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The Product Development Process From Discovery, Through the FDA, and Into the Clinic

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INTRODUCTION

To drive the discovery, development, and commercialization of therapeutic orthopaedic products into routine clinical practice with greater speed, certainty, and financial efficiency, a symbiotic relationship between academic, clinical, and industrial investigators is essential. Approaches that successfully weave the technology, tools, and clinical applications from the laboratory bench to the clinical bedside stand a greater chance of being successful in the marketplace. The purpose of this chapter is to provide practical information and insights regarding the pathways and processes required to bring innovations, particularly in the field of implantable devices, orthobiologics, and regenerative medicine, to the commercial market. The chapter will provide an overview of the product development cycle, with emphasis on recent changes to the regulatory landscape and requirements for reimbursement in the hospital and office setting. **Figure 1** illustrates the major programmatic elements and stage gates that must be navigated in the journey from product concept through scientific validation, clinical testing, FDA approval, market launch, and reimbursement. Virtually all products follow this course, though subtle differences exist depending on the nature of the product (eg, device vs biologic) and the regulatory burden necessary for market launch (eg, 510(k), PMA, or BLA). At the close of the chapter, readers will have a greater understanding of the multiyear, multistep, interactive process involving multiple government agencies, private third-party payors, industry sales planning, and the efforts required to successfully commercialize new products.

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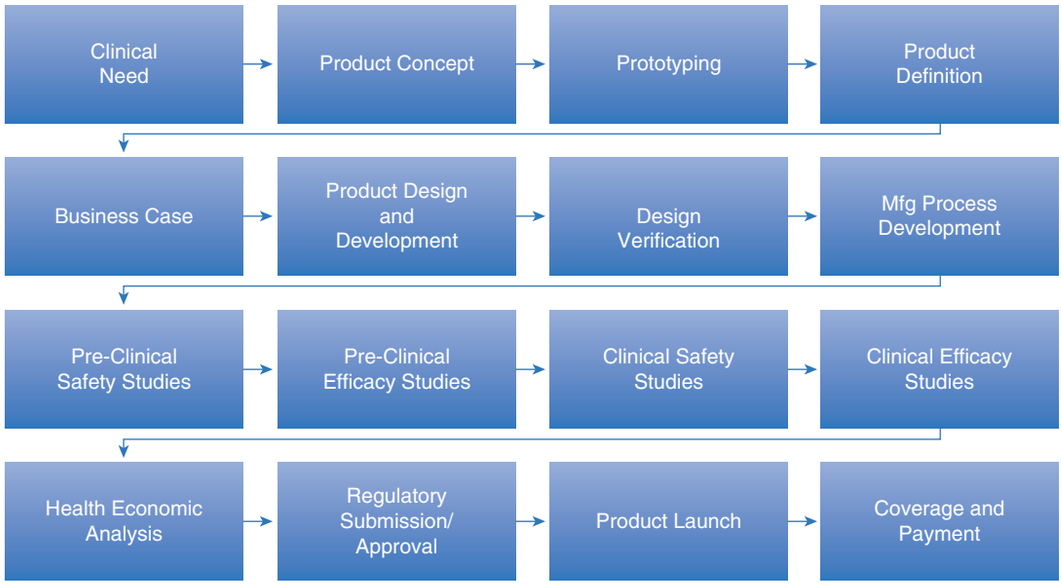

FIGURE 1 Illustration of the product development process. Any successful product development effort must navigate most, if not all, of the steps defined in this sequence. Depending on the device, drug, biologic, or combination designation, plus the Class of the product (I, II, or III), the requirements for Clinical Studies will vary from none to multiple randomized controlled clinical trials. The precise sequence of these steps may also vary depending on the nature of the product.

INNOVATING IN ORTHOPAEDICS

DEFINING AN UNMET NEED

Product development is the formalized process by which new technologies, concepts, and ideas are shaped into tangible, marketed products. Ideally, the cornerstone of any product development effort starts with the identification of a specific "unmet need" (ie, the problem). Within interventional orthopaedic care, unmet needs are abundant and may include objectives such as:

- Improving patient outcomes
- Reducing variability in patient outcomes
- Improving patient safety
- Addressing surgeon/OR staff safety
- Reducing economic cost (ie, product cost or waste)
- Improving operating room efficiencies (ie, reducing procedure time and complexity)

Once a clinical need is clearly established, an inventor or product development team can then examine possible ideas, concepts, and strategies to address the problem, through the creation of a medical device or biologic implant (for the purposes of this text), such as a surgical or diagnostic instrument or implant. In this very early stage of product development, the concept may be further fleshed out through the creation of prototypes, drawings, or models to determine if the initial design concept has merit. Prototype designs can be vetted in a variety of ways, such as through "simulated use" testing, cadaveric studies, laboratory studies, engineering testing, or "hands-on" evaluation from orthopaedic surgeons who would be likely users of the device. This process is often iterative in nature, as the creation of prototypes or drawings frequently generates feedback that spurs new creative thinking or identifies opportunities and weaknesses with the original product concept. Through this dynamic process, new design or performance requirements may begin to emerge. Consequently, this process is vital to ensuring the proposed design will adequately serve its intended purpose in the market.

Too often however, the process begins exactly backward, with an invention or a design looking for a problem to solve. This scenario is frequently encountered in the process of "technology transfer" in a university setting, whereby the creators of a technology seek practical application for an invention. This situation can be challenging to navigate (and explain to the inventor) as commonly these inventions have not fully considered the drivers and dynamics of the commercial orthopaedic market, such as the size of the market opportunity, cost of development, manufacturability, regulatory pathway and timeline, cost of goods, operating room logistics/demands, sterilization, storage, and shipping requirements, among a host of other considerations. Although no doubt there are examples of commercially successful technology transfers, the product development process is notably more "efficient" and has a higher probability of returning a greater value per invested dollar if the process starts with the clear identification of the problem, a search for potential solutions and "pressure testing" of the idea (ie, surgeon feedback) before committing significant resources to further advance development.

INVENTION VERSUS INNOVATION

As part of this overall narrative, it should be noted there is a meaningful nuance between "invention" and "innovation." From a product development perspective, an *invention* refers to a novel idea, concept, or approach, whereas an *innovation* is the embodiment or implementation of an innovation into a tangible product or service. The essence of product development is the transformation of an invention into an innovation. It has been said, "good ideas are a dime a dozen, but people who implement them are priceless." This statement is no more true than in the medical technology arena, where successful innovations must not only work technically, but must address a clinical need, have sufficient commercial demand to justify the time and expense of developing the technology, be manufacturable at commercial scale, must not infringe upon third-party intellectual property, and satisfy prevailing regulatory and quality standards (which differ around the world), to name just a few critical considerations. Quite often, extraordinary scientific breakthroughs do not directly become innovative product offerings, but do so only after they have been simplified to a reproducible embodiment that addresses a specific unmet need. The notion of creating a product with elegant simplicity will have much more appeal than a technically complex solution.

PRODUCT DEFINITION

Once proof of concept has been adequately vetted through experience testing and initial customer feedback, the next step involves further defining the product in a more formalized way through the creation of a Target Product Profile (TPP). The TPP identifies and "memorializes" the desired performance elements, required features, and intended use for the proposed product. A properly constructed TPP is a tool intended to serve as roadmap to help focus and guide the R&D teams as the design matures. Creating a TPP is frequently instructive for the design team, as the process often shines a light on issues that may impact the product's future marketability. By way of example, a detailed TPP will address the following product design and business considerations:

- Clinical purpose/need and intended benefit
- Target patient population/profile
- Intended use
- Composition/configuration (including packaging)
- Product performance attributes (physical, biological, mechanical, electrical, chemical, human factors, reliability)
- Proposed labeling statements and claims
- Manufacturing considerations (anticipated unit volumes, cost of goods, identification of key manufacturing processes/quality standards)
- Storage, handling, shipping, and other environmental requirements
- Commercial objectives (markets, pricing and revenue estimates, launch dates, and targets)

In the early stages of the design process, it may not be possible to fully address all aspects within the TPP. In practice, some elements of the TPP may not be knowable without further investigation or additional research. By design, however, the TPP is intended to be a "living document" that is updated as new information is learned or uncovered. A fully complete and comprehensive TPP is a key marker of a maturing product design, as the specifications and requirements are described with sufficient specificity and clarity to provide guidance to the design team and key product stakeholders.

EVALUATING THE BUSINESS OPPORTUNITY

Once the product concept has been defined through the creation of a TPP, a medical device company will typically prepare a "business plan" before committing additional resources toward development. The purpose of the business plan is to critically analyze the merits of the concept and consider the potential challenges selling the product into the market. Chiefly, the primary purpose of the business plan is to analyze the financial opportunity for the device, that is, rationalizing if the market size, demand, and potential pricing justify the financial cost, time, and risk associated with development. The business plan provides the management team with the critical information needed to authorize resources and secure funding for the project. The individual components of a business plan will vary between companies; however, typical business plans will address all of the topics and questions provided in **Table 1**. Authorship of the business plan is the primary responsibility of the marketing team; however, by its nature, creation of a well-written business plan requires broad collaboration and input from across the organization.

PROTECTING YOUR INVENTION WITH PATENTS

The medical device industry is characterized by intense competition, both from entrenched market players and emerging startup companies. To help manage these competitive threats, inventors and companies can defend their valuable intellectual property (IP) through the use of patents and an overall "patent strategy." When managed properly, a nexus of issued patents can become a valuable asset, helping a firm maintain its competitive edge, protecting it from would-be competitors. Patents are issuable from the United States Patent Office for inventions that are novel, nonobvious, and useful, and the invention must differ from existing intellectual property or "prior art" in a meaningful way. A patent portfolio represents a collection of patents protecting a device from being copied directly, as well as variants of the design that achieve the same intended use and clinical benefit. Importantly, within the academic and clinical communities, there is often a misconception as to what benefit a patent actually provides. To be sure, securing IP (patents) does *not* give the inventor a right

TABLE 1 Defining the Key Elements of a Business Plan

Topic	Key Questions
Market opportunity	Who needs this product? Where are the customers located? What is the market size? What are the market dynamics?
Competitive landscape	What are the alternatives to this product? What are their strengths and weaknesses? How are alternative products priced and promoted? How do we effectively compete?
Revenue projections	How much revenue can be generated with this product? How quickly can revenue grow? What factors will influence revenue growth? What pricing can the market accept?
Product development plan	What are the key milestones to bring the product to market? How much will it cost? How much time will it take? What are the key risks to the plan?
Regulatory pathway	Where do we want to market this product? What are the regulatory requirements? What are the risks of the proposed regulatory strategy? What is the timeline to obtain regulatory approval/clearance?
Manufacturing plan	How and where will this product be manufactured? What are the anticipated product margins? Can the supply chain satisfy the anticipated product forecast? What is required to scale manufacturing (time/cost)?
Sales/marketing plan	How will the product be distributed? How will the product be promoted? How will the product be priced? How do we maximize the revenue opportunity?

to practice the art of what is described in the patent, but only enables the owner of the IP to legally block OTHERS from practicing the art in the IP. In many cases, the owner may have to cross- or sublicense IP from another entity to actually sell what is defined by their own IP. For example, if an inventor develops an improved way (or material) to deliver a growth factor for the repair of certain tissues, such an invention cannot be sold by this inventor without also having the basic right to use the growth factor that is claimed by the original patent for that growth factor.

Within the orthopaedic medical device sector, two companies, Kyphon and KFx Medical, provide prime examples of the value of a well-constructed patent portfolio. In the early 2000s, Kyphon introduced a "balloon tamp" and instrument set for "kyphoplasty," an interventional procedure to address pain associated with osteoporotic vertebral compression fractures. At the time, several of the major spine companies sought to design similar instrument sets; however, Kyphon's vast patent estate covering the balloon technology prevented other companies from copying the Kyphon design. After Medtronic failed in its attempt to commercialize its Arcuate device to compete with the Kyphon balloon, Medtronic subsequently acquired Kyphon for $4.2 billion to enter the balloon kyphoplasty market.

Similarly, KFx Medical introduced its novel technology for soft-tissue fixation in the early 2000s. KFx's technology for double row fixation in rotator cuff repair surgery was readily adopted by orthopaedic surgeons, but was readily copied by the major orthopaedic companies servicing the sports medicine market. However, because of the strength of its patent portfolio, KFx was able to successfully defend its intellectual property rights, resulting in a legal judgment against Arthrex and leading to license agreements with industry bellwethers Smith & Nephew, Mitek/JNJ, ConMed, Wright Medical, and Zimmer Biomet. The KFx example is notable, given the company's small size relative to the other market players, and underscores the leverage a defensible patent portfolio can provide.

DESIGNING PRECLINICAL STUDIES FOR THE FDA

The foundation for establishing the safety and efficacy of any implantable device requires testing in preclinical studies or animal models. (Human clinical studies may be required in the context of a "significant-risk" experimental device, drug, or biologic; however, the foundation of any clinical trial is predicated on preclinical work.) Because of the importance of these studies in establishing "proof of concept" for a design, the FDA requires these types of nonclinical safety and efficacy studies to be performed under GLP (good laboratory practices) conditions. GLP represents a set of international standards governing the conduct and execution of preclinical studies, which have been established to ensure their uniformity, consistency, reliability, and reproducibility.[1] These standards effectively "raise the bar" for the execution of preclinical safety trials, often requiring them to be performed at organizations with the corporate structure, expertise, and business discipline to satisfy GLP requirements. It should be noted that GLP requirements generally exceed the capabilities of a typical university environment and are more costly than comparably designed non-GLP studies. Consequently, most nonclinical studies intended to support regulatory submissions are conducted at third-party contract research labs that have the necessary infrastructure and experience to navigate GLP requirements. Those aspects of study performance and underlying architecture that fulfill the primary tenets of GLP include the following:

- Utilization of properly qualified personnel to conduct studies
- Establishment of study director to oversee research and ensure quality

- Appropriate facilities for the care, feeding, and housing of animals
- Provisions for equipment maintenance and calibration
- Standard operating procedures to document all procedure and test methods
- Provisions to ensure test articles are properly stored and handled
- Identification of test facilities, equipment, materials, and reagents
- Development of protocol, testing plan, and reporting methodology
- Provisions for archiving records and test data
- Test facilities are subject to FDA inspection

DESIGNING FOR MANUFACTURABILITY

Manufacturability refers to the ability of a given design to be fabricated at commercial scale at a cost that can be supported by the market. Manufacturability should be considered in the early stages of the product development cycle, as any design approach that cannot be fabricated in an economically feasible way should be abandoned. For many inventors, the challenges of manufacturability may be underappreciated, as the issues that may confound large-scale production may not be obvious. In practice, manufacturability (and the cost to manufacture) is influenced by a variety of factors, including design complexity, quality requirements, supply constraints, raw material costs, labor costs, and manufacturing environment needs. Real-world examples of manufacturability issues include sourcing constraints posed by the use of human allograft tissue (eg, need for cadaveric ligaments of a particular size) and implant designs with complex geometries requiring advanced 3D printing fabrication techniques. Collectively, manufacturability is a key input to the cost/benefit analysis of any project and can significantly affect the direction and scope of the recommended design solution. Lastly, from a practical standpoint, when preclinical GLP studies are required as part of an FDA application, the work must be performed using implants manufactured according to the final process, which also conforms to the tightly regulated clinical good manufacturing process (cGMP) standards.

DEFINING SUCCESS—ACADEMIA VERSUS INDUSTRY

In general terms, industry and academia measure "success" of product development differently, which itself can represent an additional challenge in efficiently translating inventions from the laboratory to the market. Within the academic framework, a technological discovery represents the foundation of product development (**Figure 2**, top panel), and the "Design of Therapy" practical discovery is advanced through bench testing, in vitro studies, and animal models. If the efforts lead to a "first in man" clinical trial, the academic community typically declares victory and is justifiably delighted. Within academia,

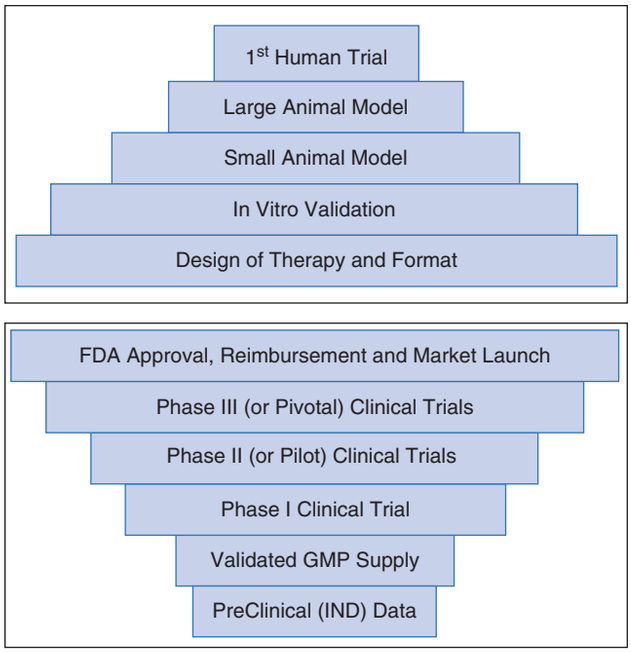

FIGURE 2 Illustration of academic and industrial foundations of product development. The top panel illustrates a typical academic hierarchy of success, which begins with the design of a therapy and ends with its first use in humans. By contrast, the lower panel turns this model upside-down, and illustrates that early human data are just the beginning of many product development efforts. Performance of a series of clinical studies, followed by FDA approval, is necessary to apply for the reimbursement required for a successful market launch.

inventions are often considered "translated" upon their first use in a human subject, and as consequence, this is often the aspirational goal of the academic researcher. However, this important academic milestone is actually just the beginning of what is required to develop and launch a meaningful product. From an industry perspective, this human use is more like the very beginning, and most professional models of product development would turn the academic pyramid upside-down (**Figure 2**, lower panel) to reflect what must be done to support the launch of a successful product.

As noted above, industry's primary objective is to develop products that achieve commercial success, a goal which often starts with human clinical use. From an industry perspective, product development planning ideally starts with commercial objectives in mind and with R&D teams "working backward" to identify the individual milestones needed to bring new technologies to market. Within the FDA's product development framework, human studies are often at the *beginning* of the product development journey. In particular, product safety is evaluated in phase I (pilot and safety) and phase II (dosing or confirmatory) human clinical trials, and if successful, phase III (pivotal) trials are used to provide evidence of safety and efficacy data to support regulatory submissions. As recently as 10 years ago, the mere approval of a product by the FDA was

sufficient to begin marketing and sales efforts, but this is no longer the case in the United States and elsewhere. Nowadays, FDA approval alone is no longer enough to support meaningful revenue generation, and companies must navigate the complex pathway of obtaining reimbursement and hospital value assessment committees. The details of this process are addressed later in this chapter.

THE ROLE OF THE FDA

The FDA is responsible for protecting public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, biologics, vaccines, and medical devices. They do this through enforcing the laws established in the Food, Drug and Cosmetic (FD&C) Act and the Public Health Service (PHS) Act. The FD&C Act establishes the basic laws governing development of drugs and medical devices, and the PHS Act does so for biologic products. These laws are translated into regulations in Title 21 of the Code of Federal Regulations (21 CFR) and are further interpreted for industry through publication of FDA Guidance Documents. The combination of these laws, regulations, and guidance documents provides the quality standards by which new medical products must be developed and marketed.

The FDA is led by the Office of the Commissioner and is divided into offices/directorates that oversee the core functions of the agency. New medical products fall under the regulatory purview of the Office of Medical Products and Tobacco, which is further divided into centers that specialize in product categories:

- *Center for Drug Evaluation and Research (CDER):* Over-the-counter and prescription drugs, including biological therapeutics and generic drugs
- *Center for Devices and Radiological Health (CDRH):* Medical devices and radiation-emitting products
- *Center for Biologics Evaluation and Research (CBER):* Biological and related products

To determine the regulations that pertain to a new orthopaedic product and which FDA center will oversee compliance, it must first be determined whether the product will be categorized as a drug, device, biologic, or some combination of these.

IS YOUR INVENTION A DRUG, DEVICE, BIOLOGIC, OR COMBINATION PRODUCT?

Determining whether the FDA will categorize a new product as a drug, device, biologic, or a combination product can often be tricky. It is critical that this is determined thoughtfully and carefully from idea conception, because the category of the product will dictate the regulations that apply to the product. This translates to the level of rigor of the quality standards and evidence required for marketing authorization. The intended use of the product is critical to this evaluation.

The appropriate product category and marketing pathway is easily determined for most implantable orthopaedic devices; for instance, a new bone plating system for fracture fixation in the feet would be considered a medical device, and therefore regulated by the CDRH. However, the framework for other medical products such as orthobiologics can be much less clear and open to interpretation. To determine the regulatory requirements for this group of products, one must carefully determine the intended use and mode of action (the means by which a product achieves its intended therapeutic effect or action). See **Table 2** for further details.

ORTHOBIOLOGICS AND THE REGULATION OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

Human cells, tissues, and cellular and tissue-based products (HCT/Ps) consist of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of such products include bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. The regulatory framework for HCT/Ps is established in sections 351 and 361 of the PHS Act, and 21 CFR 1271.[2] The FDA has been challenged with how to regulate these products and has developed comprehensive guidance documents that expand on the fundamental criteria of minimal manipulation and homologous use. An HCT/P will be regulated as a tissue (not considered a drug/biologic/device) if it meets certain criteria listed in 21 CFR 1271.10 for minimal manipulation and homologous use. These tissue products are regulated solely under section 361 of the PHS Act and, therefore, do *not* require premarket authorization from FDA. To be considered a "361 HCT/P," the product must meet *all* of the criteria as outlined in **Figure 3**. HCT/Ps that do not meet all of the criteria above are regulated as drugs, biologicals, or devices, based primarily on the mechanism of action on the body to achieve its intended purpose. These products are subject to Section 351 of the PHS Act and the applicable 21 CFR regulations, and are known as "351 HCT/Ps." These products must have premarket clearance or approval by the FDA, which typically requires a long and arduous development, qualification, and clinical trial series. Examples of such 351 HCT/Ps include culture-expanded chondrocytes for cartilage repair; ground and lyophilized amniotic membrane for modulating inflammation such as in the case of osteoarthritis; any purified stem cell preparation from fat, marrow, blood, or other tissue; and any combination of a tissue with another material. Interpreting and applying these criteria can be challenging, and therefore, it is important to communicate with the FDA early in the development process to verify there is shared understanding of the regulatory requirements.

TABLE 2 Medical Product Categories and Corresponding Agency Oversight

Medical Product	Definition	Regulatory Oversight	Marketing Pathway
Drug	Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and intended to affect the structure or any function of the body; chemically synthesized, well-defined structure, can be fully characterized	CDER	IND-NDA
Device	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, 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	CDRH	IDE-PMA, 510(k), or exempt from premarket notification requirements
Biologic	Virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, applicable to the prevention, treatment, or cure of a disease or condition; derived from or made with the aid of living organisms, complex in structure, not fully characterized	CBER	IND-BLA
Combination product	Therapeutic and diagnostic products that combine drugs, medical devices, and/or biological products. Examples: monoclonal antibody combined with therapeutic drug, device coated with a drug or biologic, prefilled delivery systems such as insulin injector pens	The Office of Combination Products (assigns a "lead-center" based on the primary mode of action)	Dependent on category of product

BRINGING YOUR PRODUCT TO MARKET

There are various processes through which the FDA reviews information about products to verify they are safe and effective before they are allowed to be sold in the United States. In order for a medical product to be legally marketed in the United States, it is required to be *cleared* or *approved* by the FDA (unless it is 510(k) exempt). The term *cleared* refers to medical devices that have used the 510(k) Premarket Notification Process, and the FDA has determined them to be substantially equivalent (similar) to another legally marketed device. The term *approved* refers to medical devices and/or biologic products that the FDA has approved through the Premarket Approval (PMA) or Biologic License Application (BLA) process, that have been determined to be safe and effective for their intended use. The PMA and BLA processes also require clinical investigations that are subject to FDA preapproval through the Investigational Device Exemption (IDE) or Investigational New Drug (IND) processes, respectively. The 510(k), IDE/PMA, and IND/BLA processes are described in detail below.

"PARTNERING" WITH THE FDA—THE PRESUBMISSION PROCESS

The marketing pathway for medical products can be very complex and lengthy depending on the product category and how it is regulated. Early interaction with the FDA will likely improve the quality of subsequent submissions and facilitate the development process for new products. The presubmission process is a voluntary program through the CDRH that provides the sponsor an opportunity to obtain feedback and advice before submitting an Investigational Device Exemption (IDE) or marketing application (PMA, 510(k), BLA), and also enables the FDA to have a full understanding of the new product early in the process. Agency guidance can include, but is not limited to, product development, planned nonclinical evaluations, proposed clinical study protocols, and statistical design. Pre-Sub feedback can be obtained through an in-person meeting, teleconference, written or e-mail response. The goal for FDA's feedback is within 75 to 90 days of submission receipt.

THE PREMARKET NOTIFICATION—510(K) PATHWAY

For medical devices, the first step in determining the appropriate marketing application is to classify the device. Devices are classified using a risk-based system based on the device's intended use and indications for use, and the level of control needed to assure adequate safety. To market a Class I, II, or III device in the United States intended for human use, there are various levels of evidence required as outlined in **Table 3**. In cases where a PMA is not already required per regulation, a

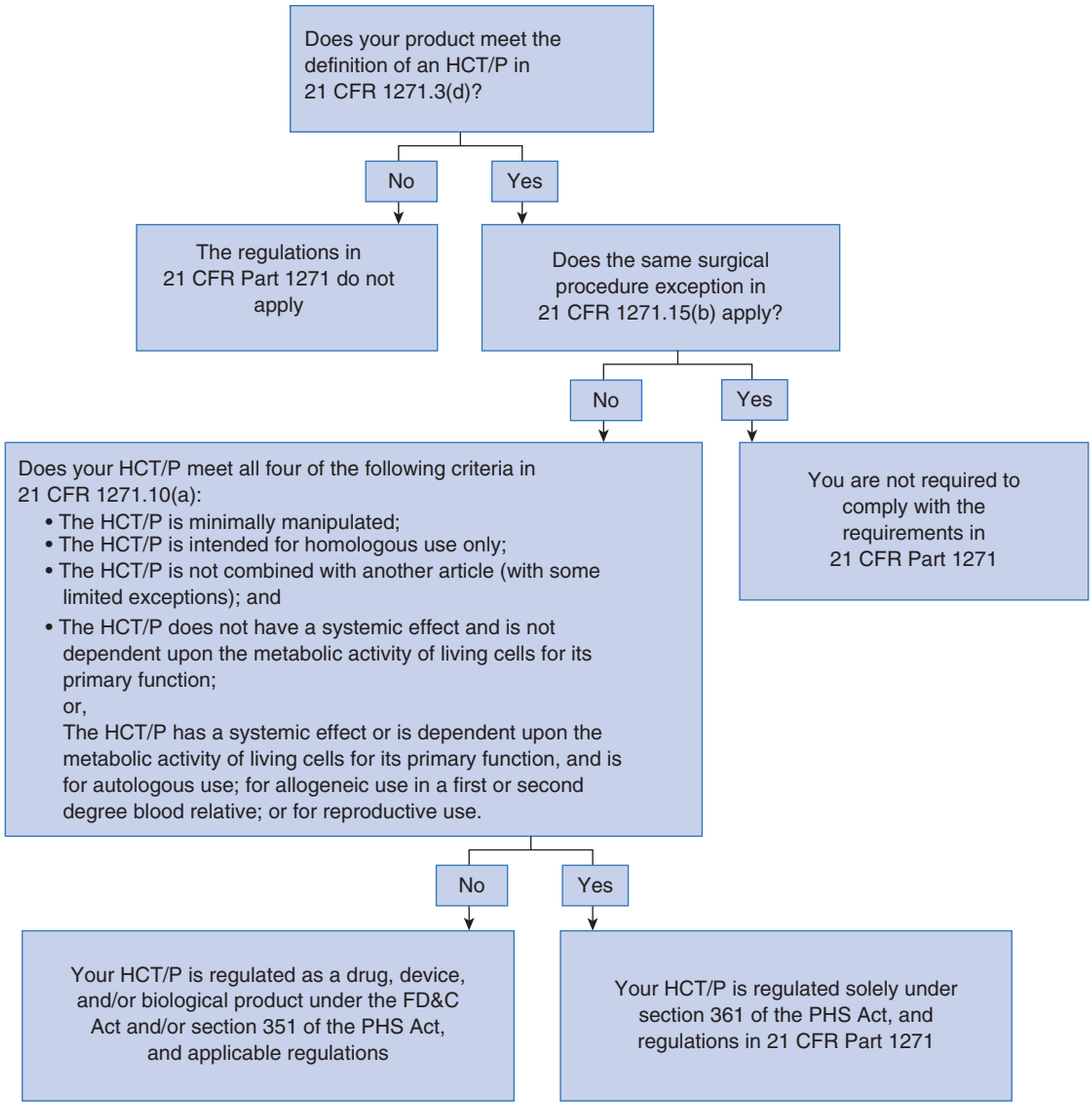

FIGURE 3 Flow chart regarding the FDA regulatory path of HCT/Ps. This diagram reflects the latest thinking from the FDA. (Reproduced from *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. Food and Drug Administration, November 2017.)*

510(k) premarket notification must be submitted to the FDA/CDRH unless the device is exempt from 510(k) requirements of the FD&C Act (such as certain HCT/Ps described above and Class I products). A 510(k) submission contains detailed technical, safety, and performance information about your device. The documentation must demonstrate the product in question is at least as safe and effective (substantially equivalent, SE) to a legally marketed device (predicate device) not subject to a Class III PMA. If the FDA determines that your device is substantially equivalent to the predicate device, they will "clear" your product for marketing in the United States. See **Figure 4** for a graphical comparison of the timeline and requirements across various regulatory pathways.

Most Class II medical devices are subject to the 510(k) program, and often a determination of SE can be supported with bench testing, logic, and animal data instead of clinical evidence. Because of this, the cost of developing a 510(k) device is much lower, and timelines are much shorter than devices subject to PMA requirements. Depending on the complexity of the submission and agency questions for the sponsor, 510(k)s are reviewed between 30 and 90 days. Although there are timeline advantages to the 510(k) pathway, such clearances to market generally lack the ability to make any meaningful clinical outcome claims. This balance must be considered as part of the overall business strategy.

TABLE 3 FDA Device Classifications and Representative Orthopaedic Products

Device Classification	Risk	Market Authorization Requirement	Examples
Class I	Low risk	Exempt from premarket notification	Tongue depressors, examination gloves, plaster cast materials
Class II	Moderate risk	Most require 510(k) clearance based on substantial equivalence to a legally marketed predicate	Bone void fillers, interbody spine fusion devices, suture anchors, resorbable mesh, and most hip and knee prostheses
Class III	High risk, surgically invasive, and many are life-supporting or life-sustaining	Investigational Device Exemption (IDE) Clinical Study and Premarket Approval (PMA)	Viscosupplements, BMP (InFuse), artificial cervical and lumbar disks

De novo: If a sponsor determines their product should be Class I/Class II but there is no legally marketed predicate upon which to declare Substantial equivalence, a de novo application can be submitted to FDA to make a risk-based classification determination.

THE IDE/PMA DEVICE PATHWAY

Premarket Approval (PMA) is the FDA's process of scientific and regulatory review to evaluate Class III device safety and effectiveness. A PMA is the most stringent device marketing application required by the FDA reserved for the highest risk devices. PMA approval is based on an FDA determination that there is sufficient valid scientific evidence to assure the device is safe and effective for its intended use. To determine that there is reasonable assurance that a device is safe and effective, the type of evidence required typically includes animal studies, nonclinical in vitro studies, and well-controlled clinical investigations.

To study an unapproved device in a clinical investigation, the sponsor must obtain an Investigational Device Exemption (IDE) before the study commences. To do this, the sponsor must demonstrate that there is reason to believe that the risks to human subjects are outweighed by the anticipated benefits, the investigation is scientifically sound, and device as proposed for use will be effective. Studies of significant risk devices must also have an IDE approved by the FDA before the study commences. See **Table 4** for clinical study comparison for drugs/biologics and devices.

The PMA application includes technical information consisting of details for manufacturing the device, nonclinical laboratory studies, and clinical investigations. The FDA will perform an in-depth scientific, regulatory, and quality system

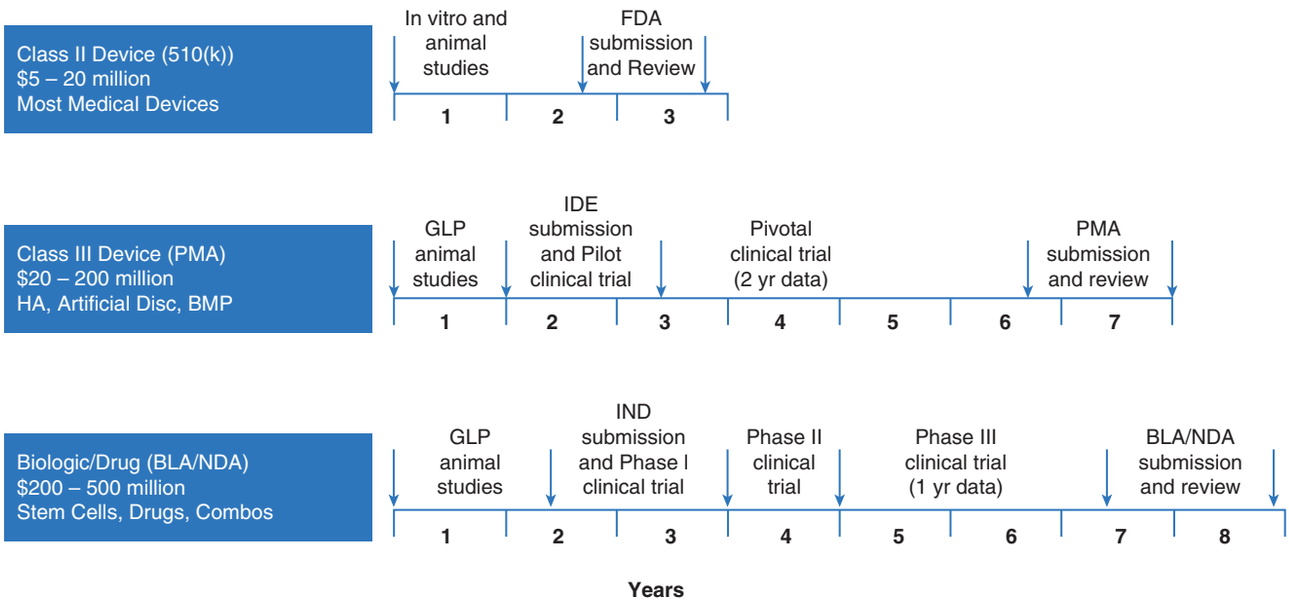

FIGURE 4 Illustration shows time/cost comparison of 510(k), PMA, and BLA/NDA premarket submissions.

TABLE 4 Clinical Study Comparison for Drugs/Biologics and Devices

Drugs/Biologics	Devices
Preclinical/GLP Animal Studies: animal testing to collect efficacy, toxicology, and pharmacokinetic information	Preclinical/GLP Animal Studies: animal testing to collect efficacy, toxicology, and pharmacokinetic information
Phase 1: First-in-human study; small group of healthy subjects (10-80) Study safety Typical Duration about 1 yr	Pilot: Small study (10-30 patients with pathology for treatment) Determine preliminary safety and efficacy Typical duration about 1-2 yr
Phase 2: Larger group of subjects (100-300 with pathology for treatment) Study effectiveness and further evaluate safety Typical duration about 1 yr	Pivotal: Larger study (150-300 patients with pathology for treatment) Determine efficacy and adverse effects Typical duration 2-3 yr
Phase 3: Large group of subjects (1,000-2,000 with pathology for treatment). Phase 3 studies are randomized, multicenter trials To confirm effectiveness and monitor side effects Usually have a longer duration (several years)	PostApproval Study: Collect long-term data and adverse effects
Phase 4: Postapproval study Collect long-term data and adverse effects	

review by appropriate personnel. An advisory panel of independent experts will also review the technical evidence and provide recommendations regarding approvability of the device, suggested conditions of approval, and labeling. In some cases, the FDA may request a preapproval inspection to verify that the manufacturer is in compliance with the appropriate regulations. There are often postapproval studies required as a condition of approval. Supplemental information is required to be submitted to the FDA periodically after approval, including any changes related to manufacturing the device. Postapproval inspections are conducted within 8 to 12 months of approval, which focus on any changes made to the device design, manufacturing process, or quality systems. FDA regulations provide 180 days to review a PMA and make a determination, but after all the interactive dialogue and various meetings take place, the total the timeline often takes a year longer. As such, these timelines must be factored into the business plan.

THE IND/BLA BIOLOGIC PATHWAY

If your product is classified as a biologic, including 351 HCT/Ps, a Biologics License Application (BLA) must be submitted to the FDA and approved to legally market your product. The BLA requires a different kind of scientific review to ensure safety and effectiveness for biologic products. It is similar to the PMA process for devices, in that the application requires submission of product manufacturing and technical information, preclinical studies, and well-controlled clinical investigations. In the field of orthopaedics, the best-known examples of products approved through the BLA pathway are the culture-expanded cartilage repair products, which in some cases have taken more than 10 years of development and study to gain approval. Other cell- and tissue-based products (for bone repair and treatment of osteoarthritis or degenerative disk disease) are currently in the clinical trial stage for the BLA pathway, but this is a long, expensive, and difficult journey. Alternatively, if your product qualifies as a "361 HCT/P" as defined above, then it is exempt from the BLA marketing application requirements. This "loophole" has led some unscrupulous organizations to launch HCT/P products without proper FDA review and approval, and they have done so with the hopes that the FDA will not have the interest, ability, or bandwidth to track them and enforce regulations. The consequences for such noncompliance can be severe and will be discussed later in this chapter.

Similar to the IDE/PMA process, to study an unapproved biologic/drug product, a sponsor must submit an Investigational New Drug (IND) application that demonstrates there is reason to believe that the risks to human subjects from the proposed investigation are outweighed by the anticipated benefits. At any stage of the clinical or animal studies, if data raise significant concerns about either safety or effectiveness, the FDA may request additional information, or they may halt ongoing clinical studies.

The BLA application includes technical information consisting of details for manufacturing the product, preclinical studies, and clinical investigations. To be considered, the license application must provide the multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc) with the efficacy and safety information necessary to make a risk/benefit assessment and to recommend or oppose the approval of the product. During this time, the FDA will perform a preapproval inspection during which production as it is in progress is examined in detail. After approval of the BLA, postmarket trials are often conducted to identify and evaluate the long-term effects of the product in a greater number of patients. Supplemental information is required to be submitted to the FDA periodically after approval, including any changes related to manufacturing. The BLA application is submitted after completion of phase 3 trials, and standard review time for an original BLA filing is 12 to 14 months from receipt date.

NONCOMPLIANCE PENALTIES CAN BE SEVERE

The FDA is authorized to take action against firms and individuals found to be in violation of the laws and regulations governing human medical products. Examples of violations include issues with manufacturing processes, lack of appropriate marketing authorization, and advertising products for uses not approved by the FDA. This is often discovered during facility inspections and review of company website materials. Specific enforcement activities include actions to correct and prevent violations, removal of violative products from the market, and punishment of offenders. The type of enforcement activity the FDA uses will depend on the nature of the violation. In the extreme, the FDA can and does work with the Federal Government to write injunctions, cease, and desist orders, and they have the ability to levy financial damages on companies and individuals, as well as criminally prosecute those responsible for the noncompliance. These are serious matters and FDA's jurisdictional reach should not be taken lightly.

THE CURRENT LANDSCAPE

The rapid growth in the field of regenerative medicine and stem cells has led to the FDA's increase in oversight and enforcement in this area. The FDA issued guidance in November 2017[2] that clarifies their position on regenerative medicine and gives the agency a solid platform to take enforcement action against offenders. Several warning letters have recently been issued[3-5] to firms promoting their 361 HCT/Ps as treating degenerative conditions, and the agency put the industry on notice by issuing a press release[6] and sending letters to firms and providers of stem cell treatments reiterating their compliance and enforcement policies.[7]

GETTING PAID FOR YOUR PRODUCT

WHAT IS REIMBURSEMENT?

A fundamental question in a new product's life cycle is "Who will ultimately pay for it?", or what is commonly referred to as reimbursement. At its core, reimbursement is the payment—typically from a third-party insurer—that is made to a physician or facility provider for medical services rendered to a patient. Although the various mechanisms of reimbursement are complex, the objective is simple—a new technology that is financially attractive to users will be adopted more broadly. Reimbursement is often thought of as a single concept but is actually the interaction of three distinct variables: coding, payment and coverage.

THE IMPORTANCE OF CODING

Facilities, such as hospitals and ambulatory surgery centers (ASCs), perform medical services and submit claims to insurance providers for the services rendered. Medical procedures, devices, drugs, and even a patient's diagnosis are translated into codes for the purpose of billing. Coding is often referred to as the language of reimbursement, because the codes that are reported on a claim are what drive the payment for those services.

New technologies, procedures, and devices may be described by existing codes or may require new codes to be created by the groups that maintain them. The American Medical Association maintains physician procedure codes, often called CPT codes (or Common Procedural Terminology). The Centers for Medicare and Medicaid Services (CMS) maintains the codes that describe devices and drugs, often called HCPCS codes (or Healthcare Common Procedure Coding System). **Table 5** provides an overview of commonly used coding modalities, and they are important because of the multifactorial nature of obtaining maximal reimbursement.

The process of determining which existing codes apply to a new technology, or whether new codes should be created, needs to be validated with the appropriate governing body of each code set. The American Academy of Orthopaedic Surgeons (AAOS) Coding and Reimbursement Committee is an adjunct to AMA decision-making, which oversees the appropriate use of CPT codes. AAOS is the appropriate group to facilitate a determination on whether new orthopaedic procedures or devices are adequately described by existing codes or will require a new code. If a new procedure is not described by existing codes, then adopters will face significant challenges in seeking reimbursement from payers. The sponsor company may need to work with AAOS to seek a new code for the procedure and use of the device; however, if a new code is obtained, it can provide significant value to the sponsor.

TABLE 5 Overview of Common Coding Modalities

Scope	Code-Set	Description	Governing/Oversight Body
Diagnosis coding	ICD-10-CM (International Classification of Diseases—Clinical Modification)	Describe patients' diseases and/or conditions (69,000+ codes)	CDC (Centers for Disease Control)
Physician procedure coding	CPT (Common Procedural Terminology)	Describe physician services/ procedures (7,000+ codes)	AMA (American Medical Association)
Device/drug codes/miscellaneous use codes	HCPCS (Healthcare Common Procedural Coding System)	Describes drugs, devices, temporary codes (5,000+ codes)	CMS (Centers for Medicare and Medicaid Services)
Procedure coding (hospital inpatient only)	ICD-10-PCS (International Classification of Diseases—Procedure Coding System)	Describe hospital services/ procedures (72,000+ codes)	CMS (Centers for Medicare and Medicaid Services)
Inpatient DRG reimbursement code	MS-DRG (Medicare Severity Diagnosis Related Group)	List of payment groups applicable to hospital inpatient encounters (1,000 codes)	CMS (Centers for Medicare and Medicaid Services)

CREATING AND ASSIGNING CPT CODES

There are two main requirements for new CPT codes to be created—a clinical evidence requirement and a substantial use requirement. Published, peer-reviewed clinical evidence must support the efficacy of a new procedure, and these clinical evidence requirements are described in **Table 6**. Depending on the utilization and technological features of the procedure and possible device, the number and nature of the publications will vary from reports of a prospective, statistically significant randomized control trial to a case series or even an "expert opinion." The AMA's definition of the various minimum levels of evidence required to secure a distinct code are provided in **Table 7**. To be clear, although none of the listed scenarios require level 1a or 1b data, it is still possible that AAOS or AMA will require that for certain situations before a new code is created. Lastly, a substantial use requirement means that practicing physicians are incorporating the new procedure into their clinical practice and are therefore able to report the time and resources necessary to perform the new procedure to the AMA. This is typically provided in what is referred to as a "clinical vignette" justification following commercial launch. The upshot of all of this is that for products cleared by the FDA through the 510(k) pathway without clinical evidence, a multiyear effort to collect postmarket clinical data is typically required before a reimbursement code is granted. For products approved through a PMA, there may be sufficient data collected before market launch to qualify for a unique CPT code.

TERMS OF PAYMENT AND SITES OF SERVICE

When a claim is submitted to an insurance provider for services rendered to a patient, that claim contains a list of billing codes that describe the services provided. The codes are tied to payment amounts that are specified in contracts with commercial

TABLE 6 AMA Level of Evidence Requirements

Category I Literature Requirements	Utilization	Typical	Typical	Limited, Specialized or Humanitarian	Limited, Specialized or Humanitarian
	Technology	New	Existing or Noncontributory	New	Existing or Noncontributory
# of peer-reviewed publications		5	5	5	3-5
Minimum # with US patient populations		1	1	1	1
Minimum # with different patient populations		2	2	1	1
Minimum level of evidence[a] for at least one article		2a	3a/3b	3b	4

[a]Level of Evidence is defined by AMA Scoring System illustrated in **Table 7**.

TABLE 7 AMA Level of Evidence Scoring

Level of Evidence	Type of Study
1a	Evidence obtained from systematic review of randomized controlled trials
1b	Evidence obtained from an individual randomized controlled trial
2a	Evidence obtained from systematic review of cohort studies
2b	Evidence obtained from an individual cohort study
3a	Evidence obtained from systematic review of case-control studies
3b	Evidence obtained from a case-control study
4	Evidence obtained from case series
5	Evidence obtained from expert opinion without explicit critical appraisal

insurers or published payment rates for governmental insurers such as Medicare. Governmental payers such as Medicare and Medicaid publish fee schedules and reimbursement terms and the stated payment amounts for each code or group of codes are publicly available, albeit sometimes difficult to access or calculate. In the case of private commercial insurance plans, payment amounts are negotiated between the provider and insurer and specified in contracts. The payment amounts in commercial insurance contracts are not publicly available and may differ from one provider to the next for the same service, depending on the terms of the contract.

Payments are also impacted by variables such as the level of care a patient receives (inpatient vs outpatient) or the locale where services are rendered. Medicare payments to ASCs, for example, are much lower than corresponding payments to a hospital for the same procedure, because providing care in a hospital is more costly than in an ASC. Medicare also lists national average payment amounts for each service, and then modifies those amounts to reflect the area wage index, or relative cost factor for that geography. A Medicare payment for a procedure in San Francisco, CA, may be 30% to 40% higher than in Topeka, KS. It is important to look at payment amounts across insurers, across various venues of care, and in different geographies to develop an understanding of the payment landscape for a given product or service.

WHY DOES REIMBURSEMENT MATTER?

Facility providers such as hospitals and ASCs review the potential financial impact of a new technology before they decide to adopt it. This is a discipline often referred to as "value analysis," and is characterized by a process typically consisting of a committee of hospital stakeholders that review the business implications of adopting a new, possibly more expensive technology. If the reimbursement that the hospital or ASC will receive from insurers is sufficient to cover the cost of a new technology, they will be more likely to adopt it. Hospital and ASC buyers are reluctant to adopt new technologies that will hurt the financial performance of their institution. However, if a surgical innovation can reduce, for example, surgical time, blood loss, or infection rates, these compelling features could sway a site's decision to adopt the new technology. Developing an understanding of the "bigger picture" economic impact of a new technology on a hospital may uncover value beyond episode-of-care economics. Importantly, commercializing organizations must understand that approvals for use are often required for each individual hospital, or hospital system, and as such, resource planning and the months required to secure approval must be considered in any product launch.

WHAT DETERMINES COVERAGE FOR NEW TECHNOLOGIES?

At its core, coverage is simply whether an insurance company will pay for a therapy and under what conditions. Insurers evaluate new and existing therapies to determine whether they are medically necessary to treat a certain condition or disease. Therapies that are shown to be effective, based on the body of published clinical evidence, may be deemed medically necessary and therefore covered. Therapies that lack sufficient clinical evidence may be noncovered. In some cases, insurers have not evaluated the effectiveness of a therapy at all and are silent on coverage. That said, in the setting where payors are silent or even have policies for noncoverage, it is still possible to build a modest market for the self-paying segment of the population. This can lead to the creation of more and better clinical data, as well as a substantial use justification with health economic data, that eventually are useful in establishing a reimbursement case and code.

Truly novel technologies seldom have a body of published evidence sufficient to persuade insurers to cover a new technology. Medical innovators need to assume that clinical evidence, over and above that which is required for regulatory approval, will be necessary to obtain coverage from insurers. Evaluating the coverage landscape for a new medical technology will inform whether insurers will pay claims for the therapy and how much clinical evidence will be needed to improve the coverage profile. Because creating new procedure codes and/or payment groups can be a lengthy and complex process, evaluation of the requirements and synthesis of a thoughtful strategy is an essential aspect in the business case analysis of whether to invest the resources necessary to bring a product to market.

SUMMARY

The product development process from scientific discovery, through the FDA and into the clinic requires discipline, tenacity, and perseverance. Fortunately, in the field of orthopaedics, the pathways for demonstrating preclinical, as well as clinical, safety and efficacy are very well established and governed by a variety of clearly documented guidelines promulgated by the FDA and the US Code of Federal Regulations. Navigating these development hurdles is resource intensive, and at the very least, requires several million dollars for a simple device cleared through the 510(k) pathway (eg, interference screws or fracture fixation devices), but may require hundreds of millions of dollars for a novel biologic or combination product requiring a BLA or a PMA (eg, Carticel or Infuse BMP-2). Even after successfully meeting the FDA's requirements for market launch, one must consider the reimbursement landscape and requirements for getting paid. More specifically, it is no longer enough to "simply" obtain FDA approval for one's product to be successful in the marketplace—today, there is an entirely different set of requirements to fulfill in order for a new technology or product to get reimbursed in the hospital or ambulatory care setting by Medicare or third-party payors, and in fact, each of these settings is oftentimes different from one another. Therefore, careful development planning, and the creation of a commercialization strategy early in the process, is essential to determine whether the investment will meet the revenue and profitability objectives of those underwriting the project. With that in mind, ensuring that developers have a robust understanding of the product development process, or that they engage with partners who themselves have a keen understanding of the journey from "bench to bedside," will increase the likelihood of both clinical and commercial success. When meaningful technological advancements are properly shepherded through the FDA (and other regulatory bodies), it is possible to make both important clinical contributions to the field of orthopaedics, as well as create significant value for those who invest the time and money to succeed.

REFERENCES

1. U.S. Food and Drug Administration. Good Laboratory Practice for Nonclinical Laboratory Studies. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58. Updated September 4, 2018. Accessed June 29, 2019.
2. U.S. Food and Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal. Published November, 2017. Updated December, 2017. Accessed June 29, 2019.
3. U.S. Food and Drug Administration. Warning Letter, Genetech, Inc. Available at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/genetech-inc-561808-11292018. November 29, 2018. Accessed June 29, 2019.
4. U.S. Food and Drug Administration. Warning Letter, Cord for Life Inc. Available at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/cord-life-inc-572770-03292019. March 29, 2019. Accessed June 29, 2019.
5. U.S. Food and Drug Administration. Warning Letter, US Stem Cell Clinic, LLC. Available at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/us-stem-cell-clinic-llc-524470-08242017. August 24, 2017. Accessed June 29, 2019.
6. U.S. Food and Drug Administration. FDA sends warning to company for marketing dangerous unapproved stem cell products that put patients at risk and puts other stem cell firms, providers on notice. Available at: https://www.fda.gov/news-events/press-announcements/fda-sends-warning-company-marketing-dangerous-unapproved-stem-cell-products-put-patients-risk-and. December 20, 2018. Accessed June 29, 2019.
7. U.S. Food and Drug Administration. Mary A. Malarkey, Director, Office of Compliance and Biologics Quality. Center for Biologics Evaluation and Research. Available at: https://www.fda.gov/media/119936/download. December 20, 2018. Accessed June 29, 2019.