Drugs and Devices
A Regulatory and Clinical Trial Comparison

By

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Abstract

Although drugs and medical devices are both health care products, they are distinguished from each other in the regulatory environment based on their mechanism of action, which leads to separate regulatory pathways for approval. Our goal in this tutorial is to identify the differences between drugs and devices and how these differences affect regulatory processes and clinical trials. Also, we will consider similarities in the context of the ultimate goal for each, which is to achieve a safe and effective product that is approved for use.

I. Definitions

A drug is defined in FD&C Act, sec. 201(g)(1) as:

- *articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease* and *articles (other than food) intended to affect the structure or any function of the body of man or other animals*

A medical device is defined (FDA) in FDCA section 201(h) as:

- *an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is*
    - *recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them;*
    - *intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or*
    - *intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.*

II. Introduction

The purpose of clinical research is to deliver new therapeutic modalities to the market place by answering scientific questions with respect to safety and effectiveness. Although clinical research is not required for most medical devices, for those devices where it is required the clinical trial process is different from that of drugs. In this tutorial we will compare the clinical trial process between drugs and medical devices and begin our discussion by considering what Bernard King [4] suggests are the seven key characteristics of a well controlled clinical study:

1. *Protocol contains clear statement of study objectives*
2. *Summary of proposed or actual analytical methods are included in the protocol and report*
3. *Study design permits valid comparison with control to provide a quantitative assessment of the therapy effect*
4. *Methods of assessment of subjects responses (efficacy and safety) are well-defined and reliable*
5. *Study report provides sufficient details of study design, conduct, and analysis*
6. *Patients were assigned to treatment and control groups in a way that minimized bias (e.g., randomization)*
7. *Adequate measures were used to minimize bias of subjects, observers, and data analysis (e.g., blinding)*

III. A Regulatory Overview

Table 1 adapted from Gropp [1] is a side by side comparison of drugs and devices. As indicated in the introduction, not all medical devices require clinical trials.

Table 1 (Regulatory Differences)

Drugs	**Medical Devices**
Clinical trials generally required	Clinical trials often unnecessary
Phased clinical trials	Un-staged clinical trials
Often randomized double blind studies, sometimes with placebos	Often unfeasible and/or unethical to attempt double blind studies and/or placebo trials
No explicit risk stratification	Risk-based classification
Emphasis on kinetics, metabolism, and disposition in body	Emphasis on interaction with body, possible failure modes
Good Manufacturing Practices	Quality Management Systems

Hence, while drugs have only one classification, devices have three classes as follows per the FDA Code of Federal Regulations, 21 CFR Part 860:

1. Class I (low risk)
    a. General controls

2. Class II (moderate risk)
    a. Performance standards/May require clinical trial data in some cases

3. Class III (high risk)
    a. PMA or Pre-market Approval/Clinical Trials

Therefore, medical devices have different risk-based classes which require proportional regulatory controls. Class III devices require clinical trials and so are more similar to the drug process in that respect. When one examines the regulatory processes more closely, distinctions emerge due to inherent differences between drugs and devices.

IV. A Macro Perspective of the Differences

There are 3 key requirements that the FDA generally requests at a minimum from sponsors of new drugs in an IND or Investigational New Drug Application [9]:

(1) develop a pharmacological profile of the drug

(2) determine the acute toxicity of the drug in at least two species of animals

(3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

The purpose of these requirements is to understand the intended use of the drug and to determine how animals are affected in order to make a determination that the drug is safe enough to use in human trials. In [3] Karen D. McElvany states: *"The FDA requires that animal studies be reasonable predictors of the pharmacological activity of the investigational agent. In addition, toxicity studies must be designed such that they are likely to reveal adverse events that could be relevant to humans."*

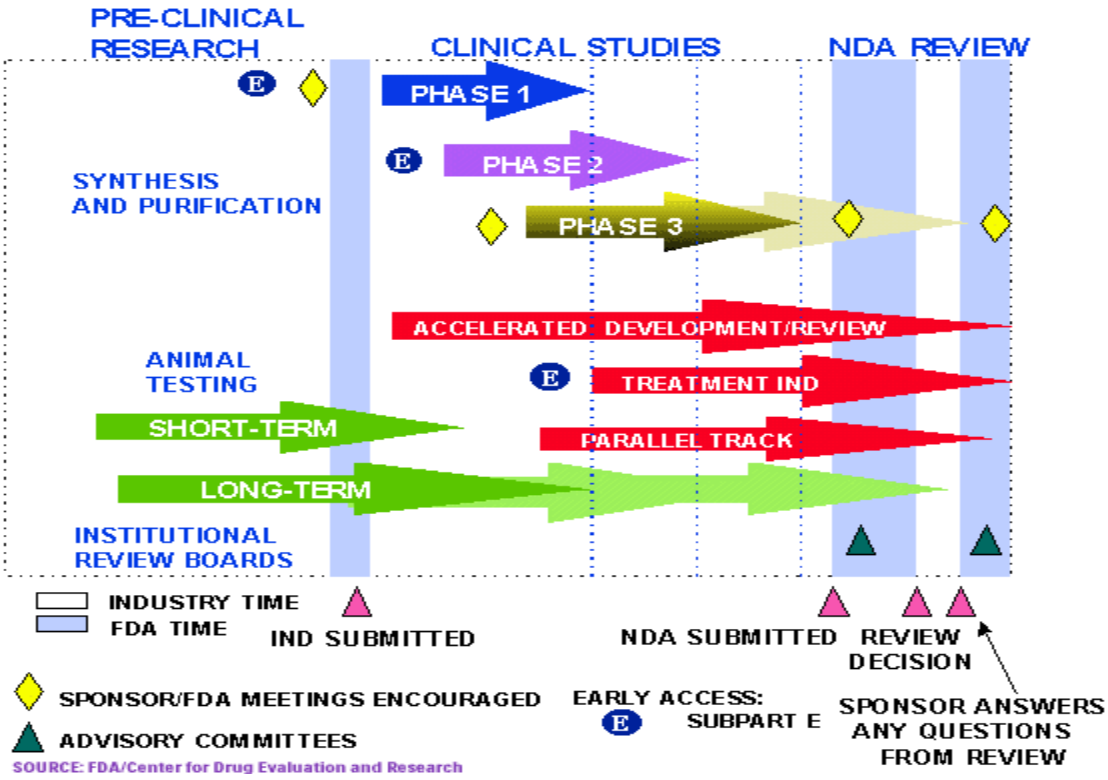
Following this pre-clinical stage, as shown in **Figure 1** below, clinical studies for drugs consist of three phases, which if successful, lead to an NDA or New Drug Approval.

Phase 1 is sometimes referred to as the "First-in-Man" study since it includes the use of a new drug in humans. Typically, this study is a safety study performed in 20 to 80 healthy patients in order to determine the metabolic and pharmacologic actions of the drug in humans and any side effects associated with increased dosage.

Phase 2 is conducted using several hundred people to determine if the preliminary data indicates that the drug is effective for particular indications in the patients. This is a proof of concept study and is closely monitored for side effects and risks.

Phase 3 is conducted after the previous studies have indicated a measure of safety and effectiveness. This is a confirmatory study that is expanded from several hundred to several thousand people and evaluates the overall risk/benefit of the drug.

Figure 1 (From the CDER Handbook)



Unlike drug regulation which began prior to WWII, the regulatory oversight of medical devices began in 1976 when the Medical Device Amendments requirements were signed into law. Previous to this, a task force was assigned to analyze medical device regulations and this committee (the Cooper Committee) concluded that medical devices were different enough from drugs such that the drug process for approval was not desirable. Hence, the law that was passed was focused on risk with much burden falling upon health care professionals to use good clinical judgment when deciding to use devices. Initially, devices could be approved without the need for clinical data. However, over time these requirements were refined, and high risk Class III devices were required to have clinical data before approval.

The requirements that the FDA requests from sponsors of new devices in an IDE or Investigational Device Exemption are in 21 CFR Part 58 [9] which defines a non-clinical laboratory study as a *"means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article."*

Following this pre-clinical stage, unlike the multi-phased drug trials, Class III devices follow a PMA or Pre-market Approval Process which includes a pilot study followed by a pivotal trial as mandated by 21 CFR Part 812.

Pilot studies are usually held at one site and involve a limited number of participants (typically fewer than 25). Similar to Phase 1 drug studies, pilot studies are held when there has been limited experience with human participants. Rather than testing a hypothesis, pilot studies are aimed at gathering preliminary safety and performance evaluations. However, pilot studies are not equivalent to Phase 1 drug studies since these drug studies are typically done with healthy participants to test the safety of the drug.

While drugs require more than one clinical trial, devices need only a single pivotal trial. A medical device pivotal trial is comparable to a Phase 3 drug trial where the safety and effectiveness is evaluated in sick patients using a larger group of participants.

The intent of the original medical device regulation was "reasonable" assurance of safety and effectiveness. Thus, the medical device approval process is more flexible because the regulations require only "reasonable" assurance of safety and effectiveness while a drug clinical trial requires "substantial" evidence of safety and efficacy. As a practical matter this means that one can make a case for "reasonable" assurance for devices by presenting scientific evidence that does not have to come from well controlled clinical studies. In the article [8], it suggests that "reasonable" assurance rests on answering these questions:

1. Are there reasonable assurances, based on valid scientific evidence that the probable benefits to health from use of the device outweigh any probable risks?

2. Is there reasonable assurance based on valid scientific evidence that the use of the device in the target population will provide clinically significant results?

V. Comparative Differences

As shown in **Table 2** adapted from Gropp [1] there are distinct differences between drugs and devices. Furthermore, the development processes have significant differences that result in clinical trial differences. Generally, devices are created to accomplish an existing task more effectively which often means the intended patient population and intended use of the device is known in advance. In contrast, the drug process may result in the creation of some molecular entity for which the clinical application is unknown. The following excerpt from [5] explains this further:

"Consider robotic devices intended to provide the surgeon with the ability to manipulate, cut, and suture tissue via a computer-assisted surgical system. Although the original FDA clearance of this device was based on data collected on the device performance during 2 specific surgical procedures (laparoscopic cholecystectomy and Nissen fundoplication), these 2 procedures were already performed laparoscopically, and the clearance was based on a demonstration of device performance. FDA clearance was not based on clinical outcomes, but rather a demonstration that the device, in the hands of a trained surgeon, can be safely used to perform the surgical tasks."

Table 2 (A comparison)

Drugs	**Medical Devices**
Discovered	Designed
Stable formulation once developed	Constant iterative improvements
Highly mechanized manufacture	Often manufactured by hand operations
Consumed by use	Available for study after use
Systemic toxicity	Adverse events most often local in nature
Large populations of exposure	Relatively limited populations
Pure molecules	Complex component and assemblages
Short half-life in body	Biocompatibility
Long market life	Durable
Drug interactions of concern	Rapid product cycle
Wrong use/dose	Device malfunctions possible
Clinically studied	Often studied on bench

From **Table 2** a notable difference is the incremental changes (iterative improvements) in the design of devices. In this respect, the techniques for safety and effectiveness are differentiators that make devices inherently different from drugs. To this end, as stated in [5], "*device regulation requires that the FDA tailors the data requested from a manufacturer to address the specific*

safety and effectiveness questions that need to be addressed before a marketing authorization can be granted." Thus, a clinical trial may provide data that demonstrates safety and effectiveness while also providing information that leads to improvements in device design and instructions for use before marketing. Thus, for example, if a pacemaker has been approved through the Class III PMA process, iterative improvements do not require another clinical trial for the same essential functionality of a pacemaker. Rather than such redundancy, the clinical studies focus on what has changed. Hence, the FDA accommodates non-traditional PMA approaches to approval by means of Streamlined PMA's and Product Development Protocols.

For example, a Streamlined PMA is a process intended for devices and technology that are well known to the FDA [9]. This process may be used when there is either:

- *an FDA guidance document or other published methods for review which have been evaluated by FDA, or*
- *an FDA review history dealing with like products (two or more of a kind)*

For the Product Development Protocol Process, the clinical evaluation and necessary information for marketing approval are put together into a single regulatory mechanism. This allows manufacturers of devices that are already well established in an industry to be able to come to an early agreement with the FDA as to what is required for a new device approval [9].

VI. Similarities

Despite the differences between drugs and devices there are also many similarities. In terms of the actual mechanics of the clinical trials, both allow superiority and non-inferiority design options. Both use primary and secondary effectiveness end points. And, both are hypothesis driven, using statistical 5% Type 1 error and 80-90% power [6]. Furthermore, both drugs and devices follow the same regulations for electronic medical device records, human subject protection, financial disclosure, and IRB requirements. In fact, even in the areas where they differ, namely 21 CFR 312 for drugs and 21 CFR 812 for devices, there still remains a core of similarities. See **Table 3** from Maddock [7] below.

Table 3

Federal requirements	DRUGS	DEVICES
21 CFR 11	Required	Required
21 CFR 50	Required	Required
21 CFR 54	Required	Required
21 CFR 56	Required	Required
21 CFR 312	Required	Not required
21 CFR 812	Not required	Required

SIMILARITIES	312	812
Requires that the appropriate submission be made to the FDA before beginning an investigation	v	v
Requires annual updates on study progress	v	v
Requires amendments when changes are made	v	v
Addresses the issue of promotion and charging for the product	v	v
Specifies requirements for labeling	v	v
Addresses waivers	v	v
Describes both sponsor and investigator responsibilities	v	v
Requires that the investigation be conducted in compliance with the investigational plan, signed agreement, federal regulations, and conditions of approval imposed by the IRB	v	v
Requires the selection of qualified investigators	v	v
Requires that sponsors provide information to investigators	v	v
Requires that the investigation be properly monitored	v	v
Requires that IRB approval be obtained prior to beginning the investigation	v	v
Specifies to whom significant new information should be provided	v	v

VII. Summary

As we have discussed, drugs are different from devices and these distinctions have resulted in some differences in the clinical trial approach. However, despite such differences, it could be said that both drugs and devices are similar in that they meet the criteria of the seven key characteristics of clinical trials identified by King [4]. That is, they possess clear protocols, use analytical methods, quantitative assessment, have well defined subject responses, detailed study designs, and use control groups to minimize bias.

While some may argue that these key characteristics are realized at a higher bar for drugs, it should be appreciated that such distinctions are due to the inherent differences between drugs and devices. Granted the device process is more flexible and does not always demand clinical data. Yet, for devices that are considered high risk one should consider that there are notable similarities in the approval process. Hence, it truly may be said that the differences are in the details as expressed in [7], *"So while the investigations of drugs and devices have their differences, by design these differences are intended to accomplish the same goal: to safeguard those research participants while bringing safe and effective products to the market as quickly as possible."*

References:

[1] M. Gropp, “Differences Between Pharmaceuticals and Medical Devices and Implications for Regulatory Systems”, 2007

[2] Karen Becker and John Whyte, “Clinical Evaluation of Medical Devices,” 2006 Humana Press Inc.

[3] Karen McElvany, “FDA Requirements for Preclinical Studies”, University of North Carolina School of Medicine, Chapel Hill, N.C., US

[4] Bernard King, “Clinical Development”, Macnas Consulting International, 2010

[5] Richard P. Felten, Neil R.P. Ogden, Carlos Peña, Miriam C. Provost, Michael J. Schlosser, Celia M. Witten, “The Food and Drug Administration Medical Device Review Process”, AHA, Inc., 2005

[6] Phillip Lavin, “Getting Ready for the Medical Device Approval Process: Lessons Learned from the USA FDA PMA Approval Process”, 2008

[7] Sandra Maddock, “The Difference is in the Details: Drugs v. Devices”, 2010

[8] Andrew Gelman, “Disconnect Between drug and medical device approval”, Statistical Modeling, Causal Inference, and Social Science, October, 2010

[9] www.fda.gov