Development and Regulation of Combination Products
A Focus on Drug-Eluting Stents

By Gerald T. Rigdon

Abstract

Drug Eluting Stents (DES) are a combination medical device product whose primary purpose is to combat Coronary Artery Disease (CAD). The forerunner of DES, bare-metal stents, paved the way by changing the field of interventional cardiology in providing an effective, less invasive method of treatment. DES represent the next generation of scientific advancement by the use of drugs to address the reaction of the human body to the injury incurred by the stent implant. Moreover, DES are also representative of a new approach to medical treatment that includes combining multiple treatment solutions, often acting as a single entity. While these creative combinations offer much promise in treating disease, they also raise regulatory concerns due to their complexity. This paper will present the evolving regulatory environment for combination products over the past twenty years, and will attempt to clarify how such products are presently regulated in the context of DES.

Keywords

CAD – Coronary Artery Disease

DES – Drug Eluting Stent

FDA – Food and Drug Administration

PMA – Premarket Approval from the FDA

SMDA – Safe Medical Devices Act

According to the American Heart Association statistics published in 2006, Coronary Artery Disease (CAD) afflicts over seventeen million people and is a leading cause of death. During the past thirty years, less invasive surgical procedures have emerged to combat CAD, and Drug Eluting Stents (DES) are at the forefront of this modern technology. These Class III medical devices are combination products that are regulated in the United States by the Food And Drug Administration (FDA), and tested for safety and efficacy.

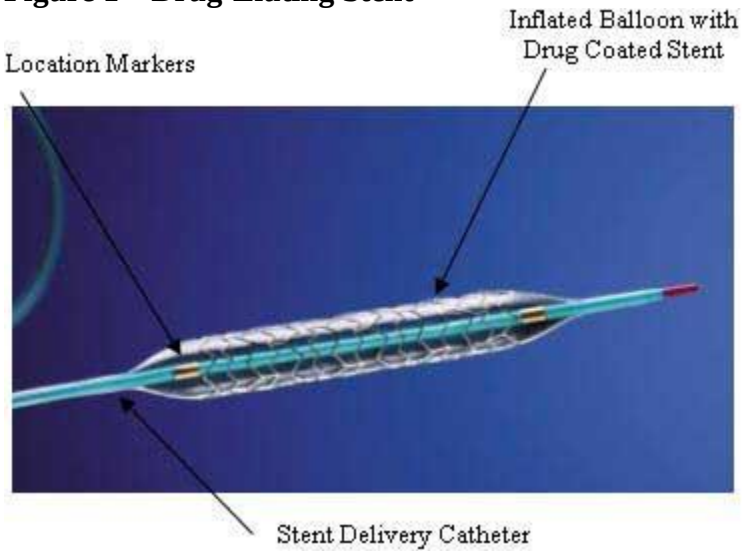
In general, the purpose of stents is to treat CAD, or more specifically stenosis. During the 1980's interventional cardiologists treated CAD with balloons by inflating them inside arteries in order to open them, hence allowing better blood flow. During this time it was discovered that following some procedures the artery collapsed after the balloon was deflated, resulting in emergency bypass surgery. Later, it was discovered that approximately 30% of the coronary arteries treated by balloon angioplasty soon began to close up again, a condition known as restenosis.

The initial stents were bare metal tubes that were inserted during balloon angioplasty. The stent is mounted on a balloon and left inside the artery following inflation in order to combat restenosis. However, during the early procedures physicians found that restenosis persisted in 25% of the stent cases within six-months and thereafter learned that restenosois was due to the body's response to what is called a "controlled injury" rather than a recurrence of CAD. This discovery led to the next evolution of stents, known as DES. These stents release a drug that prevents cell proliferation, a normal response from the body to injury or the existence of a foreign object. Without the use of a drug, there is a higher likelihood of fibrosis (excessive corrective tissue) and thrombosis (blood clotting), resulting in restenosis.

The first piece of legislation that recognized the importance of regulating combination products was the Safe Medical Devices Act (SMDA) of 1990. In the summary report before Congress [1] it "*Directs the Secretary to designate a component of the Food and Drug Administration to regulate products that are a combination of a drug, device, or biological product.*" The FDA's authority is found in the SMDA Section 503 (g) where it specifically states that the regulation is based on the '*primary mode of action*' of combination products.

This legislation was ahead of its time in the context of DES. In fact, the first bare-metal stent was implanted in France in 1986 and the first stent approved in the United States occurred in 1994. However, the evolution to DES was another decade in the making since DES is actually a product of the 21st century (See **Figure 1**).

Figure 1 – Drug-Eluting Stent



Although the SMDA in 1990 made a provision that would encompass DES, other complexities were not foreseen. Following the original SMDA legislation in 1990, the three centers in the FDA that regulated combination products were those for Biologics Evaluation and Research (CBER), Devices and Radiological Health (CDRH), and Drug Evaluation and Research (CDER). Yet, it became increasingly difficult to determine which FDA center had jurisdiction. While 21 CFR part 3 had described four categories

for combination products, it wasn't until 2002 that an establishment of an Office of Combination Products (OCP) occurred as a result of the Medical Device User Fee and Modernization Act (MDUFMA).

To further address the problem of jurisdiction, in 2005 the FDA went back to the original SMDA language and decided that the regulation was to be based on the '*primary mode of action*', which until that time was not clearly defined. However, in August, 2005 in the Federal Register there was as a section entitled "***Definition of Primary Mode of Action"*** which provided clarity as follows:
"Primary mode of action is the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall therapeutic effects of the combination product" [3].

In light of this historical progression, DES are identified as a *'single entity group'* [1] under 21 CFR part 3, managed by OCP that now operates with a more defined understanding of the '*primary mode of action'*. Although this combination product contains a drug, it is the stent itself that is the '*primary mode of action'* in combating Coronary Artery Disease. Thus, OCP directs CDRH as the lead review office with CDER review and consultation for the drug specific parts of the submission.

DES are classified as Class III medical devices, and as such require compliance with the Premarket Approval (PMA) process. For approval, DES must follow 21 CFR part 814 from the FDA. This process requires a clinical trial which generally requires at least 1500 participants and compliance with Investigational Device Exemption (IDE) regulations in connection with human clinical investigations. One such trial presently being conducted by Boston Scientific is described in the following corporate press release:
"The randomized, controlled PLATINUM Workhorse clinical trial completed enrollment in September 2009 with 1,531 patients at more than 130 sites worldwide and compares the PROMUS Element Everolimus-Eluting Coronary Stent System to the PROMUS (Xience V) Everolimus-Eluting Coronary Stent System. One-year data from the trial will be presented at the Scientific Session of the American College of Cardiology/i2 Summit in March 2011" [2].

While companies like Boston Scientific manufacture DES, one could imagine future combination stent products that may be "biologic-eluting" rather than "drug-eluting." With these types of combination product possibilities, the applicable regulations would continue to be based on the '*primary mode of action'*. Thus, like DES, if the stent was the *'primary mode of action'* then "biologic-eluting" stents would be regulated in a similar way with the CDRH office in the lead. However, in this case it would be CBER instead of CDER in a support role for the biologic component.

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[1] *"A product comprised of two or more regulated components, i.e., drug/device, biological product/device, drug/biological product, or drug/device/biological product that are physically, chemically, or otherwise combined or mixed and produced as a single entity."* – 21 CFR part 3

Submitting for DES for FDA approval involves 21 CFR part 814, Drug CFR, DES balloon catheter DES guidance, bare stent guidance, and all other applicable laws and regulations for the development, testing, manufacturing, labeling, marketing and distribution of medical devices. The United States provides three options for a device to have commercial distribution:

1. *The first process requires that a pre-market notification (510(k) Submission) be made to the FDA to demonstrate that the device is as safe and effective as, or substantially equivalent to, a legally marketed device that is not subject to pre-market approval (PMA), i.e., the "predicate" device. An appropriate predicate device for a pre-market notification is one that (i) was legally marketed prior to May 28, 1976, (ii) was approved under a PMA but then subsequently reclassified from class III to class II or I, or (iii) has been found to be substantially equivalent and cleared for commercial distribution under a 510(k) Submission. Applicants must submit descriptive data and, when necessary, performance data to establish that the device is substantially equivalent to a predicate device. In some instances, data from human clinical trials must also be submitted in support of a 510(k) Submission. If so, these data must be collected in a manner that conforms to the applicable Investigational Device Exemption (IDE) regulations. The FDA must issue an order finding substantial equivalence before commercial distribution can occur. Changes to existing devices covered by a 510(k) Submission that do not raise new questions of safety or effectiveness can generally be made without additional 510(k) Submissions. More significant changes, such as new designs or materials, may require a separate 510(k) with data to support that the modified device remains substantially equivalent. The FDA has recently begun to review its clearance process in an effort to make it more rigorous, which may require additional clinical data, time and effort for product clearance.*

2. *The second process requires the submission of an application for PMA to the FDA to demonstrate that the device is safe and effective for its intended use as manufactured. This approval process applies to certain class III devices. In this case, two steps of FDA approval are generally required before marketing in the U.S. can begin. First, we must comply with the applicable IDE regulations in connection with any human clinical investigation of the device in the U.S. Second, the FDA must review our PMA application, which contains, among other things, clinical information acquired under the IDE. The FDA will approve the PMA application if it finds that there is a reasonable assurance that the device is safe and effective for its intended purpose.*

3. *The third process requires that an application for a Humanitarian Device Exemption (HDE) be made to the FDA for the use of a Humanitarian Use Device (HUD). A HUD is intended to benefit patients by treating or diagnosing a disease or condition that affects, or is manifested in, fewer than 4,000 individuals in the U.S. per year. The application submitted to the FDA for an HDE is similar in both form and content to a PMA application, but is exempt from the effectiveness requirements of a PMA. This approval process demonstrates that there is no comparable device available to treat or diagnose the condition, the device will not expose patients to unreasonable or significant risk, and the benefits to health*

> *from use outweigh the risks. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting smaller patient populations.* [2]

While it is beneficial to introduce an advanced device into the market as early as possible, there is a certain risk ensuring its safety and efficacy considering that FDA approval for combination products is a challenging task. Risk-based Classification, Level of Regulatory Control & Submission Type (see **Table 1**) shows the high risk involved with respect to its safety and efficacy and therefore requires the toughest regulatory controls and Premarket Approval.

Table 1 - Risk-based Classification, Level of Regulatory Control & Submission Type

510 (K) Exempt	Class I	Class II	Class III
Very Low	Low	Medium	High
General Control (may or may not be GMP exempt)	General Controls Premarket Notification or 510 (K)	General & Special Controls 510 (K) submission	General & Special Controls Premarket Approval

Source: [6]

ISO [7] has defined "Risk" as, "combination of the probability of occurrence of harm and the severity of that harm". Combination products are a recent advancement considering the patient health benefit, but at the same time there may be some serious risk concern associated with these newly developed products. In order to focus on high safety and efficacy standards medical device or combination product has to pass through high quality standards. Risk Assessment is one of the parameters to measure the high quality standards by analyzing and evaluating the risk associated with the newly developed product. Therefore, to establish an efficient Risk Management Process for a product, complete Risk Assessment should be performed. Risk Analysis and Risk Evaluation are the two main components of Risk Assessment which are applied to all development aspects of a combination product.

Further, in order to carry out the full Risk Assessments it is important to identify its risk score level based on Risk Assessment classification for combination product with drug and devices. The risk score levels can differ depending on the risk factors like the type of contact as well as the time duration for the product exposure. General consideration and views regarding *Drug Safety* and *Drug Approval Process* from the Center for Drug Evaluation and Research [8] says: "The larger number of patients (typically 300-600) exposed for more than 6 months allows detection of adverse events that develop only after longer exposure." Risk Assessment for combination product is classified using a risk matrix (see **Table 2**).

[2] United States Securities and Exchange commission, form 10-K, annual report, December 31, 2009, Commission file No. 1-11083

Table 2 - Risk Assessment Classification for Combination Product by using Risk Matrix

Risk Factors		Risk Score Level				Drug/Device Combination Product Risk
Contact Type	Exposure Duration	Drug	Class I	Class II	Class III	
Implanted Direct Contact	Long Term	Medium-High	High	Very High	Extremely High	III
	Short Term	Medium	Medium-high	High	Very High	III
Implanted with Barrier	Long Term	Medium	Medium-high	High	Very High	III
	Short-Term	Low-medium	Medium	Medium-high	High	II
Extracorporeal direct contact	Long term	Low-medium	Medium	Medium-high	High	II
	Short Term	Low	Low-medium	Medium	Medium-high	II
Extracorporeal direct contact through barrier	Long Term	Low	Low-medium	Medium	Medium-high	II
	Short Term	Very Low	Low	Low-medium	Medium	I

Source: [9]

As a combination product DES development and approval is supported by guidance from the FDA [4]. Although this guidance was published as recently as 2008, the FDA continues to offer even more recent guidance such as the 2010 guidance [11] on third party auditing. While this particular guidance is broader in scope, there isn't anything in the regulations that would prohibit combination products like DES from taking advantage of these types of audits. This is another example of the evolving regulatory environment which influences combination products.

There has been tremendous advancement in medical device technology since the SMDA twenty years ago. Granted, there was some measure of foresight in this important Act of Congress. However, as the past two decades can attest, much has changed and been clarified out of necessity. With the rapid pace of advancement we can expect the FDA to continue evolving in order to meet the demands of its charter. The next two decades will no doubt be fascinating to experience in the world of regulatory affairs as combination products become every increasingly prevalent in addressing the medical needs of society.

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