Streamlining The Medical Device And Combination Product Regulatory Approval Process

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***Abstract* – The rise of combination products in the medical device and pharmaceutical worlds, combined with the timeline differences in bringing drugs and devices to market (an average of 12 years for a drug; 1-5 years for a device), has led to the practice of developing the device constituent part of a combination product separately from the drug as a general drug delivery system, with minor changes to ensure compatibility with a certain drug or risk level. Unique regulatory requirements or submission requirements, particularly when involving a separate regulatory center or body, add a considerable amount of time and money to the approval process and reduce the financial and speed-to-market benefits of this approach. Streamlining the approval process, while maintaining standards for safety, efficacy, and reporting, can help bring therapies to patients faster and reduce the cost of bringing new therapies to market. Using TRIZ tools, regulatory processes will be analyzed to identify areas that can be optimized to reduce time and cost to market without compromising efficacy and patient safety.**

***Index terms* – FDA, medical device, drug, combination product**

I. INTRODUCTION AND BACKGROUND

The rise of combination products in the medical device and pharmaceutical worlds, largely resulting from the growth in research and use of biologics has led to the ever more common use of pre-filled syringes, auto-injectors, subcutaneous infusion over short or long time periods using a pump, and other non-oral dosing routes of administration. Due to the timeline differences in bringing drugs and devices to market (an average of 12 years for a drug[1], and 1-5 years for a device[2]), the device constituent part of a combination product is sometimes developed separately from the drug as a general drug delivery system, and minor changes are made so ensure compatibility with a certain drug asset or risk level. Unique regulatory requirements or submission requirements, particularly when involving a separate regulatory center or body, add a considerable amount of time and money to the approval process. Streamlining the approval process, while maintaining standards for safety, efficacy, and reporting, can help bring therapies to patients faster and reduce the cost of bringing new therapies to market.

II. MOTIVATION

There are industry initiatives to use the same auto-injector "framework" to deliver multiple drugs, with color and other branding changes to differentiate between products.[2,3] This would greatly reduce the time and cost it takes to bring the device constituent part of a combination product to market. Clinical studies and human factors (HF) studies are often the largest cost in bringing a product to market.[4] After the initial device clinical and HF work, the same device could be bridged using engineering work and abbreviated studies, such as with specific patient populations, to show the applicability of past results.

Unique regulatory requirements, however, add additional work when submitting a combination product to different markets or with differing constituent parts. European regulatory agencies, for example, do not recognize combination products and have drug and device constituent parts submitted separately, with any cross-labeling acknowledged by both companies or by the company filing later. The FDA, however, requires combination products to be submitted as a unit, with the primary agency center determined by the primary mode of action of the combination product and lesser involvement by a secondary agency center for the secondary mode of action of the product. These different approaches to combination products mean different tests and vastly different regulatory filings.

Unique regulatory requirements or submission requirements, particularly when involving a separate regulatory center or body, add a considerable amount of time and money to the approval process. Streamlining the approval process, while maintaining standards for safety, efficacy, and reporting, can help bring therapies to patients faster and reduce the cost of bringing new therapies to market. Using TRIZ tools, different processes used by regulatory bodies will be analyzed to identify areas that can be optimized to reduce time and cost to market for combination products with a device constituent part without compromising efficacy and patient safety.

III. MARKET IDENTIFICATION

Virtually everyone on the planet will take a drug or use a medical device at some point in their life. The US alone has a population greater than 300 million people.[5] All medical devices and drugs go through regulatory approval processes that the Food and Drug Administration (FDA) has established and conducts.[6] This process is designed to ensure drugs are safe

and effective, but it has a number of drawbacks in getting treatments to patients quickly and inexpensively. Some Americans, recognizing the lower cost of healthcare in other countries, engage in "medical tourism", the practice of traveling to another country for the express purpose of obtaining medical care.[7] This includes traveling to Mexico or Canada to purchase less expensive medications, travel to have surgery for a lower cost, and travel for procedures or drugs not approved in the US. For example, one day in the hospital in Spain costs an average of $424, while the US average is $5220.[8] A 4-week supply of Harvoni, the first approved cure for Hepatitis C, costs an average of $32,114 in the US and only $18,165 in Spain. The same drug and manufacturer, but half the cost when purchased in a different country. Further, Harvoni requires 12 weeks of treatment, meaning a patient with average insurance could save $55,000 by seeking treatment in Spain instead of the US.[9]

Medical tourism represents the "competition" that regulators in the US face. The FDA itself is not directly impacted by medical tourism. The pharmaceutical and medical device manufacturers, healthcare providers, and insurance providers are the entities impacted by medical tourism. Some of this can be considered beneficial - US insurance companies can pass the financial burden of expensive hepatitis treatment onto the Spanish government in the earlier example. Those buying medications like insulin in Mexico or Canada are likely buying from the same manufacturers at a lower cost. Some of that is the price difference to the manufacturer[8] and some of it is passed on to the government healthcare programs that subsidize medication. Medical device and pharma companies, insurance companies, healthcare providers, and industry advocacy groups are ultimately the drivers to target for change. The US spent almost $40 billion in 2015 on healthcare costs that could have eliminated by seeking or completing treatment earlier.[10] This leads to an additional force on the regulatory bodies from "internal" government sources, including members of Congress and the President .[11]

Growth rate in the market for medicines and medical devices is derived from several sources. Birth rate, life expectancy changes (or indirectly, death rate), economic factors (fewer people put off healthcare costs when they have more money to spend), healthcare costs in other countries (lower costs outside the US increase medical tourism, while rising prices decrease medical tourism), and healthcare costs in the US (more expensive drugs mean fewer people can afford them). Improved healthcare in the US with lower costs could also induce "reverse" medical tourism, where patients travel to the US for a higher quality of care than they find in their home countries. Currently cost of healthcare in the US makes this rare, as Canada and most of Europe have comparable healthcare with drastically lower prices.[8]

The predictability of the healthcare market depends largely on economic health of a country and its government. A government initiating austerity measures due to economic distress is less likely to be able to fund expensive hepatitis treatments[12] when there are less expensive options in the short term, even if the long-term cost is higher. Patients worried about the cost of treatment and how to pay may opt to delay treatment, choose a less expensive option with more downsides, or forgo the procedure altogether if it is not life-threatening.

In total, the market impacted by the difficult regulatory approval process of the FDA and the high cost of medicines and medical devices is enormous and includes virtually everyone in the US.

IV. VALUE PROPOSITION

Regulatory requirements vary by country, although some countries (such as European Union member states) accept approval by other countries with few or no additional regulatory requirements. Unique regulatory requirements or submission requirements, particularly when involving a separate regulatory center or body, add a considerable amount of time and money to the approval process. Streamlining the approval process, while maintaining standards for safety, efficacy, and reporting, can help bring therapies to patients faster and reduce the cost of bringing new therapies to market. Another large cost is in early safety studies performed in animals. Lately, a large amount of work has been done to reduce number of animals and "level" of animal used. Zebrafish have been introduced as a useful model for many early tests on toxicity.[13] The lower cost of using zebrafish can also reduce the cost to bring therapies to market, as costly safety studies can be done earlier, eliminating unsafe drugs before further work is done to develop them. Reducing the number of dogs or monkeys used in more substantial studies later is not only advantageous for ethical reasons but also for cost reasons.

The FDA is broken into different "centers" based on a therapy's primary mode of action.[14] These centers cover drugs (Center for Drug Evaluation and Research, CDER), biologics (Center for Biologics Evaluation and Research, CBER), and devices (Center for Devices and Radiological Health, CDRH) separately. Several other centers exist for veterinary medicine, tobacco, nutrition, and toxicology. There are also offices for regulatory affairs, policy and legislation, foods and veterinary products, and medical products and tobacco. The approval process for the three centers, as well as two European countries, is compared in Figure 1.

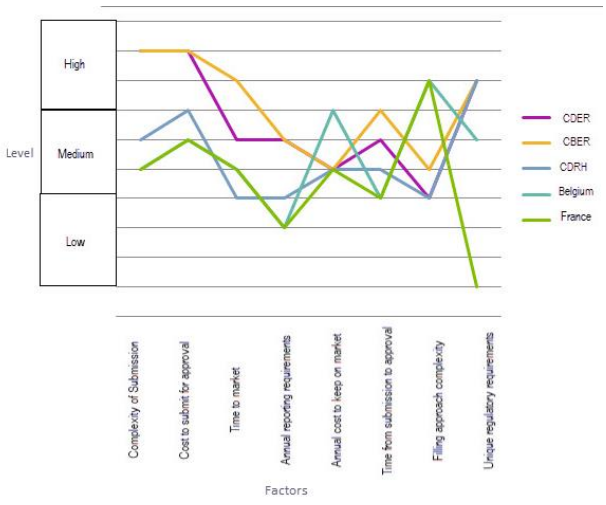


Fig 1. Example approval process factors for various regulatory bodies.

The FDA approval process consists of 5 phases: Discovery and Development; Preclinical Research; Clinical Research (with 4 sub-phases), FDA Review; and Post-Market Safety

Monitoring. An Investigational New Drug (IND) or Investigational Device Exemption (IDE) is filed to move into the Clinical Research Phase. A 510(k), Premarket Approval (PMA), or New Drug Application (NDA) is filed to move into the FDA review phase. Which of these is filed depends on which center the filing is being submitted to, and the primary mode of action of the therapy. With combination products, there is a lot of grey area on which process should be followed, and companies ultimately are subject to whatever the FDA determines is the appropriate path, although companies can submit a response arguing that a different process is more applicable to a therapy.

Outside the US, it is common for device and drug or biologic constituent parts of a combination product to be submitted separately, as two different regulatory submissions.

V. CAUSE AND EFFECT ANALYSIS – SIMULINK MODEL

A. *Areas Of Optimization*

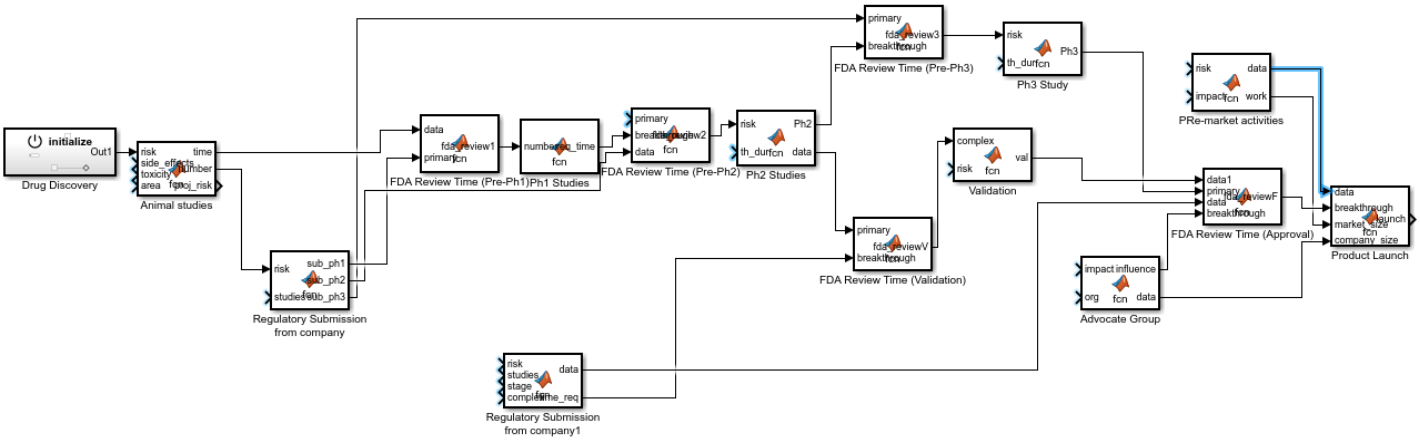
Because regulations are set by law and by the FDA, changing these procedures requires a large amount of time and effort, and the agreement and support of a large number of people. Because such a large, concerted effort would be needed to change these parts of the approval process, my preliminary focus will be on optimizing the parts of the approval process that are outside the FDA's regulations. However, parts of the FDA approval process found to be particularly crucial to improving the cost, time required, and effectiveness of the overall drug/device development and approval processes are included as areas to optimize.

One important area to minimize, here noted as "project risk", is the likelihood of an asset not making it to market. The longer an asset is developed and the more resources are spent on it, the higher the project risk grows. Activities that can reduce the project risk are particularly valuable in reducing cost to market, and the earlier these activities can be performed the better as less money will have been put into developing an unsuccessful asset. Pharmaceutical companies often note the need to recuperate losses for failed assets when defending high drug costs.

to stress-test an asset. If a larger number of assets can go through an animal test that is successful at identifying unsafe or ineffective drugs, more drugs that are safe and effective can be brought to the later stages of development, which are considerably more expensive.

Another area for improvement is in sharing information on failed assets. Implementing this would take significant effort by regulatory agencies and industry, as well as a considerable dedication of time and resources to establish. Similar efforts are underway for sharing failed academic research, which similarly lacks a way to be share unfavorable results; failed studies cannot be published the way that successful research can be, and there is little to no funding for reviewing and confirming failed results. Because of the high cost of failed assets, eliminating the duplication of work on a failed asset by multiple companies will reduce development costs. Companies will undoubtably have concerns over intellectual property rights and sunken cost, as well as the initial cost of sharing information, both from a compliance perspective and from a perspective that other companies are benefitting from research that one company paid for. Regulations on the publication of data will be needed to enforce the sharing of data. One option to reduce anxiety over sharing data would be to include timeframes for sharing information, such as information should not be published in the first year after an asset is deemed a failure but must be published within three years of failure. Another mechanism to reduce anxiety would be to include financial compensation if a company terms an asset a failure and another company later successfully develops that asset, i.e. Company A publishes that Toxical has toxicity issues in the failed asset database. Company B addresses the toxicity issues and brings Toxical to market successfully. Company A receives 5% of revenue from Toxical for the first 5 years of sales for the first indication, and an additional 6 months for each new indication added. This would encourage companies to publish failed assets, as it offers an alternative mechanism for recouping cost of a failed asset that does not exist today. The type and extent of

Fig. 2. Simulink model – Regulatory processes



B. *Identifying And Eliminating Tradeoffs*

Using the Simulink diagram shown in Figure 2, I identified animal studies and activities within discovery as the best places

information published on failed assets would also need to be covered, as companies will not want to share confidential information on processes, cell lines, proprietary technology,

test methods, etc. The financial compensation mechanism could be used to incentivize companies to provide extra information on how they tested and developed an asset to a company attempting to bring a failed asset to market.

Furthermore, the failed assets could be analyzed by companies for similarities in structure, mode of action, etc. to identify similarities in failed drugs versus successful ones. This would help companies identify assets likely to fail and perform additional studies early on in order to determine if the asset is worth proceeding with, without requiring a significant investment of time or money.

TABLE 1.

Contradiction	Solution
Review times that get drugs to market quickly while still ensuring safety and efficacy	Require shorter review times by law, while funding and staffing the FDA adequately
	Create an early-stage center in the FDA to focus on responses for early research questions, with an emphasis on more interactive discussions
	Encourage more open dialogue between the FDA and industry
Providing feedback that is quick and thorough	Allow companies to provide multiple options for the FDA to review, so that the best option can be found
	Allow and encourage FDA to provide broader feedback earlier in the development process
	Require the FDA to provide timelines for response to all submissions

The primary tradeoff or contradiction found is sufficient review by an impartial body, here the FDA, to ensure safety, and secondarily efficacy, of a drug, device, or combination product, with a quick time to market. Pharma and device companies, in order to ensure the best odds for approval down the road, go to the FDA for feedback throughout the development process. This means that there are many times where the FDA reviews documentation submitted by a company for a particular asset. Most of these opportunities have a legally required response time, mandated by the Prescription Drug User Fee Act (PDUFA), ranging from 6 months for a priority review to 12 months for a typical review.[15] After implementation of PDUFA, reviews completed within 12 months went from approximately 40% to nearly 100% (with the one missed application receiving a response 3 days after the 12-month deadline), far exceeding the target of 70%.[15] Clearly, imposing a deadline for response resulted in benefit for both patients and industry. The 21st Century Cures Act, which included the renewal of PDUFA ("PDUFA VI"), further increased communication between the FDA and industry, as well as reduced response times for some submission types.[16] This increased communication includes a response from the FDA containing a timeline for review and a response including any significant issues found. These items should allow companies to address issues in a timely manner, plan more accurately, and allocate resources more efficiently.

Giving the FDA sufficient resources to review submissions quickly, requiring reasonably quick responses by the FDA, and creating an office that focuses on open dialogue for early phase submissions as an optional chance for industry to have open dialogue that can be funded by the companies themselves the way other submissions are. Early phase submissions are less time sensitive, have more opportunities for corrections or additional data collection, and are an ideal area for innovation in experimental and manufacturing methods as the drug or device is not yet being used by patients and will be studied comprehensively in use down the road before approval, are several ways to cut down review time. Companies will always be motivated to get their product to market quickly in order to maximize profits, compete with other companies, and benefit patients. The FDA is ultimately beholden only to the laws governing it. Creating laws that require quick responses, paired with adequate staffing and funding to meet these requirements, can push the FDA to ensure quick review times and better communication with industry. This early research submission time is also a great time for the FDA and industry to have more dialogue about what the FDA would like to see down the road and improvements that could be made to methodology to shorten studies, use fewer animals, or improve statistical analysis. Currently, the FDA only provides feedback on whether or not they agree with a specified approach and generally does not recommend different methods. A more open dialogue could be a way for the FDA to recommend improvements without significant additional work – instead of seeing one path and providing improvements, the FDA can see three or five and recommend the best approach, or even provide several options and comment on the validity of each. The FDA has the broadest view of research at this stage, and could be a source of sharing scientific knowledge for the betterment of mankind and the furthering of scientific knowledge, with a lower chance of concerns around sharing data.

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About the Author

Morgan Hunt is an engineering project manager at AbbVie, Inc. working on drug delivery device systems. She graduated from Northwestern University in 2015 with a Bachelor's in Biomedical Engineering and a minor in Spanish. Morgan began working for AbbVie in 2015 and has worked on combination products in both Operations and R&D. Morgan part of a combined Master's in Engineering and Master's in Business Administration through Purdue University and Indiana University's Kelley School of Business.