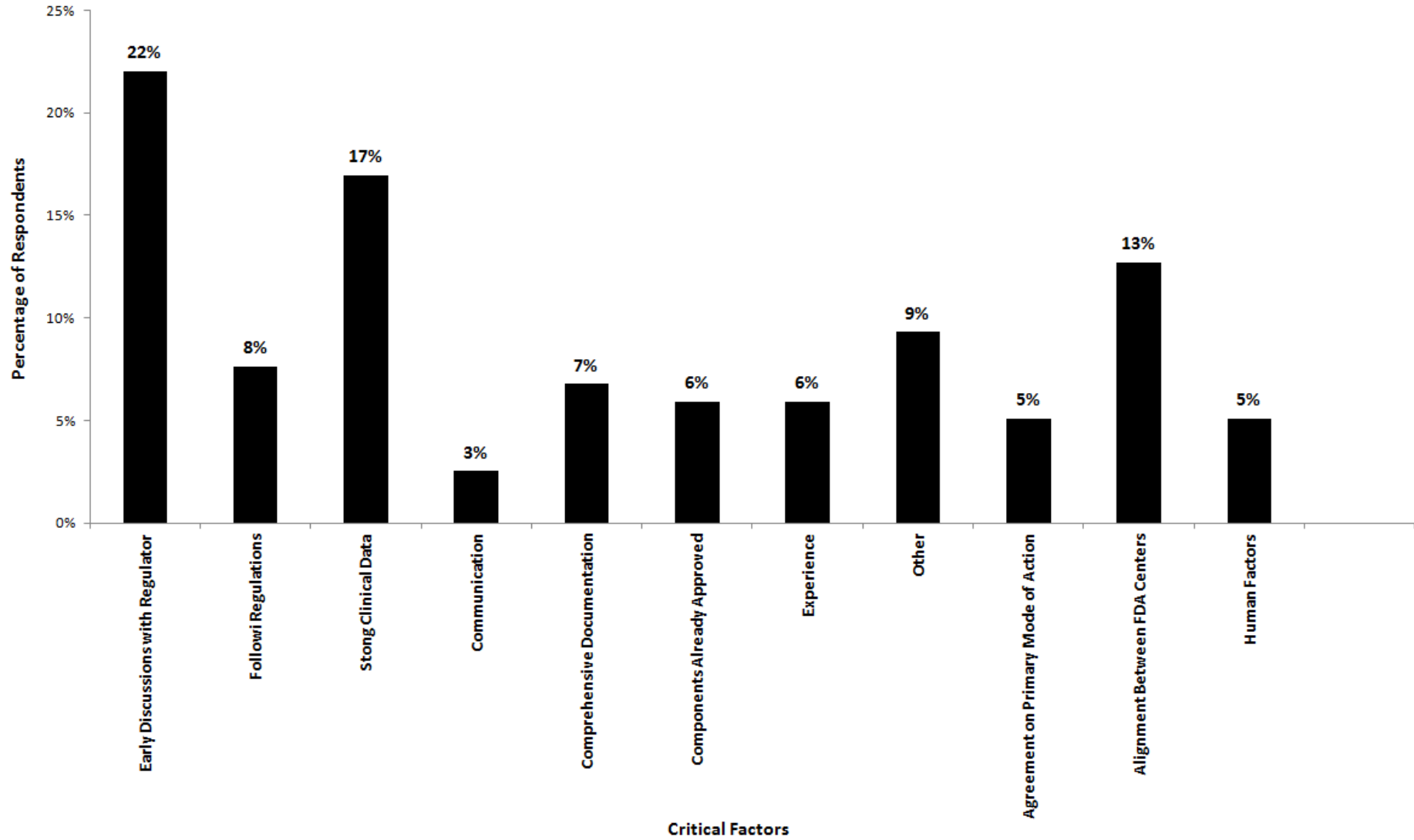
### **6.5.3 Opened Ended Questions Responses – The Critical Factor for Obtaining Regulatory Approval in the United States**

The next question in this section was open ended and did not provide respondents specific answers from which to choose. Respondents were asked to describe the most critical factor in obtaining prompt regulatory approval of combination products in the United States. There were 120 responses and were categorised into 13 categories, shown in Figure 41.

Respondents gave a wide range of answers. The largest group, 22%, indicate that having early discussions with the regulator was important when trying to get prompt regulatory approval. 17% percent referred to having strong clinical data. Another 13% of respondents indicated that alignment between FDA centres was important. 8% percent wrote that following regulations was important. 7% percent highlighted having comprehensive documentation. Respondents stated that having everything explicitly clear in the documentation means that there will be not rounds of questions. In an open response question, one survey respondent stated that “understanding the requirements and being able to explain how those requirements have been met in a language that transcends either device or drug background is critically important. Rounds of question could significantly delay the approval process.” Survey respondents mentioned ‘rounds of questions’ as a problem in the open ended questions. The activity and contribution of every component must be clear, and explained in context of the combination product.

The other smaller categories were as follows: components already having regulatory approval (6%), firm's experience (6%), agreement on primary mode of action (5%), human factors (5%), and communication (3%). An 'other' category encompasses the 9% of responses that did not fall into the other categories.

Figure 41 Critical Factors for Obtaining Prompt Regulatory Approval for Combination Products in the United States





Two factors that were given as answers to this question did not appear in the interview phase of the study, namely: having strong clinical data, and alignment between FDA centres.

Examples of the statements grouped into some of the categories shown in the table above are included below:

Theme	Sample Quotations
Early discussions with the regulator	‘Again early direct contact gets the expectations aligned’, ‘Early; open interaction with FDA, Understanding FDA thinking and approach to your product is key - and the earlier the better.’
Following regulations	‘Follow the rules, do not reinvent the wheel’ ‘Properly following the combination product regulations’
Strong clinical data	‘Adequately designed and executed clinical trial, Rate limiting step for filing for approval’ ‘Safety and efficacy of the drug component if the device is a method of delivery’
Communication	‘Regular interactions with FDA during development’ ‘keep regular communication with the appropriate authorities’
Comprehensive documentation	‘Comprehensive and coherent documentation, Pre-empts doubts and questions and instils confidence in the product and the manufacturer’; ‘well written description of the most essential element of the product, usually one element of the product is predominantly responsible for efficacy and/or safety, and if this element is described well and under control, the thoroughness of the sections characterizing the other elements may be weighed less heavily in the approval decision.’
Experience	‘Human factors: use an experienced consultant’; ‘Knowing the data you will need to present, and having the right technical personnel to gather it.’

Agreement on primary mode of action	‘Agreement on primary mode of action, To determine whether the drug or device side of the FDA will have primary review responsibility’; ‘understanding the primary mode of action, Determines which division of FDA will review submission’
Alignment between FDA centres	‘Clear determination of who will have jurisdiction, To know the audience who will be reviewing your data/submission and ensure that you are explaining in a way that they will understand’, ‘Clear understanding of the jurisdiction (which FDA Office has primary jurisdiction) and engagement of all involved parties in the planning stages, especially for non-clinical and clinical testing’
Human factors	‘US based Human Factors data, demonstrating that the target patient group of US patients can use the device is a key focus for the agency and providing this is several formative and summative studies helps’

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## **6.6 Integration of Survey and Interview Findings**

What follows is a discussion of the integration of the survey and interview findings. The conceptual model developed after the analysis of the interview data in chapter 4 was revised to reflect the findings of the analysis of the survey data (Figure 42).

Figure 43 illustrates the differences between the initial conceptual model developed from the interview findings and the second model that portrays the integration of the survey and interview findings. The factors highlighted in yellow in figure 43 are factors that were not identified in the interview phase but were new factors found after the surveys were analysed.

Figure 42 Revised Conceptual Model of Factors that Facilitate Regulatory Approval for Drug/Device Combination Products in the EU and US

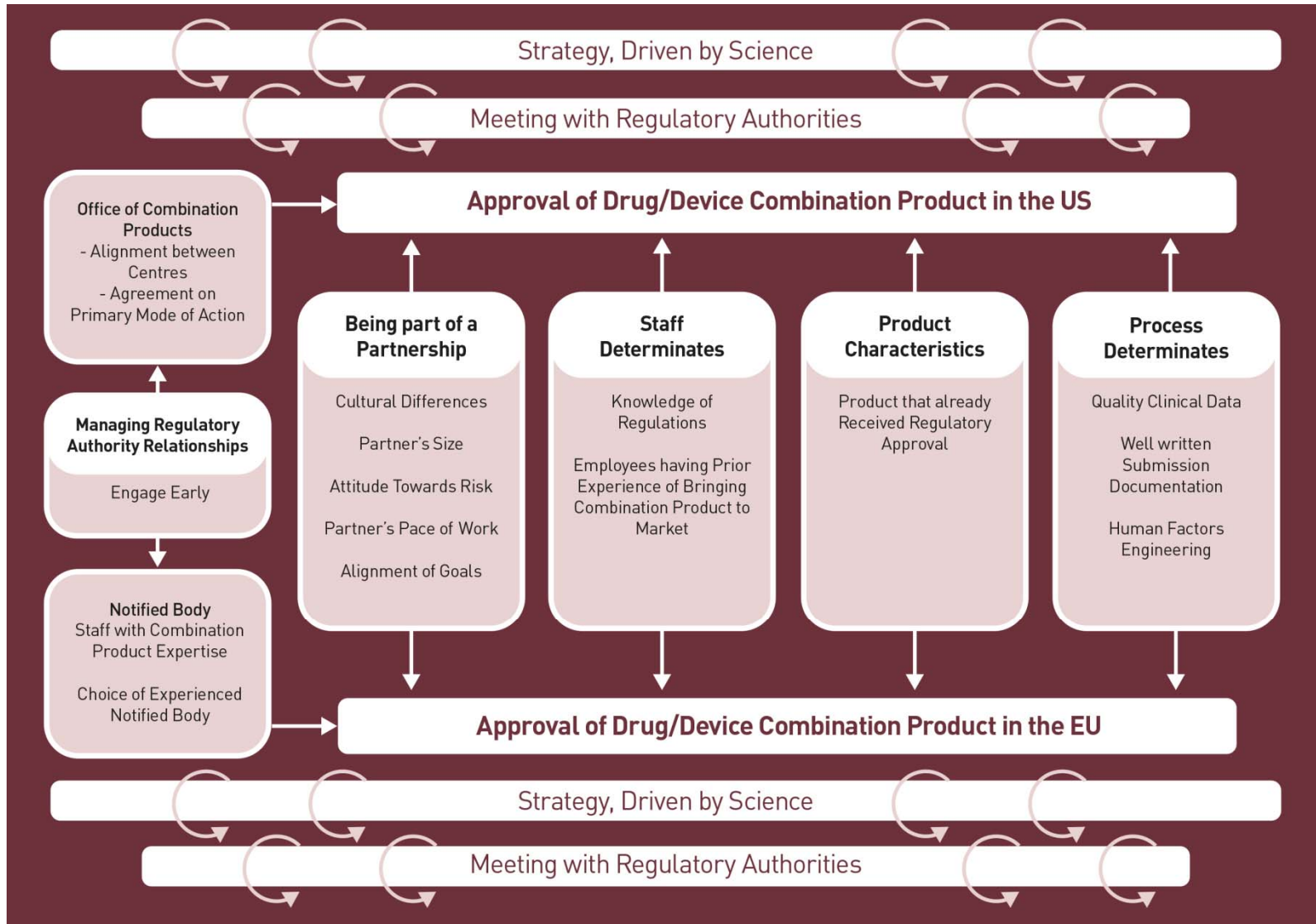
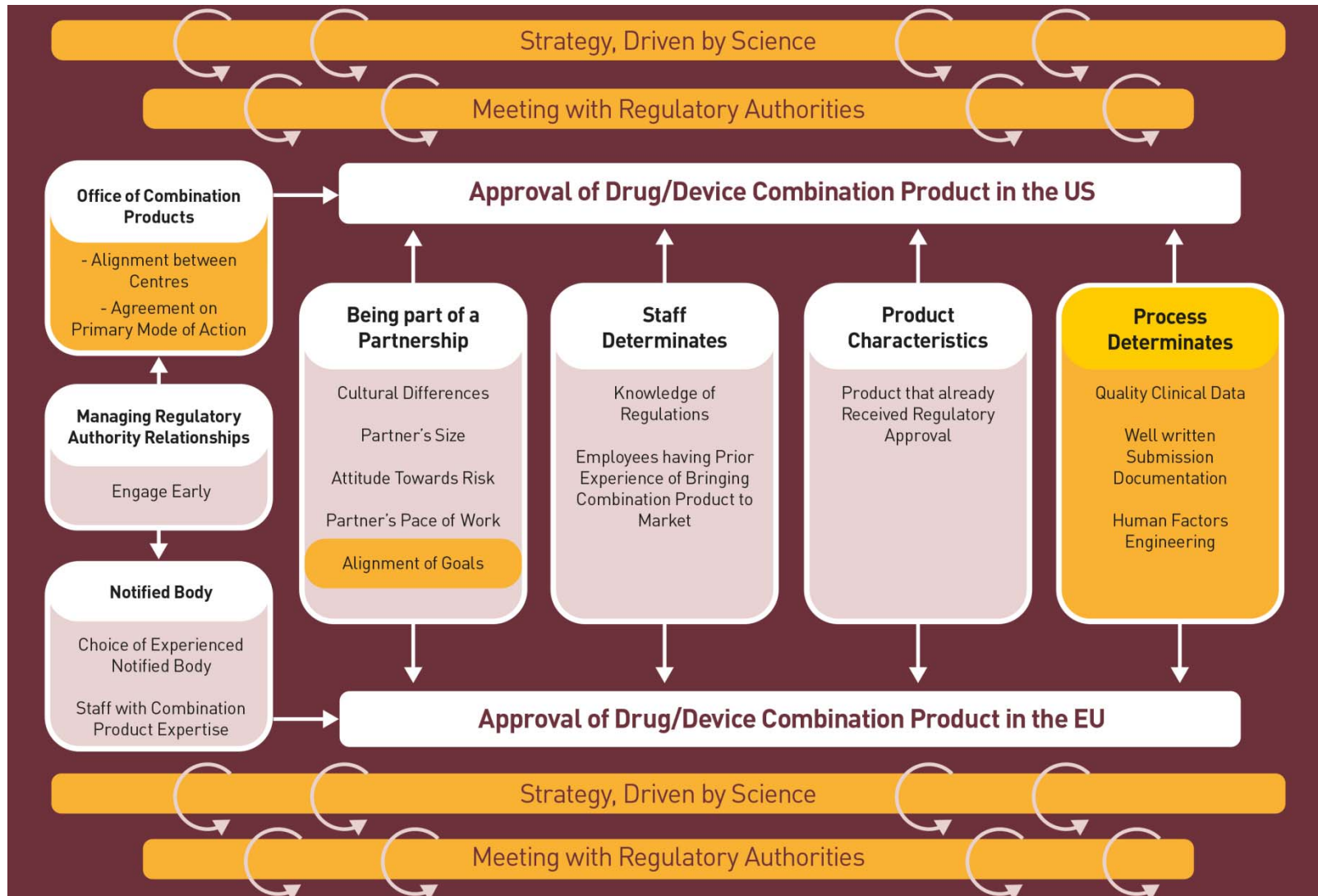


Figure 43 Revised Conceptual Model Indicating the Differences between the Initial and Second Conceptual Model of Factors that Facilitate Regulatory Approval for Drug/Device Combination Products in the EU and US



The surveys participants suggested cited the relationship between the Notified Body and Competent Authority frequently with respect to the EU context. Respondents commented that the chosen Notified Body needs to have a good working relationship with the drug agencies (i.e., the component authorities). As Chapter 2 discussed, obtaining a CE mark for a drug-device combination product requires consultation with one of the European drug agencies; the comment that using a Notified Body that has experience with this procedure is beneficial reflects this requirement. Another survey participant described the possibility of requesting scientific advice from the European Medicines Agency for any medicinal product for use in humans, at any stage of development and irrespective of whether the product is eligible for the centralised procedure. The Committee for Medicinal Products for Human Use (CHMP) provides scientific advice via the Scientific Advice Working Party (SAWP), a standing working party established under the CHMP with the sole remit of providing scientific advice to companies. One respondent observed that the consultation with the selected medicines Competent Authority is probably the longest component in the EU process and is managed by the Notified Body not the company, so interactions are limited. This finding highlighting the importance of these interactions between notified bodies and competent authorities aligns with media attention to European regulatory agencies in recent years (Enriquez, 2015, Cohen, 2012a, Campillo-Artero, 2013).

Survey respondents (95%) agreed with the interviews respondents that having regulatory knowledge and experience when bringing a product to market was extremely important or very important. These findings are consistent with those reported in previous studies on the topic, such as those of Fitzgerald (2011), Gispén-de Wied and Leufkens (2013) and Slikker et al. (2012). Survey respondents noted that it is particularly important to have a knowledgeable person involved in the product development team. One respondent said, “understanding all of the requirements is necessary for efficient and cost effective product development, preclinical, clinical, manufacturing activities to reach commercialisation.” Luk and Junnarkar’s (2013) conclusions in their review of the critical challenges to the design of drug-eluting medical devices, which state that companies need to bring together an experienced team of product developers with diverse competencies early on in development, concur with this comment. They outlined how such diverse teams can help companies anticipate and proactively resolve any foreseeable misalignment in technical, quality, and regulatory practices related to the drug–device interface. They go on to say that without such a diverse team,

misalignments will be ignored and key failure modes will be missed until late in development, causing undue delays to design validation and product approval. Survey responses also corroborate Hourd and Williams's findings (2008) that investment in strong personnel resources contributed to success for UK medical-device enterprises. Similarly, in a review of the management of the drug discovery/development interface, Kennedy (1997) states that a good project teams play a critical role in early drug development, stating that the involvement of key discovery scientists as active participants is essential. A close involvement of the core development strategy groups with the discovery groups in the predevelopment and post market submission facilitates transitions (Kennedy, 1997).

Next the factors that came up in the survey open responses that did not appear in the interview phase are considered. The biggest differences between the interviews findings were in the answer to the survey open-response questions. The open response category identified having strong clinical data, knowing the primary mode of action, comprehensive documentation, and human factors engineering as important aspects of achieving success, none of which the interviewees identified.

17% of survey respondents described having strong clinical data as important in navigating US regulation while 24% considered it important with respect to EU processes. One open response in the survey said "High quality clinical data (statistical significant positive clinical data) ... our reviewers are scientists that base their decisions on data analysis. So back up your claims with quality data!" Interviews respondents did not mention this factor at all, but others' research concurs that poor clinical data can be a significant problem when trying to get approval for a new medical product (O'Grady, 2009, Schneider and Schaffner-Dallmann, 2008). Schneider and Schaffner-Dallmann emphasize this fact in relation to marketing authorization applications for biotechnological products in the EU in particular.

In open responses, 5% of survey respondents distinguished knowing the Premarket Market Approval (PMA) in seeking approval through US processes, although no respondents mentioned it in relation to EU processes. As interviewees mentioned, it is crucial to be able to answer these questions: (1) what is my product intended to do? And (2) through what means can the intended use be primarily achieved? To answer the first question, you need to identify

the claim or the intended use. Is it to diagnose, cure, mitigate, treat or prevent a certain disease or condition? The next step will be to identify the “primary mode of action” (PMOA) for your product to achieve such a result. This determination has a large impact on the regulatory pathway of the drug/device combination product, determining the product’s classification and attending regulatory requirements. Others’ research also emphasize the importance of determining the primary mode of action of a drug/device combination process and getting agreement with the FDA (Foote and Berlin, 2005, Costa et al., 2010).

As Foote and Berlin (2005) emphasize, “issues about the consistency, predictability, and transparency of the process used to assign an FDA Centre with primary responsibility for review and regulation”. Waters (2011) also discuss the problem with drug/device combination product classification, reporting that a former FDA official who oversaw combination product regulation in the United States said that many developers push to have their combination products evaluated by the FDA’s Centre for Devices and Radiological Health. The reason for this was that the device centre often sets a lower bar for approval than the Centre for Drug Evaluation and Research or the biologics equivalent. Waters quotes the official as saying, “It puts the agency in a really difficult place” (Waters 2011, p.1024). In their open responses 13% amount of people stated this is the most important factor in regulatory processes. Waters further states that this variability in regulation and ultimate approval presents an opportunity for sponsors to game the system. In the interview phase of this research project this was exemplified by an interviewee. He discussed how if a product is preloaded it would be in a higher class rather than if the surgeon loaded it in the hospital. This was a strategic decision made by the CEO.

Another factor not mentioned in the interview stage was having comprehensive documentation. Survey respondents mentioned this in relation to both the EU and US regulatory environments. Respondents describe the importance of well written documentation. As a drug/device combination product proceeds from pre-clinical to clinical studies to approval, there is associated regulatory documentation at each step, as outlined in Chapter 2. These results support other scholars’ findings that regulatory writing must be comprehensive and scientifically accurate (Wood and Foote, 2009, Schindler, 2015, Morley, 2014, Modali, 2014).



Another factor mentioned in surveys, but not interviews, was human factor validation. Some combination products are designed for self administration (e.g. autoinjectors, pen injectors, inhalation products and pre-filled syringes, etc.), and 59.4% of the survey respondents referenced their involvement with such a product, so it is not surprising that they described the complexity of managing human factors in relation to products. One survey respondent commented: “New drugs, especially biologics have higher volume dosages and higher viscosities, which often impact user experience. For example with the above variables, it might be very hard for the patient to inject anything in the body or inject a partial dose, which can bring the efficacy of the drug down”. One survey respondent described the importance of “US based Human Factor data”. Responses such as these suggest that human factors should be considered early in the design process, and methodical analysis and testing ought to be carried out right through all the development stages and involve participants from the end-user population. Some respondents described how drug/device combination product usability frequently takes centre stage later in the process and is frequently the bottle-neck for acquiring marketing approval. They described how manufacturers who only summarize the outcomes of their usability validation study will be met with requests for additional document submission. This factor only came up in relation to US regulatory processes, not EU processes, a finding not explained by differences in the systems. Others’ findings affirm the importance of human factors in relation to combination products. Combination products are unique in that their safety profile and product efficacy often depends on user interaction (Elphick et al., 2015). For example for dosing devices, problems that occur including inappropriate device for the drug product, related to drug viscosity, dosing, or patient population (Pritchard, 2015, Elphick et al., 2015).

Survey findings support the views of Towns (2014). This study describes the recent focus across U.S. Food and Drug Administration centres, offices, and divisions on issuing new draft guidance outlining expectations in the execution and reporting of usability testing. It provides insight into how the new guidance has been put into practice in the development and review of Injectable combination products, and identifies some of the unwritten recommendations/expectations that have been gleaned from these regulatory interactions (Towns, 2014). Both research findings and the CDRH databases suggest that human factors are not getting the attention that it requires as part of the product development process. This deficiency could allow errors that have the possibility for patient injury or even death. Another

recent article highlights the importance of human factors for drug/device combination products (Edwards et al., 2015).

There is some discussion in the literature about inhalation products and human factors engineering (Lastow, 2015). The development of any inhalation product that does not consider patient needs will fail. The needs of the patients must be identified and aligned with engineering options and physical laws to achieve a robust and intuitive-to-use inhaler. A close interaction between development disciplines and real-use evaluations in clinical studies or in human factor studies is suggested. The same holds true when a marketed product needs to be changed (Leiner et al., 2015). Caution is warranted if a change to an inhaler leads to a change in the way the patient handles the device. Finally, the article points out potential problems if many inhaler designs are available, which may confuse patients and create a risk when patients cannot recall how to handle different inhalers (Leiner et al., 2015, Lastow, 2015).

Another human factor consists of needle-stick injury when using prefilled syringes (a growing market as discussed in Chapter 1) (Robinson et al., 2014, Guerlain et al., 2010, Schwirtz and Seeger, 2010). A total of 59 published cases of needle-stick injury were reported in the United States between 1985 and 2009 (Simons et al., 2009). A review of the hazards of unintentional injection of adrenaline from auto-injectors concluded that the number of occurrence of unintentional injection is most likely rising (Guerlain et al., 2010).

Because of the rising instances of UI-induced adverse events, the FDA has begun to include HF/UE reviews as a routine part of their pre-market approval process at the Center for Devices and Radiological Health. This process is described in a draft guidance issued in June 2011 entitled ‘Applying human factors and usability engineering to optimize medical device design’. The international regulatory community has also incorporated IEC 62366, Medical devices – Application of usability engineering to medical devices, as a part of the approval process outside the United States. Both the FDA HF/UE guidance and IEC 62366 outline a process including activities throughout device development culminating in validation testing with the final UI design in simulated use environments.

Interviewees emphasized the importance of managing regulatory relationships, including advocating early engagement both with notified bodies and the office of combination respondents. Survey respondents concurred. Opened ended questions reinforced these findings, particularly in relation to EU regulatory processes, with 30% of respondents mentioning the management of regulatory relationships (compared to 20% for US processes). This finding supports the views of researchers such as Kulkarni (2011), Bidault and Cummings (1994) and Feigal, Tsokas et al. (2012). These researchers have commented that effective interaction between key stakeholders like regulatory authorities is central to successfully navigating the regulatory process (Feigal et al., 2012, Kulkarni, 2011, Bidault and Cummings, 1994). The distinction between perceptions of the importance of this factor for US and EU processes may reflect the number of different regulators involved with combination products in the European Union as compared to the centralised body in the United States. Interviews emphasized the role of the Notified Body over the roles of the different authorities, such as the Competent Authorities and the European Medicines Agencies.

The term “alignment” came up frequently in the survey open responses, in relation to both EU and US regulatory authorities. A number of open responses mentioned the interrelationships between the different European regulatory agencies. One survey respondent indicated that the most important thing is to you get alignment between the manufacturer, the Notified Body and the Competent Authority . Pointing out that these three entities typically have different backgrounds he indicated they need to be “aligned”. A number of survey respondents describing the US regulatory authority also mentioned alignment, saying it is necessary to ensure alignment between Center for Drug Evaluation and Research, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research and the Office of Combination Products (13%). These results resemble findings by Feigal et al. (2012) that effective interaction between key stakeholders and the FDA is central to successfully navigating the regulatory process and advancing new cell-based therapies into clinical trials, suggesting this insight is applicable to drug/device combination products.

Some respondents commented that correct jurisdictional determination of the lead centre is key in the US regulatory process. In their examination of transdermal patches and drug-eluting stents case studies regarding what obstacles do this product types encounter as a result

of them being combination products, Couto. et al. (2012) concur with these assertions. Their analysis found that the biggest obstacle to introducing a novel combination products is the determination of the regulatory centre that is to oversee its approval. Respondents also commented that the first product of a new type of combination products presents a learning opportunity for the regulator and the sponsor. The uncertainty about the entire class of combination products is considerably reduced once the first product is approved and the leading regulatory centre is determined. The sponsor pioneering a new type of class combination products has a pivotal position in reducing this uncertainty by advising of the decision on the primary function of the combination product. The research also proposes that this decision has a significant impact on the type (pharmaceutical, biotechnology, or medical devices) of the companies that will lead the introduction of these products into the market. This discussion on alignment is further described by this open response:

There is not 100% consistency across the Divisions at FDA despite the regulations and guidance. Requirements may differ depending on the maturity of the therapeutic area in terms of types and number of approved products, the evolution [of the] FDA's thinking about specific products, indications and therapeutic areas over time, the benefit risk question in relation to the disease state and available products, opinion of the Division Director, etc.

Prior research has not distinguished regulatory strategy as critical in the process (see for example Couto et al. 2012). These findings support the observations of Gryziewicz (2005) who describes the experience of developing an ocular drug/device combination product for the purpose of delivering a drug into the retina. They describe the coordination required between the FDA Divisions responsible for each facet of the product in the regulatory process, and the increased difficulty this imposes on sponsor companies in determining who is primarily responsible for the review of their application. Their sponsor had to seek to convince reviewers from two centres within FDA to exchange information on their review and the status of their review. As they describe, such reviews can add considerable time to the FDA review and approval process. Reviewers from both centres must be involved from the start of the development process; the researchers say this is critical.. All of the reviewers feedback are reviewed and included into the product development strategy. They describe how a device company will often work closely with CDRH staff to develop a drug/device combination product, only to learn at the application review stage that the consultation by the CDRH reviewer with CDER brings up new issues that could have been incorporated into the

clinical study design. This clearly demonstrates that early communication with the FDA during the product development process, in accordance with the comments of survey respondents. They advocate that assuring that representatives from both Review Divisions are present at FDA Sponsor meetings facilitates the detection and debate of issues early in the process (Gryziewicz, 2005).

Respondents also said that meetings at all stages in development can be beneficial in moving a product and an application forward. They can be particularly helpful for new chemical entities, novel indications for unmet medical needs, orphan drug products, and biologics, where the regulatory pathway is uncharted and/or aspects of the clinical program (e.g., efficacy endpoints) are uncertain. In contrast, presubmission meetings focus on providing sponsors the opportunity to ask questions regarding the content and format of their upcoming New Drug Application/Biologics License Application submission, providing FDA with an opportunity to see the final pivotal study data prior to receiving the application, and allowing dialog regarding any major barriers to application filing.

Survey respondents' comments support the findings of Vu and Pariser (2015). This study showed that during financial year 2008 – 2012, applications that included a pre-IND meeting during development (n=49) had shorter clinical development times (median = 6.4 years) than applications (n=83) that did not have a Pre-Investigational New Drug meeting (median = 8.3 years). Booz Allen Hamilton (2010) likewise found that that during financial year 2002 – 2004, end-of-phase 2 (EOP2) meetings had a positive impact on first-cycle approval rates. Of 46 products with EOP2 meetings, 52% received first-cycle approval. Only 29% of the 21 products submitted during these years received first-cycle approval when an EOP2 meeting was skipped (Booz, Allen & Hamilton, 2010). The FDA have developed a guidance document regarding how these meetings operate and how to get the maximum out of them (FDA, 2009b).

Respondents commented that staff should be knowledgeable about regulations and technical aspects of their device. Some drug firms may only have experience with FDA device or pharmaceutical submissions, so they require people complementary technical expertise, which they may look for in the form of consultants, new hires, or partnerships with other

forms. It seems likely that the 13.3% of survey respondents who are consultants fill this need often.

In relation to partnerships, the interview phase of the research described the importance of the attitude towards, risk, the size of the partners, and the culture of the different partners. Survey respondents concurred with respect to all of these factors, with 51.28% considering the impact of cultural differences between partners, as very important and extremely important, 20.51% considering the impact of working with partners of difference sizes as very or extremely important, 60.9% considering the impact of the different partners' attitudes towards risk very or extremely important, and 57.05% considering the pace of work of the different partners very or extremely important.

The open ended question revealed some interesting comments with respect to what's important in partnership. 'Alignment of goals' (20%) was the largest category among open responses, followed by 'understanding of cultural values' (10%). 'Having a collaborative relationship' (10%), 'working with an experienced partner' (9%) and 'having trust in the partnership' (9%) also appeared on survey responses. When asked to describe the most critical factor for successful partnerships involving companies bringing a drug/device combination product to market, 20% of respondents stated that alignment of goals was the most important factor.

The fourth theme that interviews identified was that drug/device combination products consisting of products that have already received regulatory approval experience an easier regulatory process. Approval of individual components provides regulatory authorities with the assurance of safety and efficacy of each individual component; sponsors much therefore only prove that combining the two confers a significant benefit. The cross tab of component approval status and product type revealed that prefilled syringes had the least amount of components approved. But a cross tab of regulatory approval status versus development stage revealed that they encompass all areas, indicating that combining products that have been previously on the market does not impact getting the product approved.

This chapter addressed research question 3 using cross tabulations were constructed in SPSS: Are there are there differing perceptions across organisations types, annual sales and number of employees regarding the different facilitating factors for obtaining regulatory approval in the European Union and United States?

The first relationship considered was that of the importance of early engagement with notified bodies and the organisation type, annual sales, and number of employees. The results show that organisations types and sizes do not correlate with different perceptions of the facilitating factors for obtaining regulatory approval in the European Union or United States, except that 60% of Contract Research Organisations (CROs) emphasized early engagement with the office of combination products, more than other organisation types. CROs offer clinical trial and other research support services for the medical device, pharmaceutical, and biotechnology industries as well as universities and government institutions (Maloff, 1999). Organizations and businesses that contract with CROs do so to acquire specific expertise without hiring permanent staff. Some CROs manage almost all aspects of a clinical trial, from site selection and patient enrolment through final regulatory approval from the Food and Drug Administration and European Medicines Agency. Often CROs work with a variety of different product types which also adds to their level of experience of dealing with the FDA. It seems likely that the experience level of CRO staff drives their emphasis on early engagement.

The second relationship investigated using cross tabulations was that between the importance of partnerships and the organisation type, annual sales and number of employees. Perceptions across organisations types and sizes and the importance of partnerships overall do not differ, although respondents who worked in smaller companies (1-10 employees) were more likely to emphasise partnerships. This finding likely reflects the limited resources of small companies.

The third relationship investigated using cross tabulations was that between the importance of the characteristics of the organisation's staff and with the organisation type, annual sales and

number of employees. The results did not show a difference across organisations or types and sizes.

The fourth relationship investigated using cross tabulations was that between the importance of the components having regulatory approval prior to inclusion in the drug/device combination product with the organisation type, annual sales, and number of employees. The results did not show a difference across organisations types and sizes.

## **6.7 Conclusions**

The chapter presents and analyses the findings of the online survey using Excel, SPSS, and NVivo 10. The online survey explored in a larger sample the factors identified in the interviews that have an impact on obtaining regulatory approval of drug/device combination products in, jointly and severally, the European Union and the United States. The survey results were used to ascertain whether the findings contradicted, confirmed, or complemented the findings of the research interviews. Research questions 2, 3 and 4 were answered here.

Firstly in this chapter, the sample demographics were reported. Descriptive statistics were used to display the demographic information. The analysis of the sample demographics showed that the data was collected from appropriate respondents. Respondents were in senior positions in their organisations and/or had significant experience with drug/device combination products. They also had experience with a large variety of drug/device combination product types. Respondents worked in medical device, pharmaceutical, biopharmaceutical, and biotechnology companies. These types of companies represent types that are involved with drug/device combination products.

The size of survey respondents' employers reflects the range of size of companies in the life sciences sector, including everything from micro-entities to large organisations. The sample was also representative of a large variety of drug/device product categories. A marginally larger portion of the sample has experience of the US regulatory system for drug/device



combination products than the EU system. An interesting finding is that, among the devices respondents thought of, as per the direction of the survey, the product stages were distributed across the stages of development. This demonstrates that it a very active space, suggesting predictions that this is a growth area within the medical technology market are accurate (Transparency Market Research, 2015).

Overall, survey findings resembled interview findings, indicating that the management of regulatory relationships, being part of a partnership, having staff with specific traits, and having products with certain product characteristics are important. The respondents were asked specifically about each of these factors, indicating the importance of each of these factors. Not only did it deem them important in the Likert questions but they were also mentioned again in the open responses. Opened ended questions give respondents the freedom offer details, including information the researcher did not foresee.

## **7 Final Conclusions and Recommendations**

*This chapter gives an overview of the research undertaken in this thesis. It provides reflections on the research process, outlines the study's main contributions to knowledge about the regulatory process for combination devices in both the European Union and the United States, and makes recommendations for future research.*

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### **7.1 Introduction**

This chapter concludes the research by tying together and synthesizing the insights of the foregoing chapters, as well as discussing the implications of these insights for future researchers. To this end, the chapter outline is as follows: Section 7.2 gives an overview of the research study. Section 7.3 describes how the research aims and objectives have been achieved. Section 7.4 outlines the key contributions made by this research. Section 7.5 presents the limitations of the study. Section 7.6 presents the recommendations for future research and further advancement based on the findings that have emerged.

### **7.2 Study Overview**

This study has employed an exploratory sequential mixed methods design (Chapter 3) using a mixture of qualitative and quantitative techniques (Figure 1) to gain a deep understanding of the facilitating factors organisations use to obtain regulatory approval of drug/device combination products. Qualitative methods drove the study, with rich information gathered from in-depth, face to face interviews with leaders in the chosen organisations augmented by a quantitative approach (Chapter 6). A survey of a larger sample of similarly situated workers, sought to clarify the themes interviewees identified and capture a broader industry perspective (Chapter 6). A conceptual model was developed to organise the identified facilitating factors that emerged from the interviews (Figure 9), firstly from the interviews and then augmented with the qualitative results (Figure 43).

The approach taken in the study had the aim of eliciting the experiences of industry professionals with firsthand knowledge of the drug/device regulatory frameworks with the processes in both the European Union and the United States, embedding their experiences in a conceptual model that other industry professionals can utilise. The stories professionals shared will inform others working in this area and thereby help bring potentially life changing products to patients. It will also lay a foundation for further research, which currently is lacking in this area (as Chapter 3's review of the literature sets out).

Drug/device combination products combine two or more single-entity products. They include drugs combined with medical devices, drugs combined with biologics, and medical devices combined with both a drug and a biologic. Drug/device combination products are unusual from a regulatory point of view, as they include products that originate in the pharmaceutical, biopharmaceutical, biotechnology, and medical device sectors, which differ conventionally. Because of this, combination products do not fit into a single regulatory framework and they are thus more complex than average products in terms of determining the optimum regulatory pathways involved with getting them to market (Zenios, 2009, Chowdhury, 2014a).

A number of scholars have discussed the complexity and the long periods involved with bringing a novel life sciences product like a combination product from idea to marketplace. Few firms enter the area with the understanding of the regulatory issues and expertise they need to succeed (Mitri and Pittas, 2009, Kramer, 2007, Eselius et al., 2008, Juanola-Feliu et al., 2012). These papers, however, do not empirically test these assertions. By explicating individual experiences with the EU and US drug/device combination product regulatory frameworks, this research has sought to identify the factors that facilitate obtaining timely regulatory approval for drug/device combination products, to investigate the problem such research has identified and provide a remedy for firms newly entering the area.

This thesis consisted of seven chapters. Chapter 1 introduced the context of the research problem. It also outlined the rationale and motivations for the research. Chapter 2 summarizes the current legislation and regulatory framework relevant to combination products. Three product sectors interact in relation to the research questions: medicinal

products, medical devices, and processes specific to drug/device combination products. Chapter 3 discusses the literature concerning the factors that affect getting a drug/device combination product onto the market in the European Union and the United States. The literature has a significant gap regarding the overall understanding of how the regulatory frameworks in both jurisdictions treat drug/device combination products. Chapter 4 outlines the exploratory mixed method research methodology. It also explained the logic for this choice and its relevance to the research questions. Chapter 5 and Chapter 6 reported on the qualitative and the quantitative study respectively, including the integration of these two phases, and the development and evolution of the conceptual model. This final chapter presents the final conclusions and recommendations

### **7.3 General Conclusions in Relation to the Research Aim and Research Questions**

This thesis has explored the facilitating factors for obtaining regulatory approval of a drug/device combination product in the European Union and the United States, based on the understanding of professionals who interact with processes in these jurisdictions.

In summary Chapter 2 addressed the first research question: *what are the US and EU regulatory frameworks for drug/device combination products?* The goal of the chapter was to outline the legalisation and guidance documents that make up these regulatory frameworks, identify the regulatory agencies involved, and explicate the regulatory pathway to market for drug/device combination products. It therefore elucidated the concrete steps that bringing a drug/device combination products to market involves.

In agreement with a host of existing research, see for example Hamrell 2006, Grignolo 2013, and Edwards et al. 2015, the review found that drug/device combination product regulatory frameworks are complex. It also found, corroborating the finding of Jefferys (2005), that there are significant differences regarding how drug/device combination products are regulated in the European Union and US and the route to market for a drug device combination product is complex and not clear-cut in both regions. The complexity reflects in part the wide variety of items categorized as drug/device combination products. It would be hard to design a regulatory system that would meet the needs of all of the types of

combination products by providing a swift approval process while protecting users. Differences identified in Chapter 2 include the fact that the US legislation defines combination products, whereas the European Union has no such official definition. In Europe, drug/device combination products fall into a broad category of ‘borderline products’. The FDA provides guidance documents specifically for combination products, which the European Union does not. The US framework also includes the Office of Combination Products, an agency dedicated to defining regulatory paths for drug/device combination products, whereas the European Union has no such office. The EU framework regulates combination products as either medicinal products or medical devices, and provides no specific documents for these products.

Chapter 3 addressed research question number 2: *what does the literature say about the facilitating factors for obtaining regulatory approval of drug/device combination products in the European Union and United States?* This review identified a lack in the literature with respect to drug/device combination products regulations. No quantitative or qualitative studies have focused on drug/device combination products. Whereas researchers have addressed individual regulatory frameworks for medical device and medicinal products, including their impact on product safety, combination products’ relationship to regulatory frameworks remain underexplored. Most research related to drug/medical device regulatory processes have addressed the impact on the marketplace of medical device regulation in the United States or the safety of the EU medical device regulations. The literature that exists on drug/device combination products primarily focuses on the US regulatory system. Articles such as Lauritsen and Nguyen (2009) and Sweet, Schwemm et al. (2011) have focused on the factors that influence which FDA centre will take the lead when reviewing the product, a narrower focus than the current products undertakes.

Neither quantitative nor qualitative studies have addressed the regulatory process of drug/device combination products as a whole in either the United States or the European Union. Scholarly work on the individual regulatory frameworks typically involves commentary on the frameworks rather than investigations. There is a dearth of literature regarding manufacturer’s perceptions of their experience of the regulatory frameworks that govern combination products.

Chapters 5 addressed the research question 3, *what are the facilitating factors for obtaining regulatory approval in the European Union and/or the United States?* The qualitative phase of the study, depicted in Chapter 5, involved 19 semi-structured interviews with leaders in organisations that produce drug/device combination products (Table 6). Chapter 5 provides analysis of these interviews, highlighting the factors participants identified as facilitating regulatory approval of a drug/device combination product in the United States and/or the European Union. Four themes and seven subthemes emerged from the data.

Interview participants emphasised the importance of effective collaboration with partners involved with obtaining regulatory approval. These partners enable medical device manufacturers who do not have the resources to bring a complete drug/device combination product to market on their own to pursue the process, typically by partnering with a large pharmaceutical company that supplies the drug that is one of the components of the product. Bidault and Cummings (1994) and Kley and Kitney (2007) report similar findings about partnerships and their importance. The formation of partnerships in order to bring an innovative medical technology is reported as a common practice in the life sciences sector (Kleyn et al., 2007).

Interviewees also emphasized the importance of managing regulatory relationships. The majority of participants who have experience of the EU regulatory framework for drug/device combination products deemed the strategic selection of a Notified Body as critical. Participants also referenced prompt engagement and communication with regulators as an important strategy, something Wonder, Backhouse, et al. (2014) likewise identify. Similarly, participants experienced with the US process felt that companies wanting to enter into the US combination product market should engage early with the Office of Combination Products if they do not know the designation of their product, or engage early with the relevant FDA centre if they know the designation.

Research participants also highlighted in interviews the impact of the type of drug/device combination product on its likelihood of gaining regulatory approval. A subtheme that emerged suggested that classification of a combination product could be strategic, because certain types of drug/device combination products have more challenging requirements than

others. In the European Union, the medical regulations for a combination product classified as a medical device are less burdensome than those that govern medicinal products. Likewise, in the United States, if the combination product's primary mode of action is the drug, a combination product faces a more costly and lengthy route to approval than if its primary mode of action is the device part.

Interviewees also identified smart leveraging of existing technology as a strategy to employ, part of an overall feeling that experience with regulatory processes confers an advantage. This finding mirrors those of Abraham and Davis (2007), which is that such expertise is critical for developers of innovative biomedical technology, a category that includes some drug/device combination products.

The researcher used the results from the interview phase of research as input to develop a quantitative survey. Chapter 6 reports the results of this survey, which used a larger sample of professionals knowledgeable about regulatory processes for drug/device combination products to explore the factors identified in the interview phase as facilitating the approval process for drug/device combination products. Respondents were in senior positions in their organisations with significant experience with a variety of drug/device combination products. Overall, the survey corroborated the results of the qualitative phase. It also provided some new insights—facilitating factors not identified in the interview phase. As such, it provided a useful complement to the findings of the first phase of the study, and additional answers to the third research question, *what are the facilitating factors for obtaining regulatory approval in the European Union and/or the United States?*

Chapter 6 presents and analyses the findings of the online survey using Excel, SPSS and Nvivo. As described below, it addressed research questions 4, 4a and 4b.

Research question number 4 is: *does the survey corroborate the factors identified in the interviews?* Overall, the survey results corroborate the results of the interview phase. Questions were structured to elicit responses regarding the management of regulatory relationships, being part of a partnership, having staff with specific traits, and a product having certain product characteristics as the key elements to facilitate the regulatory process

for drug/device combination products. The respondents were asked to indicate the importance of each of these factors, and then provided answers to open-ended questions about which factors facilitate the regulatory process in both jurisdictions. In addition to collaborating the findings of the interview phase, surveys identified additional elements such as having strong clinical data supporting a product, the product's primary mode of action being chemical rather than mechanical, comprehensive documentation, and engineering well designed to address human factors.

Research question 4a was: ***are there differing perceptions across organisations types and sizes (by annual sales or number of employees) regarding the different facilitating factors for obtaining regulatory approval in either jurisdiction?*** Cross tabulations were constructed in SPSS to answer this question. Analysis of responses relating to the importance of early engagement with notified bodies showed minimal variation across organisation types and sizes. However 60% of respondents employed by Contract Research Organisations felt early engagement early with the Office of Combination Products in the United States had a determinative effect, more than respondents employed by other types of organisations. The same cross-tabulation was applied to the importance of partnerships. Here again, most respondents agreed about the importance of this factor. However employees of smaller companies (1-10 employees) were more likely to emphasise partnerships than employees of larger companies. The third factor investigated using cross tabulations was that of the importance of the characteristics of the organisation's staff. Here again, respondents across employer types and sizes agree about the importance of an organisation having staff with regulatory knowledge, but no noteworthy correlations appeared. The fourth factor investigated using cross tabulations related to the importance of the components having regulatory approval prior to inclusion in the drug/device combination product. Again, respondents across organisation types and sizes felt this was important, although employees of smaller companies were more likely to emphasise this factor.

Research question 4b asked, ***Are there significant relationships between organisation types, sizes, product type, market and obtaining regulatory approval in the European Union and the United States?*** Fisher's exact test was used to determine if there were significant relationships between organisation types, sizes, product type, market, and obtaining



regulatory approval in either jurisdiction. The results showed that there is no statistical significant difference between the proportion of companies receiving regulatory approval by revenue number of employees or organisation type. Product type and market, however, showed a significant difference. Drug delivery dominates combination products, specifically in the form of drug eluting stents. Pre-filled syringes also are a large group. These products were more likely to achieve regulatory approval than other types of products.

## **7.4 Main Contributions of Thesis**

The contributions of this research are threefold: contribution to theory, methodology, policy, and practice.

### **7.4.1 Theoretical Contribution**

A conceptual model was developed that depicted the facilitating factors for obtaining regulatory approval of a drug/device combination product, relevant to the European Union and United States systems, respectively. This model provides, for the first time, a comprehensive understanding of these factors, providing a foundation that could be adapted to reflect specific drug/device combination products.

Current literature acknowledges that developing and commercialising combination products is a uniquely challenging process (Zenios, 2009, Pietzsch and Paté-Cornell, 2008). However, it does not explore the process. No study available reports on the experiences of companies who have been successful in navigating the regulatory process. The current study addresses this gap.

### **7.4.2 Contribution to Methodology**

The procedures used to answer the research questions and achieve its goals and objectives constitute a contribution to the literature. The methodology used is described as an exploratory sequential design which could be applied to develop a model for facilitating factors for other types of life science product groups. Researchers investigating other regulatory frameworks might adapt the method—starting with the review of the regulation,

then a review of the literature, followed by an application of the research procedures until enough data has been collected—to suit their own purposes.

Scholarship increasingly recognises the advantages of mixed methods research. In particular, combining quantitative and qualitative research enables evaluation researchers to be flexible and holistic in their investigative techniques, as they endeavour to address a range of complex research questions that arise (Tashakkori and Teddlie, 2010). This study has shown how methods can be effectively combined to obtain valuable information from professionals. This research demonstrated originality of approach in interviewing thought leaders in the life sciences sector as well as conducting a survey that spans two of the largest jurisdictions for drug/device combination products in the world.

### **7.4.3 Policy Contribution**

Policy makers can use the research as a reference for developing regulation for innovative products in general and drug/device combination products specifically. By analysing users' experiences of regulations, the thesis provides useful information for reform and development of new processes. Policy developed based on its findings will ultimately improve regulatory environments, easing speed to market without compromising user safety.

### **7.4.4 Contribution to Practice**

People who partook in this research are not inclined to freely share information, thus the information gleaned from the research is noteworthy. Convincing leaders in companies that have brought new novel medical technologies to market to divulge their firsthand experiences of the regulatory process is unusual, because the medical technology sector is highly secretive. Drug/device combination products are a relatively small product group, and a small pool of people have firsthand experience of the process. By interviewing and surveying senior personnel in a highly competitive sector of the life sciences industry, the project provides a significant research contribution, and the applied nature of this research provides life science professionals with strategies and an implementation framework that can be

immediately translated to practice, aiding organisations in obtaining regulatory approval for combination product.

The remainder of this section will detail the practical implications of the findings relevant to five stakeholder groups—senior managers, life sciences entrepreneurs, investors, regulatory managers, and medical personnel. These groups can use the conceptual model to see where they should focus when seeking to obtain regulatory approval of a drug/device combination product. Regulators will benefit from this research as it shines a light on the experiences of other stakeholders in the regulatory process.

The study shows stakeholders that it is important to communicate early with regulatory bodies. This includes determining product jurisdiction and identifying the critical requirements for approval as early as possible. Stakeholders should understand all of the evolving requirements, and prepare a supportable position. Understanding regulatory nuances relevant to the product early in the process constitutes a distinct advantage.

### **Important Insights for Manufacturing Companies Seeking Approval**

#### ***Findings Specific to US Authorities***

If a company is seeking regulatory approval for the US market, therefore, it is important to develop a good working relationship with the FDA. Managers need to contact the Office of Combination Products at the beginning of the development stage. They should discuss their idea for the drug/device combination product and work with the FDA from the beginning. All stakeholders should seek early input from the FDA, as late surprises can derail development.

Companies should have a clear understanding of which FDA Office has primary jurisdiction over their product and should engage all involved parties in the planning stages, especially for non-clinical and clinical testing. Significantly, most FDA reviewers do not have experience with combination products. Drug division reviewers do not understand devices. Therefore, it is imperative to get alignment between DER, CDRH, CBER and OCP and to determine the cross-centre consult activity. Meeting with FDA CDER early and asking them to consult CRDH—or meeting with CRDH early and asking them to consult FDA CDER has a powerful effect. Working with the division that will ultimately approve the device and getting them to rule on how the product will be reviewed and approved is imperative. This

ensures alignment of expectations and thinking, and minimizes surprises. Being aware of the expectations of the agencies, which can differ, early on eases the process later. Such pre-submission regulatory planning allows companies to develop appropriate data and strategy. Stakeholders need to understand who will be reviewing their submission and ensure that they explain in a way that they will understand.

### ***Findings Specific to European Authorities***

Choosing a Notified Body that has a good relationship with a Competent Authority who has experience in regulation of the drug component is vital. Similarly, a good working relationship with Notified Bodies is crucial. This begins with choosing the Notified Body wisely. Things to consider include: Has the Notified Body approved drug/device combination products in the past? Has it approved combination products that are related to my product? Has it worked with Competent Authorities that have worked with combination products in the past, and how good is that relationship? Research suggests that some organisations might benefit from hiring a consultant with expertise in these questions.

For a device-centric company, the drug submission documentation can be daunting. It is critically important to identify requirements of this submission early so that the company can undertake appropriate testing, clinical investigation etc. to demonstrate safety and performance. The Competent Authority piece is critical here as well. The Notified Body must agree with the manufacturer's approach prior to discussions with the Competent Authority.

Pre-submission meetings are critical to ensure that Notified Bodies agree in principle on the clinical study, DV testing, and stability programs, among others. Notified Bodies cannot act as consultants, but discussing a product with these entities nonetheless avoids surprises later in the regulatory process.

Consultation with the Competent Authority designated to the drug portion of the product is probably the longest component of the EU process. The Notified Body manages this component, and the manufacturer has minimal involvement. It is essential to have a good first submission to the Competent Authority, as subsequent questions may delay or prevent the approval or create significant cost constraints at a late stage in the development. The fact that

Notified Bodies may take the opinion of the Competent Authorities verbatim makes this particularly significant.

### ***Human Factors in Relation to Regulatory Approval***

This study calls attention to the importance of human factors in relation to combination products. Manufacturers who address this too late in the process may not be able to obtain regulatory approval or to do so with the speed they require. The comments of participants suggest an experienced consultant may be necessary to address this issue. Participants emphasise that for the US environment in particular, demonstrating that the target group of US patients can use the device is a key focus; providing formative and summative studies helps consultants navigate this aspect.

### ***The Importance of Clinical Data***

Results support the common sense assumption that companies need to have an adequately designed and executed clinical trial to achieve regulatory approval of a drug/device combination product. While the component separately may have a known safety and/or efficacy profile, the combination often does not. By its nature, the combination almost always presents a higher risk. Clinical trials require the right technical personnel to design studies to provide the data the regulatory agencies will require, including quality clinical data as well as statistically significant positive clinical data providing convincing evidence of safety and efficacy that support a positive benefit/risk ratio for patients. Manufacturers must be prepared to provide objective evidence specific to the combination and interplay of components for intended use, to explain how changes in the drug-device configuration will make it adequate for commercial purposes (such as scale-up for manufacturing.). They must be able to clarify the activity and contribution of every component, and to explain each in the context of the combination..

### ***The Role of Product Characteristics***

The findings of this study reveal that it is considerably easier to obtain approval for a combination product when all of the components have been approved separately in the past. Participants describe shorter review times, easier testing hurdles, and other advantages.

The US environment has a special process for products with a predicate, called the 510(k) route. This can make the regulatory process very quick i.e. will typically take less than 6 months. By contrast, a product with only new components must take the De Novo process, which can be very lengthy—a matter of years. This is very expensive. Study results suggest that biocompatibility is one of the most rigidly evaluated areas in both environments.

### ***The Importance of Regulatory Writing***

Findings emphasize the importance of a well written description of the most essential elements of the product. Documents that reflect missing knowledge or a failure to provide an overview of the product incur additional questions and discussions that slow the process. It is therefore important for a manufacturer to possess appropriate technical writing skills. From a device perspective, it is important to be able to demonstrate that there is a plan for the development which will meet the necessary requirements and guidelines whilst also addressing any potential risks. All of the development studies do not have to be completed before IND (early clinical trials), but it is necessary to demonstrate that all of the development studies, including studies of biocompatibility, extractables, human factors and usability as well as stability will be completed before submission. In most cases one element of the product is predominantly responsible for efficacy and/or safety, it is particularly important to describe this element thoroughly, as it has the greatest impact on the approval decision.

### ***Staffing Factors and Partnerships***

Organisations seeking to bring a drug/device combination product to market should ensure that their regulatory staff is knowledgeable. Regulatory qualifications, such as degrees in regulatory affairs and membership in professional regulatory associations suggest the right level of knowledge. Managers should also encourage staff to attend regulatory conferences in

order to keep abreast with the latest changes in the regulations and meet with other regulatory professionals, in essence, for a community of practice.

In the case of two companies partnering to bring a drug/device combination product to market, the two companies can partner to bring the correct personnel to bear. This brings other complications, however, according to the study. However, it seems likely that partnerships will continue to be necessary, since growth in the combination product group has not yet led to convergence in the educational sector, and training in science and engineering has not been integrated. In this environment, cultural barriers will persist.

To remedy the problem of cultural barriers participants suggest that companies should agree on company values at the outset to avoid any misunderstandings, and understand one another's tolerance for risk. Participants emphasise the need to adopt a culture of openness, good communication, and integrity between both parties. Partners must include relevant signatories on the review of all major documents to ensure clear communication at all times about all decisions that are technical in nature or could affect product quality, efficacy, and safety. Participants also describe the need for both partners to have a clear understanding of skillsets of both organisations and the pace of work of both organisations. They must have shared goals for the product and alignment on the path to obtaining approval.

### ***Special Concerns for Small Companies Partnering with Larger Companies***

Participants urge employees of small companies to be aware that larger companies can take a different approach to pacing their work and tolerating risk than they may take. Small companies have much more at stake with a single product and therefore are likely to be more aggressive in development and pay more attention to the product. Larger companies are more risk adverse but each product has less impact on their future. Participants say that partnerships between large companies and smaller companies can lead to conflict as innovators employed by smaller companies feel unheard. The smaller company needs to be comfortable that it won't be discarded at a moment's notice and the larger company needs to be confident that the smaller company will perform as expected. If a smaller company's lack confidence in interact with a regulatory agency, however, partnering with a larger company may aid the early engagement that participants identify as crucial.

### ***Special Concerns for Medical Device Companies Partnering with Pharmaceutical Companies***

Pharmaceutical chemists and device engineers are trained differently, so partnerships between companies of these types must cross train and problem solve outside their established modes of interaction. According to participants, the most important thing that companies can do entering into such partnerships is build trust so that differences do not become an obstacle to effective partnership. Pharmaceutical companies have rapidly changing portfolio priorities, which makes it difficult for them to commit to complicated combination products. Effective partnership for such products requires ensuring a long term commitment by pharmaceutical funders.

### ***Crucial Insights for Regulators***

Findings suggest that manufacturers of combination products experience roadblocks in anticipating cross-centre consult activity, and that clarifying this early in the process would significantly smooth processes. They also suggest that reviewers should increase their knowledge of products combination products and that in the European context; Notified bodies should ensure that they have a good relationship with Competent Authorities. Overall, more guidance documents need to be written to relate to combination products.

Participants suggest that regulators should encourage manufacturers to meet with them during the process. The European commission are proposing to increase the number of opportunities for these meetings, and study findings suggest these should be taken up so that manufacturers can answer expert group questions prior to submission of regulatory documents. Findings suggest that insights such as these can vastly improve the regulatory process without in any way compromising its efficacy in protecting the public from harm.



## 7.5 Limitations

The research has a number of limitations;

- The first limitation is that the sample is not strictly representative of all the organisations bringing a combination product to the market. Due to the variety of companies involved in this area it was not feasible to develop a sampling frame that would be representative of the entire population of such organisations. However this limitation has been mitigated by the in-depth nature of the investigation. Participants in both phases of the study are information rich and brought vast experience of the processes the study sought to explore; interviewees in particular are thought leaders and subject matter experts in their individual fields of expertise. However, in further studies, subsets of the population could be explored and an appropriate sampling frame could then be developed.
- The second limitation of not being able to use a sampling frame is that this study data is from a non probability sampling method and therefore findings cannot be considered widely generalisable in statistical terms. However the mixed method mitigates this limitation. The grounds for drawing generalisations from studies based on non probability samples are based on the notion of “theoretical saturation” and “analytical generalisation” instead of on statistical generalization (Lewis et al., 2007).
- The third limitation is that the researcher’s experience and beliefs influenced decisions regarding the scope and design of this study. For example, the researcher’s experiences affect the choice of research domain, the selection of professionals invited to participate, and the nature of probing undertaken by the researcher in the interviews. The researcher is an experienced medical device industry professional who has firsthand experience of a successful process of bringing a drug/device combination product to market. The researcher’s resulting intimate knowledge of the processes of drug/device combination product regulation balances this limitation, extending what Betz 2010, p 86 terms “the range and sensitivity of human sensing” . The researcher also took measures in both the design and execution of the study to balance the inherent researcher subjectivity with the need for credible and objective findings. Academic peers provided feedback on the research design through conference presentations and publications, including a doctoral symposium.

## 7.6 Recommendations for Future Research

The thesis identified a wide range of enabling factors, many of which are worthy of separate research. There is, therefore, a great deal that could be investigated further.

- One avenue for further study would be research into the specific individual factors identified in the study and their impact on approval.
- Research should investigate the role of the Office of Combination Products in the United States, to determine whether a parallel office would improve processes in the European Union.
- Studies should address the fate of combination products with uncertain classifications sent to the Office of Combination Products to determine their chances for approval and what agency provides such approval ultimately.
- Future research should replicate or draw on the methods of the current study with variations in factors such as setting, population, and/or data collection method. The growth of the drug/device combination field should prompt the development of a comprehensive body of research to guide manufacturers and other stakeholders.
- Future studies should focus on other type of combinations in the life sciences, such as companion diagnostics and combination products involving tissue engineering components.
- Research should focus on specific product groups within combination products.
- Future research should address the same questions in relation to other regulatory systems, in other regions.
- Research should address why only a few generic drug-device combinations have received US FDA approval.
- Post-market surveillance of drug/device combination products was outside the scope of this research study but warrants investigation.
- Future research should be aimed at sorting out the classification of drug/device combination products.
- Future research should focus on the experiences of manufacturers implementing drug/device combination products quality systems.

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## **Appendix A**

### **Regulatory Agency Semi-Structured Interview Protocol**

## **Study Title: An Investigation of the Successful Commercialisation of Drug/device Combination Products**

### **Introductory Remarks:**

Thank you for taking the time to talk with me today. This interview will probably take about 30 minutes to complete.

Introduce study: I will ask you a number of questions about your views and experiences but please feel free to tell me anything you want me to know. Don't feel that you have to limit what you want to say because of what I ask.

### **Background**

1. What is your job title?
2. What primary functions does your job involve?
3. How long have you worked in this organisation?
4. What is your background (qualifications etc.)?
5. What is your involvement with the regulation of Combination Products (CP)?

### **Companies Commercialising CPs**

6. Do you see differences in the way large and small companies seek approval for their CP products?
7. Do you see differences if it is a pharmaceutical or a medical a device company who is seeking approval of a CP?
8. What do you believe is the best strategy to get a CP product approved?
9. What do the companies who are successful at commercialising CP do better than the companies that are not successful?
10. When in the development of a CP does a company contact their regulatory authority, in your experience?

### **CP Regulation in the EU**

11. What is your opinion of the EU regulatory framework for CPs?
12. How, in your opinion, could the regulatory framework for CPs in Europe be improved?

### **CP Regulation in the US**

13. What is your opinion of the US regulatory framework for CPs?
14. How, in your opinion, could the regulatory framework for CPs in the US be improved?

### **General Questions**

15. Which regulatory system for CPs is better, the US or the EU?
16. Do you have any experience of the regulatory process for CPs in other markets (e.g. China, Japan, Australia and India)?
17. How do you see the regulatory framework for CPs developing in the future?

### **Final Question**

18. Is there anything else you would like to add?

### **Final Comments:**

Thank you so much for taking your time for this interview and for all you've shared with me.

## **Appendix B**

### **Manufacturer Semi-Structured Interview Protocol**

## **Study Title: An Investigation of the Successful Commercialisation of Drug/device Combination Products**

### **Introductory Remarks:**

Thank you for taking the time to talk with me today. This interview will probably take about 30 minutes to complete.

Introduce study: I will ask you a number of questions about your views and experiences but please feel free to tell me anything you want me to know. Don't feel that you have to limit what you want to say because of what I ask.

### **Background**

19. What is your job title?
20. What primary functions does your job involve?
21. How long have you worked in this organisation?
22. What is your background (qualifications etc.)?
23. What is your involvement with the regulation of Combination Products (CP)?

### **Combination Product Background Information**

24. What is the name of your Combination Product?
25. What medical Speciality does your Combination product address?
26. What is the classification of your Combination Product?
27. What markets do you sell your products in to?

### **Development process for the Combination Product**

28. Why did you develop a Combination product?
29. Can you tell me how your Combination Product was developed?
30. Who was involved?
31. Who came up with the concepts?
32. What were the obstacles you have encountered with developing a Combination product?

33. What is the life cycle of your product?
34. What made you succeed in commercialising your product?
35. When in the development of a CP does a company contact their regulatory authority, in your experience?

### **Regulation of the Combination Product**

36. What was your regulatory strategy?
37. Did you determine your regulatory strategy early in the process?
38. Did you engage with your Notified Bodies, competent authorities?
39. Who is your Notified Body?
40. In your opinion who has the better regulatory process for Combination products, the United States or the European Union, why do you believe this to be the case?
41. What do you believe is the best strategy to get a CP product approved?

### **CP Regulation in the EU**

42. What is your opinion of the EU regulatory framework for CPs?
43. How, in your opinion, could the regulatory framework for CPs in Europe be improved?

### **CP Regulation in the US**

44. What is your opinion of the US regulatory framework for CPs?
45. How, in your opinion, could the regulatory framework for CPs in the US be improved?

### **General Questions**

46. Which regulatory system for CPs is better, the US or the EU?
47. How do you see the regulatory framework for CPs developing in the future?

### **Final Question**

48. Is there anything else you would like to add?



**Final Comments:** Thank you so much for taking your time for this interview and for all you've shared with me.

## **Appendix C**

### **Contract Research Organisation Semi-Structured Interview Protocol**

## **Study Title: An Investigation of the Successful Commercialisation of Drug/device Combination Products**

### **Introductory Remarks:**

Thank you for taking the time to talk with me today. This interview will probably take about 30 minutes to complete.

Introduce study: I will ask you a number of questions about your views and experiences but please feel free to tell me anything you want me to know. Don't feel that you have to limit what you want to say because of what I ask.

### **Background**

49. What is your job title?
50. What primary functions does your job involve?
51. How long have you worked in this organisation?
52. What is your background (qualifications etc.)?
53. What is your involvement with the regulation of Combination Products (CP)?

### **Combination Product Background Information**

54. Have you been involved in the development of a Combination product?
55. What types of Combination Product have you had experience of?
56. What combination product markets do you have experience of?

### **Companies Commercialising CPs**

57. Do you see differences in the way large and small companies seek approval for their CP products?
58. Do you see differences if it is a pharmaceutical or a medical a device company who is seeking approval of a CP?
59. What do you believe is the best strategy to get a CP product approved?

60. What do the companies who are successful at commercialising CP do better than the companies that are not successful?
61. When in the development of a CP does a company contact their regulatory authority, in your experience?

### **Development process for the Combination Product**

62. Why did you develop a Combination product?
63. Can you tell me how the Combination Product was developed?
64. Who was involved?
65. Who came up with the concepts?
66. What were the obstacles you have encountered with developing a Combination product?
67. What is the life cycle of the product?
68. What made you succeed in commercialising your product?
69. When in the development of a CP does a company contact their regulatory authority, in your experience?

### **Regulation of the Combination Product**

70. What was the regulatory strategy?
71. Did you determine your regulatory strategy early in the process?
72. Did you engage with your Notified Bodies, competent authorities?
73. Who is your Notified Body?
74. In your opinion who has the better regulatory process for Combination products, the United States or the European Union, why do you believe this to be the case?
75. What do you believe is the best strategy to get a CP product approved?

### **CP Regulation in the EU**

76. What is your opinion of the EU regulatory framework for CPs?
77. How, in your opinion, could the regulatory framework for CPs in Europe be improved?

### **CP Regulation in the US**

78. What is your opinion of the US regulatory framework for CPs?

79. How, in your opinion, could the regulatory framework for CPs in the US be improved?

### **General Questions**

80. Which regulatory system for CPs is better, the US or the EU?

81. How do you see the regulatory framework for CPs developing in the future?

### **Final Question**

82. Is there anything else you would like to add?

### **Final Comments:**

Thank you so much for taking your time for this interview and for all you've shared with me.

## **Appendix D**

### **Interview Participant Information Sheet**

## **Interview Participant Information Sheet**

### **Study Title: An Investigation of the Successful Commercialisation of Combination Products**

You are being invited to take part in a research study. Before deciding whether you wish to participate, it is important to read the following information so that you understand why the research is being carried out and what your participation would involve. Please take the time to read the information carefully and consider whether you wish to take part.

#### **What is the study about?**

The study is about the product development process and regulatory approval pathway for combination products adopted by companies that have successfully commercialised such products in the European Union and United States markets. This study aims to find how combination products are developed in medical technology companies. It also aims to identify the regulatory strategy adopted by these companies in order to bring combination products to market. It is hoped that the findings from this research will provide a source of information for companies engaged in the development of combination products in order to improve their business.

#### **Why have I been asked to take part?**

We are keen to discover the opinions of the professionals who have direct experience of commercialising combination products. Your retrospective reflections of that experience will greatly enhance and inform the findings from this research study.

#### **What will happen if I decide to take part?**

Participation in this study involves agreeing to be interviewed at a place convenient to you by Fiona Masterson. The interview will last between 20-30 minutes.

**What are the possible benefits of taking part?**

There are no direct benefits for you. By participating in this study you will provide valuable information about your experiences of the commercialisation of combination products.

**Will my taking part in this study be kept confidential?**

Yes, all information will be kept confidential and secure. You will be guaranteed anonymity at all times.

**What will happen to the results of this research study?**

The results will be submitted for examination as part of the requirement for the Doctorate in Biomedical Engineering at the National University of Ireland, Galway. A briefer version of the findings may also be written up for possible publication in a relevant journal. Your identification will not be included in any publication.

**Who is the researcher?**

The researcher is Fiona Masterson, a PhD candidate in the College of Engineering and Informatics, National University of Ireland, Galway, Ireland. She has a Degree in Science and a Masters in Operations and Quality Management. Prior to returning to university to study for her PhD she worked in the area of Quality Management/Regulatory Affairs/Process Quality for ten years in manufacturing companies. The last company she worked for was the Boston Scientific Corporation. She worked for them as a Senior Quality Systems Engineer. She is currently studying in the Department of Mechanical and Biomedical Engineering in the National University of Ireland, Galway. Fiona also lectures part-time on the topics of Regulatory Affairs, Operations Engineering, Innovation Management and Product Design and Development.

**Contact for further information**



If you wish to discuss any points covered in this Information Sheet or wish to ask any questions about the study, please do not hesitate to get in contact with Fiona Masterson or her supervisor at the contact details below:

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**THANK YOU FOR READING THIS INFORMATION SHEET. PLEASE KEEP A COPY FOR REFERENCE.**

## **Appendix E**

### **Web-based Survey Participant Information Sheet**

## **Investigation of the experiences of the EU and US regulatory frameworks for drug/device Combination Products.**

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### **What is the study about?**

The study is investigating the experiences of people interacting with the European Union (EU) and United States (US) regulatory frameworks for drug/device combination products. It is hoped that the findings from this research will provide a source of information for Companies engaged in the development of combination products in order to improve their chances of success.

### **Why have I been asked to take part?**

We are keen to discover the opinions of professionals who have direct experience of the EU and/or US regulatory frameworks for combination products. Your retrospective reflections of that experience will greatly enhance and inform the findings from this research study.

### **What will happen if I decide to take part?**

Participation in this study involves completing a survey that should take no more than 10 minutes. If you do not have time to complete the whole survey in one go, please click the SAVE and CONTINUE LATER button and you will be given instructions on how to resume the survey later from where you left off.

### **What type of questions will I be asked?**

The questions that you will be asked include those about your role within your company (demographic questions), questions about the combination product that you have worked on, questions on learning about your experience with the regulatory frameworks in the EU and/or US and questions about partnership dynamics.

### **Will my taking part in this study be kept confidential?**

Yes, all information will be kept confidential and secure. You will be guaranteed anonymity at all times.

### **What will happen to the results of this research study?**

The results will be submitted for examination as part of the requirement for the Doctorate in Biomedical Engineering at the National University of Ireland, Galway. A shorter version of the findings may also be written up for publication in a relevant journal. Your identification will not be included in any publication.

### **Contact for further information**

If you have any questions about the study, please contact Fiona Masterson at the contact details below:

Fiona Masterson

PhD Candidate

College of Engineering & Informatics

National University of Galway, Ireland

Email: [fiona.masterson@gmail.com](mailto:fiona.masterson@gmail.com)

### **Academic Supervisor:**

Dr. Kathryn Cormican

College of Engineering & Informatics

National University of Galway, Ireland

Email: [kathryn.cormican@nuigalway.ie](mailto:kathryn.cormican@nuigalway.ie)

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### Background Information

1) Which job titles best describes your position in your organisation?\*

President/CEO/Managing Director

Vice President

Head of Business Development

Sales/Marketing Manager

R&D Manager

- Quality Manager
- Clinical Manager
- Regulatory Manager
- Project Manager
- Business Development Manager
- Process Development Manager
- Design Manager
- Other (please specify): \_\_\_\_\_ \*

2) How long have you been in this current position?\*

- Less than 4 years
- 5-10 years
- 11-15 years
- Greater than 15 years

3) How many years experience do you have with combination products?\*

- less than 4
- 5-10 years
- 11-15 years
- Greater than 15 years

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#### Demographic Questions

4) Please indicate which organization most closely resembles yours\*

- Regulatory Body
- Venture Capitalist
- Government

Contract/Clinical Research Organisation

Industry - Medical Device

Industry – Pharmaceutical

Industry – Biotechnology

Industry – Biopharmaceutical

Consultant (please specify type of consultant):

\_\_\_\_\_\*

Other (please specify): \_\_\_\_\_\*

5) Approximately how many employees work in your organization (total in whole organization)?\*

1-10

11-50

51-250

More than 251

6) What was the approximate annual sales (or revenue generated) in your organization in the last financial year (in US dollars)?

Less than \$5 million

Between \$5 million - \$10 million

Between \$10 million - \$50 million

Over \$51 million

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Combination Product Description

7) From the list below please select the ONE option that best describes the nature of the combination product that you will be focusing on for this survey.\*

Drug eluting patch

- ( ) Drug eluting stent
- ( ) Drug eluting bead
- ( ) Steroid eluting electrode
- ( ) Antimicrobial catheter
- ( ) Implantable cardiovascular devices
- ( ) Antibiotic orthopedic sleeve
- ( ) Antibiotic bone cement
- ( ) Antibiotic bone cement beads
- ( ) Bone fusion system
- ( ) Bone graft with peptide
- ( ) Bone graft implant
- ( ) Implantable infusion pump
- ( ) Biologic prefilled syringe
- ( ) Transdermal patch
- ( ) Prefilled injector pen
- ( ) Dry powder inhaler
- ( ) Dermal collagen implants
- ( ) Wound covering
- ( ) Surgical mesh with antibiotic coating
- ( ) Fibrin sealant
- ( ) Alcohol swab
- ( ) Insulin pump
- ( ) Dermagraft
- ( ) Blood bag containing anticoagulant
- ( ) Nebulizer
- ( ) Metered dose inhaler
- ( ) Intraocular implant

Other (please specify): \_\_\_\_\_

8) Which of the following best describes the principal market that your combination product targets?\*

Orthopedics

Drug Delivery

Wound Management

Cardiology

Ophthalmics

Plastic Surgery

Dental

In Vitro Diagnostics

Other (please specify): \_\_\_\_\_

9) What stage of development is the combination product? \*

Initial development

Pre-clinical

Clinical

Pre-market submission

Post-market

---

Description of individual components that makeup the Combination Product

10) Which of the following scenarios is correct for your product?

None of the components had regulatory approval before they were combined

One of the components had regulatory approval before it was combined

More than one of the components had regulatory approval before they were combined



All individual components had regulatory approval before they were combined

11) How important is having regulatory approval for the components of the combination product prior to their inclusion in the overall product?

Not at all important    Low importance    Slightly unimportant    Neutral     
Moderately important    Very important    Extremely important

12) How important is it to have knowledge of the regulatory requirements for combination products when attempting to bring them to market?

Not at all important    Low importance    Slightly unimportant    Neutral     
Moderately important    Very important    Extremely important

13) How important is it for employees to have prior experience of bringing combination products to market?

Not at all important    Low importance    Slightly unimportant    Neutral     
Moderately important    Very important    Extremely important

---

#### EU Regulatory Framework Experience

14) Do you have experience of the EU regulatory framework for combination products?\*

Yes

No

15) What is the classification of your combination product in the EU market?\*

Medicinal Product

Class I Basic Medical Device

Class I (sterile) Medical Device

Class I (with a measuring function) Medical Device

Class IIa Medical Device

- Class IIb Medical Device
- Class III Medical Device
- Biologic
- Not available in the EU
- Don't know

16) How important are the following attributes of the Notified Body you engage with when planning to develop a combination product in the EU?

	<b>Not at all important</b>	<b>Low importance</b>	<b>Slightly unimportant</b>	<b>Neutral</b>	<b>Moderately important</b>	<b>Very important</b>	<b>Extremely important</b>
Have prior experience with combination products	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have staff with combination product expertise	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

17) How important is it to engage early with EU regulatory authorities when developing a combination product?

- Not at all important   
  Low importance   
  Slightly unimportant   
  Neutral   
  Moderately important   
  Very important   
  Extremely important

18) What do you think is the most critical factor for obtaining prompt regulatory approval of a combination product in the EU? (Answer with a short phrase)

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19) Why is this most critical factor? (Please explain)

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US Regulatory Framework Experience

20) Do you have experience of the US regulatory framework for combination products?\*

Yes

No

21) What is the classification of the combination product in the US market?\*

Combination product

A drug

Class I Medical Device

Class II Medical Device

Class III Medical Device

Biologic

Not available in the U.S.

Don't Know

22) How important is it to engage early with the Office of Combination Products in the development of a combination product?

Not at all important    Low importance    Slightly unimportant    Neutral     
Moderately important    Very important    Extremely important

23) What do you think is the most critical factor for obtaining prompt regulatory approval for a combination product in the US? (Answer with a short phrase)

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24) Why is this the most critical factor? (Please explain)

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#### Partnerships in Developing Combination Products

25) How was the combination product developed? (tick all that apply)

Through internal development

Acquisition (acquired a company that manufactured it)

In-licensed the technology for the combination product

Out-licensed the technology for the combination product to another company

Through a joint venture

Other (please specify): \_\_\_\_\_

26) If your company formed a partnership in order to bring the combination product to market what was the motivation for doing this? (tick all that apply)

Reduces risks

Less expensive access to required competencies

- Provide access to more potential customers
- Access regulatory knowledge
- Access technical knowledge
- Access to a technology
- Access to a medicinal product
- Enhance R&D capability
- Strengthen reputation in the industry as a result of associating with world class organisations
- Expand product offering
- Speedy entry into a particular market
- Sharing R&D costs
- Spreading risk of an investment
- Other reason (please specify): \_\_\_\_\_

27) How importance are partnerships when bringing combination products successfully to market?

- ( ) Not at all important   ( ) Low importance   ( ) Slightly unimportant   ( ) Neutral   ( )  
 Moderately important   ( ) Very important   ( ) Extremely important

28) In your opinion, how important are the following factors for a successful partnership?

	<b>Not at all important</b>	<b>Low importance</b>	<b>Slightly unimportant</b>	<b>Neutral</b>	<b>Moderately important</b>	<b>Very important</b>	<b>Extremely important</b>
Cultural differences between the medical device / pharmaceutical / biotechnology companies	( )	( )	( )	( )	( )	( )	( )
Working with a partner of a greater or smaller size (either smaller or larger than your organization)	( )	( )	( )	( )	( )	( )	( )
The pace at which a partner works	( )	( )	( )	( )	( )	( )	( )
Different attitudes towards risk	( )	( )	( )	( )	( )	( )	( )

29) What do you feel is the most critical factor determining the successful partnership between two companies bringing a combination product to market? (Answer with a short phrase.)

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30) Why is this most critical factor? (Please explain)

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31) Please feel free to add any additional comments here

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32) Optional: If you would like to receive the final results of the survey please insert your email address

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Thank You!

**Appendix F**  
**Participant Recruitment Email Template**



Dear Participant,

My name is Fiona Masterson, I am a Biomedical Engineering doctoral candidate at the National University of Ireland, Galway in Ireland. My PhD is a study of the experiences of the regulatory framework for drug/device combination products in the US and EU.

As part of my PhD I am conducting an anonymous on-line survey to gather data about the experiences of the EU and US regulatory frameworks for drug/device Combination Products. Here is a link to the survey:

<http://www.surveygizmo.com/s3/1509284/combinationproducts>

In the process for searching for people who might be suitable to take my survey I found your details. I would be very grateful if you could take my survey. The survey should take no more than 10 minutes to complete.

Please feel free to share the survey link with others who have experience of the EU and/or US regulatory frameworks for drug/device combinations products!

I have attached some further information about my research to this email.

If you are not in a position to take this survey thank you anyway for reading this email.

Kind Regards,

Fiona.

Fiona Masterson  
Department of Mechanical & Biomedical Engineering,  
National University of Ireland Galway

Twitter: Twitter@CombinationProd  
e: f.masterson1@nuigalway.ie

**Appendix G**  
**Participant Reminder Email Template**

Dear Participant,

I recently contacted you requesting your participation in an anonymous survey about drug/device combination products. I am running this survey as part of my PhD research. If you have taken the survey already, you can disregard this email and I thank you for your participation.

If you have not yet had a chance to complete the survey, please do so by clicking on this link. I would greatly appreciate your input!

<http://www.surveymzmo.com/s3/1509284/combinationproducts>

Please feel free to share the survey link with others who have experience of the EU and/or US regulatory frameworks for drug/device combinations products!

Kind Regards,

Fiona.

Fiona Masterson  
Department of Mechanical & Biomedical Engineering,  
National University of Ireland Galway

Twitter: [Twitter@CombinationProd](#)

e: [f.masterson1@nuigalway.ie](mailto:f.masterson1@nuigalway.ie)

## **Appendix H**

### **LinkedIn InMail Recruitment Message Template**

Dear Participant,

My name is Fiona Masterson, I am a Biomedical Engineering doctoral candidate at the National University of Ireland, Galway in Ireland. My PhD is a study of the experiences of the regulatory framework for drug/device combination products in the US and EU.

As part of my PhD I am conducting an anonymous on-line survey to gather data about the experiences of the EU and US regulatory frameworks for drug/device Combination Products. Here is a link to the survey:

<http://www.surveygizmo.com/s3/1509284/combinationproducts>

In the process for searching for people who might be suitable to take my survey I found your details. I would be very grateful if you could take my survey. The survey should take no more than 10 minutes to complete.

Please feel free to share the survey link with others who have experience of the EU and/or US regulatory frameworks for drug/device combinations products!

If you are not in a position to take this survey thank you anyway for reading this message.

Kind Regards,

Fiona.

Fiona Masterson  
Department of Mechanical & Biomedical Engineering,  
National University of Ireland Galway

Twitter: Twitter@CombinationProd  
e: f.masterson1@nuigalway.ie

## **Appendix I**

### **LinkedIn Recruitment Email Message Template**

Message Heading: HUGE favor! Could really do with your thoughts on the EU and/or US regulatory frameworks for drug/device combination products!

Hi Everyone,

I am doing this survey as part of my PhD on drug/device combination products. This anonymous on-line survey should take no more than 10 minutes.

<http://www.surveygizmo.com/s3/1509284/combinationproducts>

Please feel free to share this link with others who have experience of the EU and/or US regulatory frameworks for drug/device combinations products.

Thanks so much!!

Fiona

PhD Candidate

College of Engineering & Informatics

National University of Galway, Ireland

Twitter@CombinationProd

**Appendix J**  
**Twitter Recruitment Message Template**



HUGE favor! I could really do with your thoughts on the EU &or US regulatory frameworks for combination products <http://www.surveygizmo.com/s3/1509284/combinationproducts> ...  
TNX!

**Appendix K**  
**LinkedIn Groups**

Clinical & Regulatory Development for Devices & Combination Products	Advamed
Combination Products Coalition	Medical Device Oppurtunity
Clinical Research Technology & Innovation	<u>Med-Tech Innovation</u>
Combination Products Regulatory & Compliance Professionals	the autoinjector forum
Controlled Release Society	<u>The Pre-Filled Syringes Symposium</u>
DIA Europe	<u>Wound Care Professionals</u>
<u>Drug Regulatory Affairs</u>	<u>Wound Care Today</u>
Drug/Device Group	<u>Regulatory Affairs Certification (US, EU, CA)</u>
Global Regulatory Affairs	<u>Regulatory Affairs Professionals Society</u>
Medical Device Development, Marketing And Sales	<u>Regulatory Affairs, Drug Safety, Quality</u>
Medical Devices Group	ClinOps
Medical Devices Startups	<u>Dry Powder Inhalers</u>
MedTex Start ups	<u>PharmaNDDS</u>
<u>Drug Delivery Partnerships International</u>	<u>Dental Implant Professionals</u>
<u>CLMA (Contact Lens Manufacturers</u>	<u>Ophthalmic Medical Devices</u>
<u>Companion Diagnostics and Personalized Medicine Group</u>	<u>reg-info.com - Regulatory intelligence for pharma</u>
<u>Medical Device Guru</u>	<u>Biotechnology/Pharmaceuticals</u>
Medical device Guro	<u>Ophthalmic and Retinal Drug Delivery</u>
Medical Device Networkers	<u>European Medical Devices Regulatory Group</u>
MyBio	<u>Ophthalmology Innovation Summit</u>
<u>Prefilled Syringe and Safety Devices</u>	<u>Professionals in the Pharmaceutical and Biotech Industry</u>
<u>Regulatory Affairs Info Exchange</u>	<u>Quality &amp; Regulatory Network</u>
<u>Global medical Device Regulatory Updates</u>	<u>Medical Device Inventors</u>
<u>Transdermal Drug Delivery Networking Group</u>	<u>Drug Regulatory Professionals</u>
Future science group	<u>DrugInfoAssn (DIA)</u>
<u>Novel Drug Delivery Systems</u>	<u>Parenteral Drug Association</u>
<u>Pharma &amp; Med Device Regulatory Affairs Professionals Networking</u>	

## **Appendix L**

**Example of the Coding Process undertaken in NVivo 10 for the Facilitating Factor  
Managing Regulatory Authority Relationships**

### Phase 2 – Generating Initial Codes

A descriptive code called *Collaboration with Regulators* was created.

Sentences/paragraphs from the interview transcripts were coded into this descriptive code.

The screenshot displays a software interface with a ribbon menu at the top (File, Home, Create, External Data, Analyze, Query, Explore, Layout, View) and a sidebar on the left with a tree view of nodes. The main area shows a table titled "Phase 2 - Generating Initial Codes" with columns for Name, Sources, References, Created On, and Created By. The row "Collaboration with regulators" is highlighted in blue, and an orange arrow points from a text box on the left to this row.

Name	Sources	References	Created On	Created By
Challenges brought by dealing with drug agency and medical device bodies in the EU	6	29	28/03/2014 18:28	FM
Choosing the most appropriate EU regulatory agency	5	8	28/03/2014 18:38	FM
Clashing of cultures (cultural differences)	11	28	13/02/2014 12:10	FM
Classification uncertainty	7	17	14/02/2014 15:17	FM
Classify the product in a way the suits them rather than the way that is right	2	2	31/03/2014 10:24	FM
Classifying the combination product as a combination product	4	5	13/02/2014 14:56	FM
Classifying the combination product as a medical device	7	12	14/02/2014 12:16	FM
Collaborating	11	95	17/02/2014 21:39	FM
Collaborating to generate sustainable relationships	4	21	08/03/2014 12:28	FM
<b>Collaboration with regulators</b>	<b>2</b>	<b>8</b>	<b>31/03/2014 09:34</b>	<b>FM</b>
Combining harmoniously	14	41	13/02/2014 11:04	FM
Coming up with product ideas	9	19	14/02/2014 12:58	FM
Commercialisation strategy	11	41	14/02/2014 10:06	FM
Communicating with EU drug agencies	4	9	28/03/2014 18:51	FM
Communicating with EU regulators	10	38	28/03/2014 18:16	FM
Communicating with US regulators	10	23	28/03/2014 18:16	FM
Communication	9	49	18/02/2014 17:01	FM
Communication between regulators	2	3	31/03/2014 12:24	FM
Competent regulatory agencies	5	10	31/03/2014 09:40	FM
Conflicting needs in the partnership	3	4	18/02/2014 09:37	FM
Conflicting priorities	4	6	18/02/2014 10:55	FM
Conflicting skill sets	8	11	13/02/2014 12:08	FM
Consolidating ownership	2	2	08/03/2014 12:37	FM

### Phase 3 –Searching for Themes

A number of codes were included under the theme *Communicating with Regulators*.

One of these codes is the initial code *Collaboration with Regulators* from Phase 2 of the coding process.

The screenshot shows a software interface with a search results table. The table is titled "Phase 3 - Searching for Themes" and has columns for Name, Sources, Referenc, Created On, and Created. The table lists various subcategories and codes. An orange box on the left contains text explaining that a number of codes were included under the theme "Communicating with Regulators" and that one of these codes is the initial code "Collaboration with Regulators" from Phase 2 of the coding process. Arrows from the text point to the "Phase 3 - Searching for Themes" folder in the left-hand navigation pane.

Name	Sources	Referenc	Created On	Created
Theme - Communicating with regulators	13	306	02/09/2014 11:	FM
Building on experience from previous regulatory submissions	6	14	02/09/2014 11:	FM
Collaboration with regulators	2	8	02/09/2014 11:	FM
Subcategory - Communicating between manufactures and trade organisations - lobbying groups	2	3	02/09/2014 11:	FM
Engage with trade organisations	2	3	02/09/2014 11:	FM
Subcategory - Communicating between regulators	2	3	02/09/2014 11:	FM
Communication between regulators	2	3	02/09/2014 11:	FM
Subcategory - Communicating between manufacture and Competent Authority	12	116	02/09/2014 11:	FM
CE Mark	4	8	02/09/2014 11:	FM
Challenges brought by dealing with drug agency and medical device bodies in the EU	6	29	02/09/2014 11:	FM
Communicating with EU regulators	10	38	02/09/2014 11:	FM
Communicating with EU regulators (2)	10	38	02/09/2014 11:	FM
Partnerships with EU regulators	2	3	02/09/2014 11:	FM
Subcategory - Communicating bewteen manufacture and FDA	13	44	02/09/2014 11:	FM
Communicating with US regulators	10	23	02/09/2014 11:	FM
FDA are demanding	5	10	02/09/2014 11:	FM
Large companies have a bigger voice with regulators	1	1	02/09/2014 11:	FM
Large companies have direct relationships with the FDA	1	1	02/09/2014 11:	FM
Required skill set to deal with the FDA	2	6	02/09/2014 11:	FM
Subcategory - Communicating bewteen Notified Body and Competent Authority	0	0	02/09/2014 11:	FM
Notified body relationship with the competent authority	1	1	02/09/2014 11:	FM
US combination product approval	1	3	02/09/2014 11:	FM

## Phase 4 – Reviewing Themes

This phase involved the refinement of the themes identified in Phase 3 of the coding process.

A final theme labelled *Managing Regulatory Authority Relationships* was created.

The screenshot displays a software interface for reviewing themes. The main window is titled "Phase 4 - Reviewing Themes" and contains a table with the following data:

Name	Sources	Referenc	Created On	Created
Reviewed Theme - Managing Regulatory Authority Relationships	14	579	04/09/2014 11:0	FM
Competent regulatory agencies	5	10	08/09/2014 15:5	FM
Pharma and medical device regulators retrenched	1	1	08/09/2014 15:5	FM
Presubmission meetings with regulators	1	2	09/09/2014 10:1	FM
Theme - Choosing which regulator in EU to hire	5	8	04/09/2014 10:2	FM
Choosing the most appropriate EU regulatory agency	5	8	04/09/2014 10:2	FM
Theme - Communicating with regulators	13	306	04/09/2014 10:2	FM
Building on experience from previous regulatory submissions	6	14	04/09/2014 10:2	FM
Colloboration with regulators	2	8	04/09/2014 10:2	FM
Subcategory - Communicating between manufactures and trade organisations - lobbying groups	2	3	04/09/2014 10:2	FM
Subcategory - Communicating between regulators	2	3	04/09/2014 10:2	FM
Subcategory - Communicating between manufacture and Competent Authority	12	116	04/09/2014 10:2	FM
Subcategory - Communicating bewteen manufacture and FDA	13	44	04/09/2014 10:2	FM
Subcategory - Communicating bewteen manufacture and notified bodies	12	118	04/09/2014 10:2	FM
Theme - Engaging with regulation authorities	14	136	04/09/2014 10:2	FM
Colloboration with regulators	2	8	04/09/2014 10:2	FM
Competent regulatory agencies	5	10	04/09/2014 10:2	FM
Dealing with experienced regulators	3	7	04/09/2014 10:2	FM
Designation of your product in the EU	3	5	04/09/2014 10:2	FM
Engaging with regulatory authorities	11	75	04/09/2014 10:2	FM
FDA are demanding	5	10	04/09/2014 10:2	FM
Office of Combination Products	4	8	04/09/2014 10:2	FM
Partnerships with EU regulators	2	3	04/09/2014 10:2	FM