Regulatory Challenges in the Manufacturing, Adverse Event Reporting and Marketing of Combination Products

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Abstract

In order to better meet healthcare needs, it is important to invent new compounds called combination products by combining different medical products, such as drugs, devices and biologics. Apart from their invention, implementing certain regulations for the production and promotion is difficult. The manufacturers have experienced a great number of regulatory and review challenges for combination products. This is because the combination products are made up of different medical products, each of which has its own regulations. There is a great dilemma, which regulations need to be implemented for the combination products. This research project discusses the regulatory challenges in manufacturing, marketing, adverse event reporting of the combination products and worldwide regulations of these products. The success of these products in spite of many regulatory challenges is analyzed by comparing the combination products approvals and recalls with approvals and recalls of devices and drugs. Similarity in regulating the combination products in different countries is also evaluated.

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1. Introduction

The usual method of marketing individual products is greatly dependent on the type of product and other similar factors. However, the challenge is to market combination products that might raise a range of regulatory and review challenges. Even though the US laws of drugs, devices and biological products share a majority of similar basic features, each is also rather exceptional. These products have stipulated marketing applications, good manufacturing practice regulations and adverse event reporting requirements. The combination of any two products to create a new one will lead to doubt regarding the regulation of that particular product, as there is no specific marketing application for combined products. Moreover, regular discussion with an additional FDA Center is necessary, though one Center leads the pre-market review (Kramar, 2005a). As per the requirement and guidance of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA), the FDA has established the Office of Combination Products (OCP) to enforce the standards of combination product regulation. Main objectives of the OCP include confirming the combination product assignments with Agency Centers and managing their "timely and effective" pre-market review and "consistent and appropriate" post-market regulation. It also standardizes the combination product regulation. The OCP will not review the combination product but assigns the responsibility of reviewing to agencies (Kramar, 2005b).

1.1 Combination Products:

Combination products were first recognized in the Federal Food, Drug and Cosmetic Act of 1990 (Shea, 2011). According to 21 CFR 3.2(e), combination products can be defined as:

(1) A product comprised of two or more regulated compounds, 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 labeling, 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, whereupon approval of the proposed product, the labeling 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 labeling, 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 (Combination Products, 2009).

In order to handle a number of unmet healthcare needs, many life science companies have collaborated to develop a wide range of combination products (Medical Device and Diagnostic Industry, 2007). Along with drugs, devices and biologics, combination products are a different category of medical products (Michael, 2009). Development of these combination products leads to a number of regulatory and scientific challenges (Medical Device and Diagnostic Industry, 2007).

1.2 Purpose:

The purpose of this project is to interpret and summarize the various regulatory challenges of combination products; analyze the success of these combination products in spite of many challenges; discuss the worldwide regulations of combination products; and check whether there is similarity in regulating the combination products worldwide.

1.3 Research Question:

Regulatory challenges in the manufacturing, marketing and adverse event reporting of combination products: To what extent are these products successful? Discuss worldwide regulations of combination products and check similarity in regulating the combination products.

2. Review of Literature

2.1 US Regulations

The Safe Medical Devices Act of 1990 (SMDA) provided the power to the FDA to regulate these products. According to section 503(g) of the Act, a combination product will be regulated based on its primary mode of action as a drug, device or biologic by one FDA Center. This also provides the FDA with authority to use any of the agency resources to evaluate the effectiveness, safety or substantial equivalence of the product. The three FDA Centers that are involved with combination products (CBER, CDRH, CDER) have signed an inter-Center agreement that describes the authority of jurisdiction based on the characteristics of the product. These agreements came into effect October 1991 (Kramar, 2005a).

In order to ensure clear and consistent regulation of combination product, FDA established Office of Combination Products (OCP) as required by the Medical Device User Fee and Modernization Act (MDUFMA) in 2002 (Kramar, 2005a).

2.1.1 Roles and Responsibilities of OCP

- Assigning combination products to a lead agency for regulatory review
- Timely and effective pre-market review
- Consistent and appropriate post-market regulation
- Resolving the issues regarding review timelines

The product jurisdiction must first be determined to assign the combination product to a particular agency for regulatory review.

2.1.2 Process for Determining Product Jurisdiction. Product jurisdiction is determined based on the product's primary mode of action. The definitions for mode of action and primary mode of action were defined in the Final Rule on 25 August 2005 (FDA, 2011). "In the new regulation, mode of action is defined as the means by which a product achieves an intended therapeutic action or effect." Primary mode of action is defined as "single mode of action of a combination product that provides the most important therapeutic action of the combination product" (FDA, 2011).

In situations where it is difficult to determine the primary mode of action, the Final Rule has proposed a decision-making algorithm (FDA, 2012). The two important factors that are considered during the assignment algorithm when it is difficult to determine the mode of action at 21 CFR 3.4(a) are consistency and safety & effectiveness. Additional factors that are to be considered include intended use and overall therapeutic effect (Swift, 2011).

A manufacturer can submit a 'Request For Designation' application to the OCP in order to determine the formal jurisdiction of a product for which it is difficult to determine the mode of action (FDA, 2012; Shea, 2008). The manufacturer should include a description of the mode of action and primary mode of action in their RFD application. The OCP then has 60 days to review the RFD and provide the formal decision. If it takes more than 60 days, then the applicant's recommendation for the formal jurisdiction will be final. If the applicant is in disagreement with the decision made by the OCP, then a reconsideration request on the received decision can be filed within 15 days (Shea, 2008).

2.1.3 Importance of product jurisdiction. It is important to determine the product jurisdiction because it plays a key role in the later phases of the combination product development and marketing. It is very important in determining the type of pre-market or post-market applications that have to be filed. It is also important in determining the size of the clinical trials, the number of clinical trials that has to be conducted, the design of the clinical trials, the quality assurance programs that have to be implemented, adverse event reporting procedures, labeling requirements and the type and amount of user fee (Ritcher, 2011).

2.1.4 Manufacturing Regulations. The Good Manufacturing Regulations have requirements to assure that a product is unadulterated, and has the necessary quality, purity and strength. Each individual constituent part of a combination product has its own GMP regulations that have to be followed during its manufacturing. 21 CFR 210 &211 have the GMP regulations for drugs, 21 CFR part 600-680 for biologics and 21 CFR part 820 for devices. Now the focus is on determining which regulations have to be followed for regulating combination products. In order to overcome this issue, the FDA has announced a draft guidance that discusses the regulations that have to be followed during the manufacture of combination products (Kendall, 2011).

2.1.4.1 Draft Guidance- September 2004. According to the FDA's official site, the application of GMPs to combination products began in September 2004, after issuing a draft guidance. The guidance states two important tenets for the GMPs of combination products (Kendall, 2011).

According to the first tenet, constituent parts (i.e., drugs, devices and biologics) of the combination product that remain separate from other parts are subjected to their own manufacturing regulations. Therefore, under the guidance, the constituent parts of these products are subject only to the GMP regulations associated with their respective parts. In the case of combination products where the constituent parts are mixed, combined and packed, the parts are subject to their respective GMP regulations. For example, In the case of combination products where the constituent parts are subject to their respective GMP regulations, such as in the case of photosensitivity therapy, whereby the photosensitive drug is subject to its own GMP regulations and the photodynamic laser has its own GMP regulations of devices (Kendall, 2011).

According to the second tenet, in combination products of combined constituents which are also packed together, the GMPs of each set apply. For instance: in the case of a

drug-coated device, the GMPs of both the drug and the device apply separately until they come into contact under the guidance of the first tenet, but once, they come into contact/combine, then the regulations of both sets apply. However, the guidance does not require a manufacturer to implement both sets of GMPs, but asks the manufacturer to make sure that it complies with both sets by following either of the GMPs (Kendall, 2011).

2.1.4.2 Warning Letter- June 2006. After the guidance document, the FDA was relatively quiet about the GMP regulatory applications to combination products until June 2006, when the FDA issued a Warning Letter on the topic. This Warning Letter was issued when the FDA, during its inspection of a device manufacturing company in Los Angeles, found that that combination products manufactured by the company do not comply with both sets of GMPs. The company asserted that combination products were subject only to device GMPs. "FDA disagreed and referred the manufacturer to the 2004 guidance, explaining that GMP regulations for both the drug and device constituent parts applied to the products" (Kendall, 2011). Even though the FDA stated that compliance can be achieved by implementing just one set of GMP regulations, it referred the manufacturer to the 2004 guidance to identify the differing provisions of the regulations. With this, we can say that along with the guidance, the letter also states that manufacturers of the combination products should consider these differing provisions to make sure that the combination products are being manufactured in compliance with the applicable GMP regulations (Kendall, 2011).

2.1.4.3 2007 Spring- Proposed Rule. This rule "provides a framework under which compliance with a manufacturer's existing GMP system, or one that the manufacturer selects, will generally meet the requirements of the other applicable set of GMP regulations." For instance: the GMP regulations for the device will be generally met by the application of drug GMP regulations (Kendall, 2011).

In short, the proposed rule, apart from recognizing the resemblances between the drug GMP specifications under 21 CFR 210 and 211 and the Quality System Regulations for devices under 21 CFR 820, also identifies exclusive conditions in each set of rules that must be maintained.

Therefore, after the Primary Mode Of Action (PMOA) determination of the combination product, the manufacturer decides whether to follow device regulations or drug regulations. If the PMOA is a medical device, then the product must comply with the Quality System Regulations with overlay of drug GMP regulations (21 CFR 210 & 211) if the drug is combined with the device. If a biologic is combined with the device, then the combination product must comply with biologic GMP regulations (21 CFR Part 600-680). If the PMOA of the combination product is a drug, then the company must follow the GMP regulations for the drug and should also show compliance with device manufacturing regulations for the device component.

2.1.5 Adverse Event Reporting Regulations. There may be confusion for sponsors or manufacturers in reporting adverse events for combination products, as they are made up of drugs, devices and/or biologics. "If a product is approved under drug regulations, then adverse events associated with the product should be reported under drug adverse event reporting regulations" (Gopalswamy & Gopalswamy, 2008). The different types of adverse event reports that are filed are:

- 5-day report: According to 803.53(a), this report is filed when an event requires remedial action to 'prevent an unreasonable risk of substantial harm'.
- 30-day device malfunction report: According to 803.20(b)(3)(ii), this report is filed in cases of devices or similar device that is marketed causes death, or serious injury.
- 15-day alert: According to 314.83(c)(1)and (e), this report is filed in the case of serious and unexpected adverse event of drugs and biologics.
- 3-day field alert: This alert is filed in cases of drugs that come under 21 CFR 314.81(b)(1) that fail to meet required specifics, with labeling errors or bacteriological contamination.
- Expedited blood fatality report: According to 600.170, in cases of fatal blood transfusion or collection, a report has to be filed within 7 days of fatality.

In 2005, the Office of Combination Products published a "concept paper" on post-market safety reporting which discussed the options that the FDA was considering in addressing this issue. Later, the FDA has published a "proposed rule," which addressed the issue of reporting adverse events. The "proposed rule mainly discuss about the FDA's thinking on requirements for the submission of post marketing safety reports and does not establish a mechanism for the safety reporting" (Michael, 2009). The safety reporting on individual constituent parts is made according to the regulations of those parts. In cases of combination products, ambiguity arises as to how to apply these regulations associated with constituents. This results in underreporting, or inconsistent safety reporting (Michael, 2009).

According to the FDA's proposed rule, "a combination product submitted for marketing approval or clearance under a single application would be, at a minimum, subject to safety reporting requirements associated with that application" (Michael, 2009). For example: a combination product which is approved under a device application provision of

the FDA, the manufacturer should submit the report of adverse event as MDR, in accordance with 21 CFR 803; if approved under NDA, submit an adverse event according to 21 CFR 314.80 & 21 CFR 314.81; if approved under biologics (BLA), submit an adverse event in accordance with 21 CFR 600.80 & 21 CFR 606.170 (Michael, 2009).

But, depending on the nature of the adverse event that has to be reported in the case of a single marketing application, additional information must be submitted if the adverse event is because of the secondary mode of action of constituent parts of a combination product.

2.1.6 Marketing Regulations. Every product (drug, device or biologic) has to undergo a pre-market approval process before entering the market, as well as post-market regulation after the product is marketed (Kramar, 2005b). There are different approval processes and applications for the drugs, devices and biologics. Now the issue is which application has to be filed for combination products and how to attain collaboration between the FDA's Centers (CDRH, CBER, CDER) (Kramar, 2012).

2.1.6.1 Premarket Review Process. In order to overcome this issue, the OCP (Office of Combination Products) developed an SOP that governs the FDA's Centers to work collaboratively in the pre-market review process of combination products. In order to ensure that the requested Center receives timely and effective advice, this SOP documents a policy that 'consults count' (Gopalswamy & Gopalswamy, 2008). This policy demonstrates that evaluation time frames for consultative reviews are just as essential as the main role for which a reviewer may be allocated. The SOP also describes the OCP's role in monitoring the combination product consultation and review process (Kramar, 2005a). A single market application is submitted for most of the combination products when it can satisfy the patient safety, effectiveness and acceptable post-market (Kramar, 2005b). The different single marketing applications that are submitted to the lead Center are: NDA or ANDA to CDER, BLA to CBER, 510(k) or PMA to CDRH. The combination product with its constituent

products is considered as a whole while reviewing the single market application. The single market application is filed in case of:

- Combination products that are chemically and physically combined into one single entity (21 CFR 3.2(e)(1)).
- Most co-packaged combination products (21 CFR 3.2(e)(2)), particularly those with constituent parts that could not be provided separately. Examples might include those co-packaged combination products where one component is not sufficiently finished to support a separate approval/clearance, or when the indication exists only in the co-packaged configuration.
- Combination products for which separate applications would create a regulatory inconsistency (FDA, 2011).

In some cases, two marketing applications might be required in order to assure the safety and effectiveness of the product. This is because some regulatory provisions that are required may not be in the single marketing application that is being filed for the product. According to the FDA's press release, some examples of combination products that might require two applications are:

- The combination products which are made up of the constituents that are separate and complex (e.g., drugs and implantable delivery pumps, device in combination with a new molecular entity).
- The constituent parts with uses beyond the combination product; e.g., a single-dose drug and a reusable delivery device that is used for delivery of other drugs.
- When a "BLA for Further Manufacture" is appropriate to ensure the identity, safety, purity and potency of certain biological products (e.g., cell and gene therapy, therapeutic proteins, monoclonal antibodies, blood products) when the

combination product as a whole is being regulated under the device or drug provisions.

- To effect labeling revisions for a constituent part that is already approved for uses that do not include the proposed combination product indication. For example, when a previously PMA-approved drug delivery device is later approved to deliver an additional drug, the labeling of both the additional drug and the device are typically changed in order to reflect their use in combination.
- To apply mechanisms necessary to ensure appropriate regulation, or unique regulatory requirements that are not available under a single marketing application, e.g., gene therapy products.
- To maintain regulatory consistency. For example, for a device co-packaged with a drug covered by new drug product exclusivity, a separate NDA or ANDA may be necessary for the drug constituent part (FDA, 2011).

In certain cases, multiple marketing applications might be required where a single application cannot satisfy the requirements. For example:

- In the case of new drugs or orphan drugs where another application is filed to obtain some benefits like exclusivity and orphan status.
- Sponsors prefer two marketing applications when two manufacturing companies are involved in manufacturing a combination product (FDA, 2011).

Though some combination products, such as wound dressings and drug catheters, are approved under the 510(k) process, a PMA is required for combination products when the drug is not previously approved under an NDA (FDA, 2011).

2.2 European Union Regulations for Combination Products

In the European Directives, there is no specific single definition for combination products. However, the products that are made up of drug, device or advanced therapy medical products are regulated under Article 1 (3), (4) and (4a) of the Active Implantable Medical Device Directive (90/385/EEC); in Article 1 (3), (4) and (4a) of the Medical Device Directive (93/42/EEC); and in the Advanced Therapy Medicinal Products Regulation (EC) No 1394/2007 (Donowa, 2009).

Combination products are regulated and assigned to the particular regulatory bodies based on their primary mode of action and intended purpose of the manufacturer. If the primary mode of action of the product is because of the device with ancillary action of the drug, then the product is regulated under medical device regulations. If the primary action of the product is because of the medicinal drug, which forms a single integral product with intended exclusive use in a given combination, then the product is regulated under medical product regulations. Advanced therapy products, such as somatic cell therapy, gene therapy and tissue engineering, are regulated under biologic regulations (Guliana, 2008).

2.2.1 Manufacturing Regulations. There are no distinct manufacturing regulations for combination products in Europe. The combination product that is assigned under the medical device category based on its primary mode of action must comply with ISO13485:2003; 93/42/EEC Art.11, Annex I sec. 10; Annex II (full quality assurance system) and Annex IV (production quality assurance system). The products that are assigned under medical products and biologics must comply with 2001/83/EEC Art.47; 2003/94/EC; EUDRALEX Vol.4 and Regulation 1394/2007 of GMP regulations, respectively. Under 93/42/EEC of medical devices, the manufacturer must apply to a notified body for assessment of its quality system (Guliana, 2008).

2.2.2 Adverse Event Reporting Regulations. If a product is approved under device regulations, then adverse events are reported according to the adverse event reporting

regulations (MEDDEV 2.12-1 rev 6) of a medical device. The manufacturer must notify the National Competent Authority about any harmful side effects. Any serious adverse event must be reported within 2 days of occurrence. Any death or unwanted health deterioration must be reported within 10 days, and other incidents must be reported within 30 days (Donowa, 2009; Guliana, 2008).

If the product is approved under drug regulations, then the manufacturer must follow drug/biologic adverse event reporting regulations (2001/83/EEC). According to Title IX-Pharmacovigilance Article 104, "all suspected serious events have to be reported within 15 days to the competent authority of member state in whose territory the incident occurred. All suspected serious and unexpected adverse events that occur in third territory have to be reported within 15 days to the competent authority of member states and to the agency" (Guliana, 2008). According to EUDRALEX Volume: 9 (Guidelines on Pharmacovigilance for Medical Products for Human Use), before placing on the EU market, periodic safety update reports (PSUR) have to be submitted immediately upon the request from the agency or for every 6 months after authorization and after placing on the market, PSURs are submitted for every 6 months (initial 2 years), once a year (next 2 years) and once every 3 years from then on (Guliana, 2008).

2.2.3 Marketing Regulations. In the case of drug/device combination products where the primary mode of action is through a device, the European Agency provides a marketing approval for the manufacturer based on a declaration of conformance process under Medical Device Directive regulations. This results in the right to bear a CE marking on devices, which gives the right to be marketed in Europe. However, the notified bodies that evaluate and grant the CE mark have to seek advice from pharmaceutical regulatory bodies in order to ensure the effectiveness and safety of the medical product when used with the device. If the medical product is approved through the European centralized procedure, then the medical device

manufacturers must seek advice from the European Medicines Agency (EMA) (Guliana, 2008).

2.3 Japan Regulations for Combination Products

There is no particular definition for the combination product. However, the products that are physically/chemically combined or co-packaged are considered as combination products. But the products that are separate and cross-labeled are not considered as combination products. The regulatory process of Japan was revised in 2005 to serve combination products, medical devices and biologics (Sullivan & Elbaek, 2007). The review and approval of combination products is based on the primary action of the product. The combination product is reviewed either by the Office of Medical Devices of the Pharmaceutical and Medical Devices Agency (PMDA), the Office of New Drug of PMDA, or the office of Biologics of PMDA (Guliana, 2008).

2.3.1 Manufacturing Regulations. There are no particular regulations for manufacturing combination products. The product that is considered as a drug based on the primary mode of action must comply with the drug GMP and PMS. The product that is judged as a device based on the primary mode of action of the combination product must comply with the QMS and PMS regulations for the device (Guliana, 2008).

2.3.2 Adverse Event Reporting Regulations. For a product that is judged as a drug, adverse events are reported based on the regulations for drug adverse events reporting. According to Article 253 of Enforcement Regulations for reporting adverse drug reactions, any unexpected serious event has to be reported within 15 days. Any known adverse reactions have to be reported within 30 days. According to Article 63 of Enforcement Regulations, periodic safety update reports have to be submitted every 6 months during the initial 2 years and yearly thereafter (Guliana, 2008).

2.3.3 Marketing Regulations. There are no specific marketing regulations for combination products in Japan. If the combination product is judged as a drug, then a drug marketing

application (SHONIN) has to be filed. If the combination product falls under the category of medical device, then a device SHONIN marketing application has to be filed. The final decision about the combination product can be obtained with this single SHONIN marketing application (Nagasaka, Lang, Shintani, Ueno, & Lewis, 2008).

2.4 Australia Regulations for Combination Products

There is no particular definition for combination products. The combination products are regulated based on the primary mode of action and intended purpose of use. The products are classified as drugs or devices or biologics based on the definition in the legislation and are regulated based on this classification according to the Therapeutic Goods Act of 1989 and the Therapeutic Goods Amendment (Medical Devices) Act of 2002 by the Therapeutic Goods Administration (Guliana, 2008).

A device that incorporates a substance which, if used separately, would be a medicine and provides ancillary action when used with a device is recognized as a Class III device. However, it should comply with safety and quality requirements for the medicine. The ancillary action of a drug should also be confirmed in regard to the intended purpose of use of the device (Guliana, 2008). The conformity assessment procedure has to be conducted in order to assess whether the safety, quality and performance of the device is adequate (Therapeutic Goods Administration, 2011b). The medicinal component that is used with the device must comply with regulations of the medical component. The medicine must also be in compliance with the GMP and have access to DMFs (drug master files).

2.4.1 Adverse Event Reporting Regulations. The adverse event reporting regulations for combination products are similar to regulations followed in other pharmaceutical markets (US, Europe, Japan and Canada). Any adverse event has to be reported to the manufacturer by the sponsor (if the manufacturing company is not located within country, Australian law dictates to appoint a sponsor located in country to act as a liaison with TGA). The manufacturers then report the event to the TGA. The post-market surveillance system of the

manufacturer reviews the adverse events associated with the products and notifies the sponsor of the events and also takes a corrective action to minimize risks associated with adverse events.

2.4.2 Marketing Regulations. In order to get a marketing approval for a device that contains a drug with ancillary action:

- A conformity assessment application is submitted to the device regulator.
- This marketing application is assessed by device programs.
- The medicine component of the device is assessed for safety and efficacy.
- A conformity assessment certificate is issued by the device regulator to the manufacturer once the assessment is done and the device is approved.

The device which incorporates the drug is then released into market (Therapeutic Goods Administration, 2011a).

2.5 Canadian Regulations of Combination Products

"[A] combination product is a therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or device) such that the distinctive nature of the drug component or the device component is integrated into a singular product" (Health Canada, 2006). Therefore, a combination product must comply with two sets of regulations. The drug component of the combination product must comply with the Food and Drug regulations, and the device component must comply with the Medical Device regulations (Health Canada, 2006; Guliana, 2008). Since the announcement of policy in November 2005, combination products are classified based on the primary mode of action of the product, which results in intended use and efficacy. The classified product is then regulated either under Food and Drug regulations or Medical Device regulations. This new policy came into effect on March 1, 2006. Until 2006, the manufacturers had to comply

with both Food and Drug regulations and Medical Device regulations during the regulation of combination products with drug and device components (Health Canada, 2006).

The following are the examples of combination products that are considered as drugs:

- Prefilled syringes
- Transdermal drug patches
- Implants, whose primary purpose is to release drugs
- Alcohol swabs
- Wound dressings, whose primary mode is to deliver a drug

The following are the examples of combination products that are considered as devices:

- Drug coated devices
- Drug impregnated devices
- Wound dressings

First aid kits must comply with both the sets of regulations.

If the principal mechanism of action, which is responsible for intended use and efficacy of combination products, is achieved by pharmacological, immunological or metabolic means, then the product is regulated under Food and Drug regulations. If the primary mode of action for achieving intended use and efficacy of the combination product is not because of the pharmacological, immunological and metabolic means, but assisted by those means, then the product is regulated under Medical Device regulations. However, the combination products must comply with safety, efficacy and quality standards of both of the components of combination products (Health Canada, 2006; Guliana 2008).

The various requirements of the new policy are as follows:

- In order to support the sale or investigational testing of a combination product in Canada, the sponsor must submit an application with the entire information (name,

mechanism of action and study design) about the product to the Therapeutic Products Directorate or the Biologics Genetic Therapies Directorate to classify the product.

- The agency classifies the product based on three criteria stated in the policy. If the agency is unable to come to a conclusion about the classification of the product, then the application is forwarded to the Therapeutic Products Classification Committee (TPCC). The committee then reviews and gives a final decision within 30 days.
- If the sponsor is not satisfied with the decision of the TPCC, then they can submit for reconsideration to the Director General in a written form within 30 days of receiving the final decision. This reconsideration process is conducted according to the guidelines stated in Health Canada Guidance: Reconsideration of Final Decisions Issued for Human Drug Submissions.
- The sponsor must also attest to the information about safety, quality and efficacy of the ancillary product.
- The review may be conducted by one agency or a group of representatives from different agencies.
- A notice of compliance must be signed by the Director General after finding the product is in compliance with all regulations.
- Combination products that are submitted as drugs under Food and Drug Regulations and devices that are submitted under Medical Device Regulations are subject to the fees payable, respectively, under regulations enacted for that purpose (Health Canada, 2006).

2.6 Drug-Eluting Stents

Drug-eluting stents are the coronary artery stents that prevent fibrosis and thrombus, which would otherwise result in blockage of stented arteries, called restenosis (Scribendi, 2013). A stent is a metal mesh tube which houses a balloon that is blown up in order to widen

the clogged artery. After angioplasty, stents are used to keep the arteries open. Drug-eluting stents that are coated with a drug (immunosuppressive class) release the medication slowly. This released medication helps in preventing the growth of tissue around the artery lining that would otherwise increase the risk of blocking the artery again (Mayo Clinic, 2011). As the stent portion of the product is used to widen the blocked artery and the drug portion helps in preventing the blockage of the widened artery, drug-eluting stents are good examples of combination parts. Therefore, I have chosen to use this product type of a sophisticated combination of device and drug when evaluating the success of the regulatory review of this class as well as when evaluating the similarity in regulatory review across the major markets of the world. The first drug-eluting stent, Cypher-Sirolimus, was released into the market in 2003 after a large pivotal study (Scribendi, 2013).

3. Methodology

The success of combination products is estimated by comparing the number of approvals with that of the number of recalls from the market during the time period of 2003 to 2012 as the first drug eluting stent is approved in 2003. The drug eluting stent is taken as an example to represent the combination products as these contribute about ninety percent of the combination products market value. The number of drug-eluting stent systems approved by the FDA is calculated and the number of drug eluting stent systems recalled from the market is estimated. By comparing these two, the percentage of recalls from the total number of approvals is calculated. This percentage is then compared with the percentage of recalls from total number of approvals of drugs and devices.

In order to check whether there is similarity in regulating the combination products, the drug eluting stent is taken as an example, and the regulations followed by different countries are observed. The various aspects that each country takes into consideration in order to regulate drug-eluting stents are also observed. Finally, analysis is performed by checking whether a given combination product is classified, reviewed and regulated similarly and on a similar basis in major pharmaceutical markets (US, Europe, Japan, Australia and Canada) to determine whether there is any similarity between countries in regulating combination products.

4. Results

4.1 Success of combination products

Using drug-eluting stents as the example, regulatory success may be related to the agencies' abilities to accurately evaluate the safety and efficacy of the regulated products. Using removal from market as a marker for an unsuccessful regulatory review, the number of market removals for New Chemical Entities, Class III devices and Drug-eluting stents and compared to the number of products approved for each group during the years 2003-2012.

4.1.1 Combination Product Approvals. According to section 503(g) of the Food, Drug and Cosmetic Act (21 USC 353 (g)), a drug eluting stent is a combination product with drug and device components. However, according to section 21 CFR 3.4, the responsibility to review the product is based on the "primary mode of action" of the combination product. As the primary action of the drug eluting stent is to maintain the patency of vessels, which is performed by the device, and the secondary action of the drug that is coated on the stent is to prevent restenosis, the FDA has assigned the pre-market review and post-market regulation of these products to the Center for Devices and Radiological Health (CDRH). The premarket review of these combination products is conducted by CDRH according to 21 CFR 814 after filing a Premarket Approval (PMA) application. However, the CDRH can review the drug-eluting stents only after consulting with the Center for Drug Evaluation and Research (CDER), as there is also a drug component in the product (FDA, 2010a).

The sixteen drug-eluting stents approved from 2003 to 2012 are shown in Table 1.

Table 1: Combination product approvals from 2003 to 2012

Year of Approval	Combination Product
2003	CYPHER Sirolimus- Eluting coronary stent
2004	TAXUS Express2 Paclitaxel – Eluting coronary stent system
2008	XIENCE V Everolimus Eluting Coronary stent on the Over-the-wire (OTW) or Rapid Exchange (RX) stent Delivery Systems
	Endeavor Zotarolimus- Eluting Coronary Stent on the Over-the-wire (OTW), Rapid Exchange (RX), or Multi Exchange II (MX2) Stent Delivery Systems
2009	TAXUS Liberte Long (2.75 – 4.00 mm X 38 mm) Paclitaxel- Eluting Coronary Stent System (Monorail and Over-the-wire Dlivery Systems)
	TAXUS Liberte Atom (2.25 mm) Paclitaxel – Eluting Coronary Stent System (Monorail and Over-the-wire Delivery Systems)
2011	PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System
	XIENCE PRIME and XIENCE PRIME LL Everolimus Eluting Coronary Stent System
	XIENCE nanoEverolimus Eluting Coronary Stent System
	ION Paclitaxel Eluting Coronary Stent
2012	Zilver PTX Drug Eluting Peripheral Stent
	PROMUS Element Plus Everolimus Eluting Platinum Chromium Coronary Stent System
	TAXU Express2 Paclitaxel Eluting Coronary Stent System (Monorail and Over-the-Wire Delivery Systems)
	ION Paclitaxel Eluting Coronary Stent System (Monorail and Over-the-Wire Delivery Systems)
	Resolute MicroTracZotarolimus-Eluting Coronary Stent System (Resolute MicroTrac) and Resolute Integrity Zotarolimus-Eluting Coronary Stent System (Resolute Integrity)
	TAXUS Liverte Paclitaxel Eluting Coronary Stent System (Monorail and Over-the-Wire Delivery Systems)

(FDA, 2013b).

The sixty Class III medical devices approved from 2003 to 2012 are displayed in Table 2.

Table 2: Medical Device approvals from 2003 to 2012

Year of Approval	Medical Device
2003	S.M.A.R.T.™ Nitinol Stent System / S.M.A.R.T.™ Control™ Nitinol Stent System - P020036
	MULTI-LINK VISION™ RX & OTW Coronary Stent System - P020047
	FX miniRAIL™ RX Percutaneous Transluminal Coronary Angioplasty PTCA Catheter - P020037
	Response™ CV Catheter System - P020052
2004	GORE VIATORR® TIPS Endoprosthesis - P040027
	NAVISTAR™ and CELSIUS™ THERMOCOOL® Irrigated Deflectable Diagnostic/Ablation Catheter - P030031
	Philips HeartStart Home OTC Defibrillator - K040904
	Guidant Cardiac Resynchronization Therapy Defibrillators (COMPANION trial) - P010012/S026
	St. Jude Medical® Epic™ HF and Atlas® + HF Dual Chamber Implantable Cardioverter Defibrillator Systems with Cardiac Resynchronization Therapy - P030054
2005	X STOP® Interspinous Process Decompression System (XSTOP) - P040001
	IBI Therapy™ Dual 8™ Ablation Catheter and IBI 1500T6 (USA) Cardiac Ablation Generator - P040042
	Xact® Carotid Stent System - P040038
	Wingspan™ Stent System with Gateway™ PTA Balloon Catheter - H50001
	GORE VIABAHN™ Endoprosthesis - P040037
	Boston Scientific Liberte™ Monorail™ and Over-the-Wire Coronary Stent Systems - P040016
	CoAxia NeuroFlo™ Catheter - H030005
	IBI Therapy™ Cardiac Ablation System - P040014
2006	The Spanner™ Temporary Prostatic Stent - P060010
	Allergan Inamed® Silicone-Filled Breast Implants - P020056
	Mentor MemoryGel™ Silicone Gel-Filled Breast Implants - P030053
	NexStent® - P050025
	Cordis PRECISE™ OTW Nitinol Stent System - P030047
	BIOTRONIK's Kronos LV-T and Tupos LV/ATx Implantable Cardioverter Defibrillator Systems with Cardiac Resynchronization Therapy - P050023
2007	Exponent® Self-Expanding Carotid Stent with Over-the-Wire (OTW) or Rapid-Exchange (RX) Delivery Systems - P070012
	Femoral Introducer Sheath and Hemostasis Device (FISH™) - P050043
	CryoCor Cryoablation - P050024
	FLAIR Endovascular Stent Graft - P060002
	CORDIS ENTERPRISE™ Vascular Reconstruction Device and Delivery System - H060001
	Protégé® GPS™ and Protégé® RX Carotid Stent Systems -

Year of Approval	Medical Device
	P060001
2008	Express® SD Renal Monorail® Premounted Stent System - P060006
	Carotid WALLSTENT® Monorail® Endoprosthesis – P050019
	Helios II Ablation Catheter– P050029
	Talent™ Thoracic Stent Graft System - P070007
	LifeStent FlexStar and FlexStar XL Vascular Stent - P070014
2009	NAVISTAR® THERMOCOOL® and EZ Steer THERMOCOOL® Nav Irrigated Deflectable Diagnostic/Ablation Catheter for Treatment of Paroxysmal Atrial Fibrillation - P030031S011
2010	Bard LifeStent and Lifestent XL Vascular Stent
	Arctic Front Cardiac CryoAblation Catheter
	Endurant Stent Graft System
	Boston Scientific Cardiac Resynchronization Therapy Defibrillators
	Medtronic Vascular Complete® SE Vascular Stent System
	Express LD Iliac Premounted Stent System
2011	OVATION Abdominal Stent Graft System
	Assurant Cobalt Iliac Balloon- Expandable Stent System
	Propel
	RX Herculink Elite Renal Stent System
	RX Acculink Carotid Stent System
	Revo MRI SureScan Pacing System - P090013
	Formula Balloon- Expandable Renal Stent System
2012	S.M.A.R.T Control and S.M.A.R.T Vascular Stent Systems
	Medtronic Valiant Thoracic Stent Graft with the Captivia Delivery System - P100040/S008
	OVATION Abdominal Stent Graft System
	Relay® Thoracic Stent-Graft with Plus Delivery System
	Omnilink Elite Vascular Balloon- Expandable Stent System
	Presillion plus CoCr Coronary Stent on RX System
	Epic Vascular Self- Expanding Stent System
	Medtronic CDRM Cardiac Resynchronization Therapy Defibrillators
	Sientra Silicone Gel Breast Implants
	EverFlex Self- Expanding Peripheral Stent System
	Absolute Pro Vascular Self- Expanding Stent System
	Therapy Cool Path Duo Ablation Catheter, Safire BLU Duo Ablation Catheter and IBI1500T9- CP V1.6 Cardiac Ablation Generator
	GORE TAG Thoracic Endoprosthesis

(FDA, 2013b).

The 209 New Molecular Entity NDAs approved from 2003 to 2012 are summarized in Table 3.

Table 3: Drug approvals from 2003 to 2012

Year	Number of Approvals
2003	16
2004	33
2005	21
2006	16
2007	16
2008	21
2009	20
2010	13
2011	24
2012	29

(FDA, 2013a).

4.1.2 Number of Recalls and Market Withdrawals of Drug-Eluting Stents. According to US Food and Drug Administration device recalls, only one drug eluting stent system has been recalled or withdrawn from the market.

Cook Medical's product, Zilver PTX drug eluting peripheral stent, was withdrawn from the market in the month of April 2013. Cook Medical has come up with a communal recall of its drug eluting stent because of its issue with the delivery system tip separation. The company has received several complaints regarding this issue, which includes one death. (Pilaw, 2013). Cook stated that the problem is with the delivery system, but not the stent itself (FDA, 2013).

4.1.3 Recalls of Medical Devices

The 15 Class III devices that have been recalled or withdrawn from the market during 2003 to 2012 are provided in Table 4.

Table 4: Medical device recalls from 2003 to 2012

Year of Recall	Medical Device
2004	Boston Scientific Express2TM (bare metal) Coronary Stent
2005	Welch Allyn Co., AED 20®, Automatic External Defibrillator
	HeartSine Technologies, Inc. Automatic External Defibrillators
	Access CardioSystems Automated External Defibrillators
	Certain Medtronic LIFEPAK 500 Automated External Defibrillators
2006	Welch Allyn PIC 50™ Automated External Defibrillators

Year of Recall	Medical Device
	Welch Allyn AED 20™ Automated External Defibrillators
2007	Welch Allyn AED 10™ Automatic External Defibrillators
2008	Boston Scientific NexStent Monorail, NexStent Carotid Stent and Monorail Delivery System
2009	ZOLL Medical Corporation, ZOLL AED Plus Defibrillator
	Welch Allyn AED 10 Automatic External Defibrillator (AED) and MRL JumpStart AED
2010	Physio-Control Inc., LIFEPAK 20 and LIFEPAK 20e External Defibrillator/Monitors
2011	Boston Scientific Innova Self-Expanding Stent System
	Millar Instruments Inc., Mikro-Tip Angiographic Catheter, Model SPC-454D and SPC-454F
2012	Cardiac Science Powerheart, CardioVive, CardioLife; GE Responder and Responder Pro; and Nihon-Kohden Automated External Defibrillators (AEDs)

(FDA, 2013c).

4.1.4 Recalls of Drugs

According to the US Food and Drug Administration press releases, three new chemical entities approved during 2003 to 2012 to date have been removed from the market (Table 5).

Table 5: Drug Recalls from 2003 to 2012

Year of Recall	Drug
2005	Neutrospec (Technetium (99m Tc) fanolesomab)
2009	Raptiva (efalizumab)

(FDA 2005; The Pink Sheet, 2009).

Two NCEs were recalled or withdrawn from the market between 2003 and 2012.

4.2 Worldwide Regulations of Combination Products

To provide an example of consistency of regulatory reviews in the major markets of the world for combination products, the process by which drug-eluting stents have been reviewed is examined. The regulations followed by different countries for review of drug-eluting stents are summarized in Table 6.

Table 6: Comparison of Regulations for Drug-Eluting Stents in the Major Pharmaceutical Markets

	Regulatory Definition	**Primary Designation**	**Review Assignment**	**Manufacturing Regulations**	**Adverse Event Reporting Regulations**	**Marketing Regulations**
US	Defined according to 21 CFR 3.2(e)(1)	Device	Assigned to CDRH; the primary mode of action is through device component	Device component has to follow Quality system regulations of devices (21 CFR 820) and drug component GMP regulations (21 CFR 210 & 211)	Events have to be reported in MDR in accordance with 21 CFR 803.	One marketing application for premarket review until the drug is new or an orphan where some benefits like exclusivity, orphan status can be obtained by filing second application for new drug or orphan drug.
Europe	No particular definition	Device	Assigned to device regulatory agency	No particular manufacturing regulations. As it is defined as a device, must be in accordance with ISO13485:2003; 93/42/EEC Art.11, Annex I sec. 10; Annex II (full quality assurance system) and Annex IV (production quality assurance system).	Events are reported in accordance with adverse event reporting regulations of devices (MEDDEV 2.12-1 rev 6)	Approved by declaration of conformance.
Japan	No specific definition	Device	Assigned to device regulatory body	Device component must comply with QMS and PMS regulations of device	Reported in accordance with device adverse event reporting regulations	As regulated under device regulations, single SHONIN application can be filed.

	Regulatory Definition	Primary Designation	Review Assignment	Manufacturing Regulations	Adverse Event Reporting Regulations	Marketing Regulations
				and drug component with GMP and PMS regulations of drug		
Australia	No particular definition	Device	Assigned to device regulatory body	Device component must comply with QSM regulations of devices and drug component with GMP regulations of drug	Sponsor reports the adverse events to manufacturer who then reports to TGA as per device adverse events reporting regulations	Conformity assessment application has to be submitted to TGA. Certificate of conformity is issued by device regulator
Canada	A therapeutic product that combines the drug and device components with distinct nature to form a single product is referred to as a combination product.	Device	Assigned to medical device regulatory agency	Device component must comply with device manufacturing regulations and drug with drug manufacturing regulations	Events are reported in accordance with device adverse event reporting regulations	Device marketing application is filed

See Section 2 above for complete citation of sources of this information.

5. Discussion

5.1 Success of Combination Products

The combination products that are discussed here are the drug-eluting stents. The first drug eluting stent was approved by the FDA in 2003 and was a Johnson & Johnson Cordis Corporation product. In the span of 10 years from 2003 to 2012, 16 drug eluting combination products were approved and released into the market. Six leading medical device manufacturing companies are producing these combination products.

Of these 16 stents, Cook's product Zilver PTX drug-eluting peripheral stent was withdrawn from the market. Cook identified the reason for this as the nonconformance of the design criteria for the inner component of the delivery system. On the whole, only one product has been recalled from the market out of the 16 products, or withdrawal rate is 6.25% in 10 years. Except for the recall of Zilver PTX, all of the other issues are minor and can be rectified with the proper marketing of the companies and better postmarket surveillance of the FDA.

Sixty Class III medical devices have been approved by the FDA between 2010 and 2012 and 15 devices were withdrawn from the market due to various reasons, during the same period for a withdrawal rate is 25%.

Of the 209 New Chemical Entities that were approved by the FDA between 2010 and 2012 are 209 two were removed from the market as of June 2013. The withdrawal rate is currently ~1%.

The frequency of the market withdrawal of combination products, devices and drugs is approximately 6%, 25% and 1%, respectively. While the numbers are very small with limited time on the market, it appears that the withdrawal rate for the combination product used as an example falls between that for devices and drugs. It appears that the FDA has not found the review of combination products appreciably more difficult than that of the other

classes as judged by market success. Further data will be required to make a more definitive statement as further marketing history is generated for this new product type.

5.2 Worldwide Regulations and Similarity in Regulating

The combination products are well defined in FDA regulations. There are distinct regulations for classifying, reviewing and regulating a combination product.

The FDA has drafted clear guidelines on which manufacturing regulations have to be followed while manufacturing a combination product. The device component must comply with 21 CFR 820 regulations; drug components must comply with 21 CFR 210 & 211 regulations; and biologic components must comply with 21 CFR 600-680. Even if a combination product is approved under drug regulation/device regulation/biologic regulation, all of the components must comply with their respective manufacturing regulations. The adverse events are reported based on the regulations under which a product is approved. The number of marketing applications and marketing approvals are determined based on the classification of the product.

There is no particular definition for combination products in Europe, Japan or Australia. There isn't an agency or office like the Office of Combination Products to regulate the combination products. The combination products are classified based on the primary mode of action, which is effective and has an intended purpose of use. The device component must follow device regulations; the drug component must follow drug regulations and the biologic component must follow biologic regulations while manufacturing a combination product. The adverse events are reported based on the classification under which the combination product is approved. There isn't any clear demarcation of how many applications have to be filed for marketing approvals.

The combination product regulations followed in Canada are much more similar to those of the USA. The combination products are clearly defined and regulated. A new policy has been drafted which accommodates the regulations that have to be followed for

combination products. The combination products are classified based on the primary mode of action.

In the case of drug-eluting stents, all the major pharmaceutical markets (US, Europe, Japan, Australia and Canada) have identified it as a device, and all the markets have classified and assigned it as a device based on the primary mode of action. Quality system regulations for manufacturing the device component and GMP regulations for manufacturing the drug component are followed in all of the countries. As the product is approved as a device, all of the adverse events are reported based on the adverse events reporting regulations of the device by all of the countries. A single marketing application is filed for premarket approval of the drug eluting stent in the USA. A single SHONIN application for a device is filed in order to get marketing approval in Japan. In Australia, conformity assessment is made by device programs, which then grants the approval for marketing.

The drug eluting stent is classified, reviewed and regulated in the same manner in all of the countries. The basis for classification of combination products is also similar in all of the countries. All of the countries have classified and assigned the combination products based on their primary mode of action and are following device manufacturing regulations for device components and, drug manufacturing regulations for drug components during the manufacture of the drug eluting stent. All of the countries reported the adverse events based on the device regulations. A single marketing application is filed under device by all of the countries. Hence, we can say that there is similarity in regulating the combination products by different countries. However, each country has to draft particular guidelines for better regulation of combination products. The guidelines may be summarized as:

- Particular guidelines on filing the marketing applications
- How many marketing applications have to be filed for different combination products?

- Distinct adverse event reporting regulations
- On what regulations have to be followed if there is any adverse event because of the ancillary action providing component
- Distinct post-market regulations
- To what extent the assigned regulatory body must seek help or information from other regulatory bodies
- Defining the combination products

It is also advisable to set up a committee like the Office of Combination Products in the USA and the Therapeutic Products Classification Committee in Canada in order to classify the combination products and assign them to the particular agency or board and also to make sure that there is a timely and effective premarket review and consistent and appropriate post-market regulation.

6. Conclusion

In the market, many products, such as drugs and devices, as well as drugs and biologics, have been combined to make new products. But this combination has the potential to offer unique regulatory challenges to the regulatory agencies. Following particular regulations for combination products is a very complex process, as they are made up of different constituent parts, each with its own respective regulations.

The regulatory review success of combination products may be estimated by the number of approvals and recalls of drug-eluting stent systems in the past 10 years. Out of 16 approvals, there is only one recall of the entire product. Twenty-five percent of Class III devices have been withdrawn during the same period while just over 1% of NCEs have been withdrawn. These preliminary data indicate that the regulatory agencies are successfully reviewing these combination products. Further data will be need to be examined as additional marketing history is generated.

Different countries follow the same process for classification and assigning the combination product. The way of regulating the combination products is similar in almost all the major pharmaceutical markets. Thus, there is similarity in regulating the combination products.

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