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FIRST PRINCIPLES OF R&D – THE ROLE OF DUE DILIGENCE

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Knowledge is power! Gathering information is critical before dedicating precious time and/or money into a new business venture or research project that appears to hold commercial promise. Due diligence is the formalized process of gathering the information necessary for a comprehensive understanding of a business's assets and upside potential value in the marketplace, as well as its liabilities and downside risks. Although the information sufficient to make an investment decision varies from case to case, the process to evaluate biotechnology and pharmaceutical products is based upon many of the same elements. The more thorough an understanding of the technology and the elements driving its entry into the market, the greater likelihood of mitigating failure and realizing a return on investment (ROI) which includes spearheading a meaningful area of research and development.

Due diligence is typically performed by a prospective investor or buyer of a business but can, and should, be applied in other circumstances as well, for example, in basic research where the

researcher is interested in ultimately translating the conducted research into practice (see Chapter 2). Due diligence can also inform financial decision-making from a private investor, institutional investor or corporation. For companies developing multiple products, performing due diligence on each of its assets can assist in deciding which products to budget for as part of a process called portfolio management (see Chapter 22). While a thoughtful review of a business and/or technology should be comprehensive and evaluate all factors necessary for successful product development through commercialization, the prudent analyst focuses first on those factors that have the greatest impact on the potential and sustained success of the business and thus may yield a "go–no go" decision. Three key questions to begin with are:

- Does the product candidate address an unmet medical need?
- Is the product candidate proprietary? Is there Intellectual Property (IP) protection in place?
- What do we know about *reimbursement* and cost to the consumer? In other words, how is the product going to be paid for?

UNMET MEDICAL NEED

The term unmet medical need is used where current treatments for a condition or disease are insufficient. This may mean these treatments lack safety and/or efficacy or only lessen the disease burden, but are not necessarily curative. Therefore, a product, product candidate, or idea for a product that will address an unmet medical need is worth pursuing scientifically and clinically, as it may contribute significantly to the treatment of the disease, and economically, as it presents a viable market opportunity and ultimately asset value. Products that meet an unmet medical need have a strong "pull" into the marketplace and don't rely on heavy promotion or a "push" to achieve significant adoption (*https://www.ncbi.nlm.nih.gov/pubmed/16597582*). Thus, unmet medical need is an excellent starting point for a due diligence analysis.

Standard of care

Defining where there is an unmet medical need begins with an evaluation of the current standard of care and practice for a particular disease. The standard of care and/or current practice may entail the use of a drug, procedure (e.g., surgery) or other curative or palliative treatment or some combination thereof, and can thus present a potentially complicated landscape of treatment alternatives. To understand this landscape, in turn, demands a deeper understanding of the disease based upon presentation (metastatic vs. nonmetastatic, extracapsular vs. capsular), age and a variety of other cofactors. Only once this current standard of care is well understood will the due diligence analyst see whether and where the product in question will sufficiently address an unmet medical need and whether and how the product is an equal or better solution than what is currently available on the market or under development by a competitor.

A recent example of an existing product meeting an unmet medical need by demonstrating an improvement over the existing standard of care is Vascepa®. Vascepa® was originally approved to treat patients with hypertriglyceridemia, a risk factor for coronary artery disease. However, agency approval to lower tryiglycerides also resulted in increased LDL-C or where LDL-C is not controlled and therefore the potential to increase cardiovascular risk (Nichols et al., 2018). While Vascepa® showed no evidence of increasing LDL-C, the drug was tested to determine if the thesis of lowering tryiglicerides without increasing LDL-C would lead to clinical benefit by a reduction in cardiovascular adverse events. Therefore, a post-market global study of 8,179 statin-treated adults with elevated cardiovascular risk was conducted using Vascepa®. The results showed a 25% relative reduction of risk of cardiovascular events as compared to statin alone (*https://www.vascepa.com/vascepa-difference*). This study thus differentiated Vascepa® from the statin-alone treated patients. This study substantially further differentiated Vascepa® from previously approved triglyceride reducing agents by defining clinical benefit by reducing heart attack, stroke and death

and therefore clear unmet medical need. Sales experts estimate that Vascepa® will achieve significant share in the already multibillion-dollar statin market.

Proof-of-concept data analysis

If the solution addressing an unmet medical need has the potential to change or improve the current standard of care, the analyst must determine if there are supporting scientific data and if those data are sufficiently compelling. Analysis of that data includes analysis of the research type, quantity and results, as well as interpretation of preclinical and clinical data and thus requires scientific and/or medical expertise and/or a sophisticated understanding of the area or field of research. Ideally, the data should substantiate that a product is doing what the researcher or inventor claims the product was designed to do. This is called proof-of-concept (POC) data and prudent investors will look for data demonstrating POC prior to investing money to initiate costly, but potentially promising preclinical and clinical development programs.

Establishing POC varies from product to product and field to field and, although such data are based upon widely accepted experimental models, rigorous experimentation doesn't always yield data that unequivocally demonstrate POC, but are merely suggestive that a product is working as believed. Scientific and medical expertise is thus required to fully interpret and understand whether the collective data package is sufficiently supportive of POC. The due diligence analyst and team of experts must make this assessment before embarking upon a costly commercial development program. Investing in research that may generate POC could take an undefined number of years and therefore such early stage capital invested is often significantly diluted by follow-on rounds of investment. Dilution is an investment term that describes a reduction in relative ownership percentage of a company. Moreover, the basic research may not yield POC or data that are sufficiently compelling to initiate a product development program that may lead to commercialization. For this reason, private investors do not

typically invest in academic research prior to POC which, instead, is funded largely by the National Institutes of Health (NIH) and other academically orientated funding sources (the NIH alone, currently invests over $37 billion per year on basic research) (*www.nih.gov/about-nih/what-we-do/budget*). Investing instead in commercial development, rather than competing with academic funding, is also less risky as it is often based upon well-defined guidance provided by regulatory bodies, such as the US Food and Drug Administration (FDA). Ultimately, it is logical to generally assume that capital put to work to generate significant growth or returns is better invested on the development or "D" side of R&D, research and development. Indeed, in recent decades, investors and the pharmaceutical industry have increasingly focused their attention and resources on development and have come to rely on basic research from academia for their "R".

Expedited regulatory paths

Historically, developers of new products with active ingredients that have not previously been approved by the FDA have followed the FDA approval pathway known as 505(b)(1) which refers to the relevant section of the Federal Food, Drug, and Cosmetic Act (*www.usFDA.gov*). This traditional path requires prospective data and demonstration of both safety and efficacy based upon an often lengthy and extensive development program. However, where particularly urgent circumstances exist, such as diseases or conditions with life threatening circumstances, the FDA has provided a number of regulatory paths designed to speed up the availability of drugs. Typically, these expedited approval paths are for products that are the first available treatment to address an unmet medical need or that have significant advantages over existing treatments. Accelerated development regulatory paths and faster regulatory approval processes effectively reduce the cost and time of development. Therefore, another important reason to begin a due diligence analysis with an examination of unmet medical need is to determine whether the product is eligible for one of these expedited, cost-saving paths. The FDA and regulatory agencies

around the world have created numerous programs that assist and offer advantages over the traditional 505(b)(1) path to product sponsors, ranging from pediatric use, orphan disease, oncology, infectious disease to name a few. Some program examples include "Fast Track," "Breakthrough Therapy," "Accelerated Approval" and "Priority Review" (*www.nih.gov/about-nih/what-we-do/budget*).

Excerpted from *www.FDA.gov*:

Because each of these approaches implies speed, there can be confusion about the specific meaning of each and the distinctions among them.

- *Fast Track*
  Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.

- *Breakthrough Therapy*
  A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.

- *Accelerated Approval*
  These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint.

- *Priority Review*
  A Priority Review designation means FDA's goal is to take action on an application within six months.

Intended product label

Another method to elucidate an unmet medical need may be to envision what the product label might look like or create an intended product label. The more clarity at the beginning of a development project on what the final product label might look like, the higher the probability of putting together a robust preclinical and clinical development program in support of the intended product candidate that the FDA and regulatory agencies in other countries will approve and authorize for sale. For

prescription products in the US, the finalized product label is the culmination of the entire dataset or package based upon the completed development program in accordance with FDA regulatory requirements. The completed regulatory submission package, if based upon a small molecule, is reviewed for marketing and sales approval through the New Drug Application (NDA) submitted to the FDA's Center for Drug Evaluation and Research (CDER) or in the case of a biologically based material through the Biologics License Application (BLA) submitted to the FDA's Center for Biologics Evaluation and Research (CBER). Upon approval, information about the drug and its use derived from the studies submitted in the NDA or BLA is summarized in the product's label and can be found inside the product's packaging.

Copycat and generic or generally equivalent products

Though a due diligence analyst generally looks for a product that addresses an unmet medical need, products that are the same or similar to existing successful products, called copycat or "me-too" drugs, are also worth considering. Initially, the market opportunity is defined by unmet medical need and the number of patients that can be treated, which renders the total market size and is what, in part, drives corporate interest and investment. The cholesterol lowering market is a good example. Consider how many statin pills are on the market today. Because lipid lowering agents represent a multibillion-dollar market, even a small share of this market can offer drug companies a substantial share without significant improvements on the original invention. Once a large market is established, copycat or me-too products often pique the interest of drug companies when revenue generally exceeds $50M per annum, which is a market size large enough to justify the investment to enter an already established market. In this instance, the larger market size doesn't require that the product is an improvement on the original invention, but simply a drug or product that has the ability to achieve enough market share simply based upon a push strategy. This is an approach used by bigger drug companies that have strong distribution, marketing and sales arms. Companies that

have the human and financial resources to add a new product without the need to build significant additional infrastructure will likely contemplate this type of opportunity.

Products that are generally equivalent in efficacy and/or safety also generate great attention. A full understanding of available treatments is essential in understanding the competitive landscape. Therefore, it is important to consider what generic and/or specialty product solutions are available for addressing a new treatment option. Moreover, these types of products often are lower cost solutions in comparison to current standard of care. This drives downward pricing pressure on prescription products used for the same indication and significantly impacts reimbursement considerations by third-party payors (discussed later in this chapter under "Pricing and Reimbursement"). Three types of products fall into this category; (1) generic drugs (2) biosimilars and (3) and a specialty class approved under the 505(b)(2) FDA regulatory pathway, which enables a previously approved drug to be used in a new way, such as a new dosage form or a new indication. Generic drugs are generally off-patent, approved through an abbreviated new drug application (ANDA), and are typically not the focus of start-ups. Biosimilars are a kind of copycat of branded biologics, however, they are not true copycats because it is difficult to generate an exact replica given that the manufacture of biologics is performed in living cells where growth conditions can lead to post-transcriptional modifications of the product. The manufacture of biologics is generally proprietary or kept as a trade secret. Therefore, biosimilars are not exact replicas of the branded product like a generic, but can be generally equivalent and the pricing for biosimilars is not heavily discounted relative to the branded product, often making them a promising investment opportunity (see Chapter 11). 505(b)(2) drug candidates are typically:

- Older or generic drugs with new uses or indications.
- Drugs where there is a change in dosage, formulation, strength, route of administration.

- New combination products.
- Prodrugs, which are biological inactive drugs that are metabolized in the body into an active drug.

The regulatory requirements necessary to gain approval in order to commercially launch a 505(b)(2) drug are generally relatively fewer compared to those for a traditional 505(b)(1) drug, typically a new chemical entity (NCE) that has not been approved before (*www.fda.gov/ForPatients/Approvals/Fast/default.htm*). Therapeutics that do not have a marketing history in the US or elsewhere also follow the approval pathway laid out under 505(b)(1). Products developed through the 505(b)(2) regulatory pathway, such as Dyloject®, Bendeka® and Zuplenz®, may require elaborate development programs and sometimes can be as costly and time consuming as the 505(b)(1) regulatory path required for a NCE. However, such products can achieve significant market share and achieve significant revenues, whether in a startup or mature company. In either case, an open market allows for multiple products that the healthcare provider or patient may select from that are often related to pricing and affordability, better safety and/or efficacy, ease-of-use, and improvements in patient compliance.

INTELLECTUAL PROPERTY: EXCLUSIVITY AND FREEDOM TO OPERATE

Two key due diligence considerations, exclusivity and freedom to operate, both hinge on the intellectual property rights at issue with the idea or product. In biotechnology, the two main forms of IP are patents and *knowhow*. Patents are a 20-year exclusive property right granted by the United States Patent and Trademark Office (USPTO) to an invention and any product made using that invention. (See Chapter 18 for more on patents.) Knowhow is a form of trade secret; it is critical information related to a product, typically a manufacturing process, which, by keeping it secret, precludes others from replicating the process or product and thus prevents competition in the marketplace. Patents and knowhow each

provide market exclusivity, precluding competitors from taking market share for a certain period of time.

Exclusivity is a key due diligence consideration because no investor or developer will want to spend the significant time, effort and expense required to develop a product through the regulatory process, without some assurance of exclusivity when the product reaches the market. Also, while the presence of IP grants exclusivity, the absence of existing IP gives one freedom to operate, that is, freely develop, market and sell a product without the potential for infringing on someone else's invention. A freedom to operate search is thus also critical due diligence to perform prior to investing the great effort and money required develop a product. Both freedom to operate and exclusivity, and various strategies to secure exclusivity, are discussed in more detail below.

How to evaluate a patent

Because patents are a key factor to a "go–no go" decision to pursue (because of freedom to operate) or invest (because of exclusivity) in a product's development, a due diligence analyst will have to conduct some basic patent evaluation. To better understand how to evaluate a patent, one must first understand how a patent is constructed. Generally, patents are comprised of several sections, the most important being claims and specifications, also called the disclosure. The claims define the subject matter that is protected by the patent. In evaluating patents, it is critical to evaluate the supportive data and examine if, in fact, they are supportive of the claims. The specifications/disclosure is a written description of the invention, drafted in

- Title of the invention
  The title of the invention is used to provide a brief description the invention.

- Cross-reference to related applications
  In the US, a patent applicant must include a section titled "cross-reference to related applications". In this section, the applicant lists any provisional patent applications that they are claiming priority to, or if the application is a continuation, the parent application number(s).

- Statement regarding federally sponsored research (if applicable)
  In the US, it is also required that the applicant include a "statement regarding federally sponsored research" if the invention was made under a government contract, or if federal grant money was used to fund the research.

- Background of the invention
  The background of the invention contains art in the field which emphasizes differences with the current invention. It may also include improvements provided by the current invention and differentiate it from preexisting inventions.

- Summary of the invention
  The summary of the invention is meant to overview the invention (i.e., the claims) rather than the disclosure as a whole. The summary often includes advantages of the invention and how it solves the problems existing in the art, such as those presented in the background of the invention.

- Description of the drawings
  If drawings are included in the application, a brief description of each drawing is included.

- Detailed description of the invention
  This section comprises the bulk of the patent and is used to provide an accurate and detailed description of the invention. It generally contains two sections:
  - A general explanation of the invention and how to practice it
    The invention is described in general terms providing an overview of the invention and its elements. Often, preferred embodiments of the invention are described. Such embodiments are generally more limited versions of the broadest concept and provided for support for a fall-back position of narrower claims if the broader concept is not patentable. This section includes key terms that are critical for interpreting the scope of the claims.
  - Specific examples of how to practice the invention
    While a patent application does not require examples, examples should help to demonstrate patentability (i.e., enablement). This section is important and necessary in support of inventions that are scientific in nature. The examples may or may not have been performed by the inventors, but are included to define the scope of the invention and, of course, in support of the claims.

- Sequence listing
  A sequence listing is required if the application includes nucleic acid or amino acid sequences. If sequences are disclosed, every nucleic acid molecule that is at least 10 nucleotides, and every protein that is at least four amino acids, must be included. In many jurisdictions, sequence listings are required to be in a specific text format. The USPTO provides a free software download called PatentIn that is often used to compile sequence listings.

- Abstract
  The abstract is a brief summary of the entire specification.
- Claims
  Claims are structured in a hierarchical fashion. A patent may contain one or more main independent claim. A number of dependent claims may follow by defining more specific features of the invention. The claim may be a physical entity, for example a product (i.e., material) or an apparatus (i.e., device, system, article). Claims may also protect a process (or method) or use. This type of claim is called a "process claim" or "use claim".

https://www.uspto.gov/sites/default/files/about/offices/ous/Cooper_Union_20130605.pdf. (For more on patent sections and evaluation see also Chapter 18.)

support of the claims, that demonstrates that the requirements for patentability are met. Patents are comprised of the following sections:

Patent considerations

The claims section of a patent specifically describes and defines what is being protected. Without sufficient protection afforded by patents and/or knowhow, it is hard to justify the significant expenditures necessary to bring a product to the marketplace. While the claims section of patent is a key element to evaluate as part of due diligence, there are a number of additional considerations in putting together a patent that provide a general understanding of the full scope or disposition of the patent. Questions to address include:

- Who owns the patent rights?
- Are all of the listed investors truly inventors?
- Has the patent office approved all the claims or is there unapproved or pending claims still under review?
- Are the patent claims sufficiently supported by the underlying data or POC?

- Has the patent been assigned or licensed to a single entity or corporation and what are the underlying contractual terms?

- Is the patent licensed exclusively to a single entity or is it licensed to multiple parties and therefore a non-exclusive license? Have only certain claims been licensed?

- How many years of patent life is left or the period of exclusivity that remains? Is it a sufficient amount of time to develop the product and generate meaningful sales that justify an investment should the product attain approval?

- Are there foreign applications that all may impact the overall value proposition?

- Are there patents filed and/or issued in the major market territories?

A comprehensive due diligence process will examine all of these elements in defining the ability to enter a marketplace with sufficient patent protection.

For products that represent significant market opportunities, there is a high probability that they will be reviewed and challenged by competitors. Therefore, careful analysis must be performed in both drafting and analyzing a patent for its relative strength. The strength of a patent, in turn, depends on how well an invention meets the three requirements for a patent: useful, novel and non-obvious. The analyst should be skilled in the art (a term from patent law for a person with the knowledge to understand a patent's claims) to be able to understand the strengths and weaknesses of a patent, relative to these criteria, which will be discussed further in Chapter 18.

A diligent review of an investor deck, published papers and all descriptive materials of a product(s) by a sponsor may reveal data or information that are *not* covered by the patent. Gaping holes in

patent protection are not uncommon. An analyst should try to envision all the potential uses for a new product or invention and determine whether the claims in the existing patent portfolio cover the full breadth and potential of the product. Also, to mitigate against the risk of gaps in patent protection, developers of drugs, medical devices and diagnostics will conduct market analysis, physician surveys and questionnaires, and other activities in advance of conducting a development program. The surveys in particular provide valuable feedback from practitioners of the art that may not have been considered during the initial construction of the patents underlying the inventions.

Exclusivity

Patents serve as the primary resource for and most widely used means to provide marketing exclusivity for commercially sold products. Because the cost of developing therapeutics, diagnostics and medical devices is very expensive, justifying the cost and development risk necessitates product protection through the issuance of patents and/or knowhow that yield exclusivity in the marketplace. A strong IP portfolio and multiple patent issuances surrounding a product (a "white picket fence" strategy, discussed below) may provide justification for product developers to invest heavily in product candidates. While the sales of therapeutics and other similar products can reach hundreds of millions and even billions in revenue, the cost associated with product development and launch, marketing, sales and distribution is similarly very large. As such, any going concern in the healthcare sector and ultimately profitable business must develop a strong patent portfolio around its product(s) with the goal of providing market exclusivity.

Exclusivity and product label

Any new learnings or novel observations that may occur during the research phase, preclinical or clinical program should be evaluated for the potential to file new patents and/or support pending

patents. An IP analysis should focus on the extent of the data available in determining whether the product label is sufficiently supported by the patent claims to provide or extend market exclusivity. A product label serves as a simple, short paragraph describing the invention in terms of its use, delivery, formulation and any other relevant information defining the niche of the product in the marketplace. (See also "Intended Product Label" section under Unmet Medical Need, above.) Product labeling is also important in mitigating off-label use and risk. For example, if one had invented aspirin today, a product label might read: "a compressed tablet comprised of 400 mg of sodium salicylate orally administered, taken every four hours or as needed to relieve mild to moderate pain such as headaches." What type of experiments would be conducted to generate POC to support this intended use? Obviously, the more data generated prior to embarking on human clinical studies, the higher the integrity of the intended product label probability of fulfilling the prophecy. As the development program evolves, so does the product label.

Exclusivity period

The length of time that a patent may provide exclusivity in the marketplace is a critical part of the due diligence calculation and value proposition. Product values, in part, are performed based upon the exclusivity period defined by the number of years that the patent precludes other product versions from entering the marketplace. The exclusivity period around the world is generally 20 years from the filing date of the original patent, though can vary depending on the territory and the original filing dates in each territory (*www.wipo.int*). However, years may pass from the time a patent is filed until the patent is issued, and still more years are often required to develop products based on that patent, thereby significantly reducing the effective exclusivity periods for many products once introduced into commerce. To this end, product developers seek to generate as much IP as possible not only to afford greater product protection, but also to extend the exclusivity period to maximize the financial returns on the invention.

Exclusivity periods and the FDA

In addition to the 20-year exclusive property right granted to an invention by the USPTO, if an invention eventually becomes a drug, the FDA also grants exclusivity to that product upon drug approval, if certain statutory requirements are met. FDA exclusivity refers to certain delays and prohibitions on approval of competitor drugs, which, therefore acts similarly to the patent right by preventing competition (*https://www.fda.gov/drugs/developmentapprovalprocess/ucm079031.html*).

"White picket fence" strategy

There are different kinds of patents and one invention can be eligible for more than one. Currently, the most commonly filed and issued types of patents in the healthcare industry are composition of matter, pharmaceutical formulations, methods and use, and machine (device) patents. Many developers of products seek and are granted multiple patents to protect one invention. Surrounding one invention with many patents is called a white picket fence strategy to protect the invention from competition or invalidation. The more patents surrounding an invention, the more difficult it is for a competitor to penetrate the marketplace with a competing product. It also makes it more difficult for patent litigators to overturn or invalidate a patent(s) when the specified product-related landscape is vast. A larger body of patents with multiple issued claims also reflects the possibility that an invention could be used in a greater number of circumstances or indications reflecting the possibility of a larger market and return for the investor.

"Composition of matter" and exclusivity

Of all the patent types, composition of matter patents offer the greatest degree of protection because they define product(s) in terms of exact chemical make-up or composition. For example, other compositions may not yield the same activity given that drugs function like a lock and key, where the key is the drug and

the lock is a receptor that modulates a biological activity. Therefore, composition of matter patents are generally of greatest value in generating market exclusivity. While other types of patents create additional value and can extend the period of exclusivity for an invention, they are generally weaker, particularly if unaccompanied by a composition of matter patent as part of a portfolio protecting a particular product. Competitors and generic drug companies expend significant effort to invalidate patents when there is a significant market opportunity and/or interest in enabling generic versions to enter the marketplace sooner rather than later.

"Composition of matter" was originally defined by the US Supreme Court in 1793 as "all compositions of two or more substances and all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids" (Patent Act, 1793). This original definition has evolved over time and currently enables inventors to claim "one-substance inventions" based upon a discrete compound also known as a new chemical entity (NCE) or molecule. NCEs and molecules are a special class of "composition of matter" having only one molecular formula (35 U.S.C. §101). The US Supreme Court in 1980 furthered the definition of composition of matter to include a genetically modified microorganism (Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980)). By claiming the exact composition of a product and understanding the component or molecule that is mediating the activity of the invention, it is impossible for others to replicate the invention for commercial sale without infringement.

Examples of composition of matter patents are as follows:

- New drug molecules (i.e., NCEs or compounds).
- Formulations of known drugs also known as pharmaceutical compositions or formulation patents.
- Food recipes, including new flavors.
- Beverages, drinks, alcohol and vitamin concoctions.
- New materials, including metal alloys and plastics.

Exclusivity through knowhow

As noted above, knowhow is a kind of "private IP" or trade secret and can include other components of technology rights such as patents, trademarks and copyrights, all in an effort to provide market exclusivity. In biotechnology, one common form of knowhow that protects innovation focuses on manufacturing. While patents can be filed on manufacturing processes, patents are public and thus the exact process is disclosed and can be replicated, thus creating the opposite of exclusivity. Although replicating a patented process without permission (such as a license) from the patent holder would be patent infringement, manufacturing patents are difficult to enforce. Therefore, manufacturers often do not seek manufacturing process patents and instead simply do not disclose critical steps in the process of making a product, keeping them a trade secret. Without precise disclosures describing how to manufacture a given product, the process can be very difficult and even risky for a competitor to attempt to replicate to produce a generic version or biosimilar.

This approach is taken for two reasons. First, for certain types of products, changing an incubation time, temperature of a reaction, size of mixing vessel may change the physiochemical characteristics and activity of a pharmaceutical ingredient, thereby changing the essential nature of the product itself. Second, because it is nearly impossible to eliminate all contaminants during manufacturing, the FDA developed guidelines for preclinical toxicology testing based upon the nature of the contaminants and their relative amounts. Therefore, any minor changes to the manufacturing process may result in a product that doesn't meet the pharmaceutical specifications based upon the original approval and product label, may be ultimately not safe or effective and puts consumers at risk. In sum, manufacturing knowhow can be difficult and even risky to replicate, and is thus a very effective way to provide market exclusivity without the benefit of issued patents.

Freedom to operate

The very first step in understanding whether an invention is novel and therefore unprotected from preexisting IP is to perform a simple freedom to operate (FOP) search. Freedom to operate means that there are no pre-existing publications or patents in the public domain that would invalidate any new patent filings or even issued patents. Therefore, it enables a developer (and future seller) of a product to develop, market and sell a new product without infringing upon the rights of another entity. The due diligence analyst should inquire if the product sponsor or licensee has performed any FOP searches. Such searches can be minimal to very extensive, which is often costly. For this reason, patent attorneys and inventors and their sponsors don't necessarily extend sufficient time and money at the beginning of a program to understand the full landscape of the prior art. The more effort placed on combing the universe in order to gain a reasonable level of comfort that your invention is truly inventive, the higher probability that your product will be free to sell without infringement issues (see patent infringement definition below). Often, this is not the case, and many products end up in litigation and inventors/developers spend an enormous amount of time, effort and cost defending IP from competitors.

A FOP search for a potential new product or new research program ultimately aimed at producing a commercial invention, should be as exhaustive a review as possible of the prior art. Analysts themselves should spend some time and effort on this exercise, which will often provide a reasonable understanding of the preexisting patent landscape and literature comprising the prior art. This enables the analyst to question the validity of both issued and pending patent(s). To accomplish this, any published data and/or information in the public domain that might relate to a new invention should be reviewed for obviousness. This includes abstracts, published papers, presentations at meetings and anything that can be resourced by the public. Any relevant information that is found should be referenced in the invention's original patent

application. These references to already public information also help the patent examiner understand how the new invention is differentiated from the prior art and serve as fodder to challenge certain patent claims or invalidate entire patents. The cost of formal FOP searches typically conducted by law firms is worthwhile in light of the subsequent time, effort and significant cost of prosecuting the intellectual property through the patent approval process and product development costs that follow. While an inventor may be thrilled by a novel idea or invention, she or he may not have been the first to come up with the idea. Some useful databases to search for prior art include Google (*www.google.com*), Pubmed (*http://patft.uspto.gov*) and Medline (*https://www.ncbi.nlm.nih.gov/pubmed*).

Patent infringement is the manufacture, sale, and/or use of an invention or improvement for which someone else owns the patent without first obtaining permission of the owner of the patent by contract, license or waiver (35 U.S.C. §271. See also Chapter 18.) To understand whether one invention is infringing upon another, which is the essence of an FOP search, requires someone who is skilled in the art, meaning someone with the sophistication to understand not only very complex inventions but also the patent specifications and claims for that invention. The assistance of someone skilled in the art is often necessary to aid IP lawyers in determining obviousness and/or whether the claims have previously been disclosed in the prior art or public domain. Any such findings may render a new invention or even an issued patent invalid. "Obviousness" is one of the legal requirements of a patent and is the criterion that patent examiners most commonly use to reject patents and that patent litigators use in their bid to overturn issued patents.

PRICING AND REIMBURSEMENT

This section will provide an overview of the general elements leading to and affecting reimbursement in the go–no go decision for a product developer and will focus on the market in the United

States. There are territories around the world, such as Spain, Greece, and Italy, where socialized medicine and community programs cover healthcare costs and cannot bear the high price of newer products and thus typically do not serve as the first or primary marketplace for such therapies. Therefore, corporations and institutions typically perform extensive market analysis first in the United States in order to develop a comprehensive understanding of the total market opportunity for each product candidate.

Product value analysis

To justify the significant investment required for development of a product, one must understand that the ROI depends on what the total value of the product is reasonably projected to be in the marketplace. This, in turn, is determined by how the product will be paid for as well as the price to the consumer, size of the addressable market, and the time period of exclusivity. Considered together, these factors will provide a sense of the overall value of the technology that enables the investor and/or product developer to better visualize a general view of the overall value proposition.

A simplistic, but meaningful approach to achieve a back-of-the envelope understanding of the value proposition may begin with the following steps:

1. Estimate the cost of the product based upon similar products and/or standard of care. Once a ballpark figure is achieved, develop an assumption related to the cost of manufacturing the product. For example, if the product's final cost to the purchaser is $10 dollars per pill and the cost to produce the product is $3 dollars, also termed the cost of goods (COGS), then the net profit will be $7 dollars per pill.

2. Calculate the number of years the IP will enable the product to be sold exclusively in the marketplace.

3. Multiply the number of pills consumed per year by patients (step 1) times the number of years the IP will preclude any competition (step 2).

Based upon the example above, if the pill is taken every day (365 days) and the exclusivity period is 10 years, then the aggregate value is $25,550 per patient. If the number of patients requiring this medication is 50,000, then the total value of the drug over the 10-year exclusivity period is approximately $1.3 billion dollars (assuming 100% patient compliance).

In this simplistic model, if the product development and launch costs are approximated at $100M, then there is approximately a 12-fold ROI return on the original investment, therefore meaningfully justifying the initial investment. Of course, sophisticated revenue modeling and forecasting take a large number of assumptions into consideration as well, such as royalty obligations, ramp-up, market penetration and segmentation and operational costs for marketing and sales. Analysis of strengths, weakness, opportunities and threats for a product and/or a company (SWOT) can be supportive in evaluating opportunity. By comparing the total cost of bringing a product to market and the magnitude of the market opportunity, a due diligence analyst can understand to what extent the product will be profitable. The greater the ROI, the more economically compelling is an investment in the asset or company.

Third party payors

While the above calculation is overly simplistic, it enables a broad view understanding of what the eventual value of the product might be in the marketplace. Healthcare analysts work diligently to attain a more thorough understanding of this value proposition, which is based upon how drugs are priced and reimbursed by third party payors such as insurance companies and government programs like Medicaid and Medicare. Healthcare fees, including

the fees for healthcare services, drugs, medical devices, and diagnostic tests, are largely covered by, and therefore largely determined by, these third party payors (see Chapter 20).

Though third-party payors strive to reduce the price the consumer will pay for a drug and in the context of overall treatment in minimizing their payouts and maximizing profits for the insurance companies and reducing healthcare costs to the patients. Despite this, the extent of coverage and affordability of healthcare continues to rise and has generated significant medical ethics and societal issues for patients and caregivers. Therefore, a detailed system of classification for disease and disease-related conditions has been developed by the Centers for Disease Control and Prevention (CDC) that insurance companies and governments have adopted to manage the cost of medical treatment. Third party payors use this international classification of disease codes (ICD or ICD 10, referring to its current, tenth revision) as a reference when they map signs and symptoms, abnormal findings, disease, injury, and treatments to reimbursement (*www.cms.gov/Medicare/Coding/ICD10/index.html*). Generally, if a product addresses an unmet medical need, there is a high likelihood that there exists a mechanism to pay for the product and an ICD 10 code that can be correlated with the medical condition. The cost of a new product is evaluated as a part of the total cost of treatment.

Pricing data enable one to model the revenue potential of a product in the marketplace and thereby determine whether the market opportunity justifies the cost of development. While pricing sensitivity studies are conducted to derive an understanding of usage by prescribers and adoption in the marketplace, the ultimate price of a product is largely influenced by how much a third-party payor will agree to pay and/or reimburse the consumer or patient for the associated treatment.

Defining the addressable market

If the product candidate truly addresses an unmet medical need and is supported by a product label and approval package, then there is a high probability that third party payors will fully cover or assist with the cost of the medication. However, though likely, this is not always the case. Therefore, even for a product that addresses an unmet medical need, the analyst should clearly define and/or understand the actual patient population that will use the product, also called the addressable market, to assure it includes all the patients to whom the product will be prescribed. Commercial organizations often conduct marketing studies by interviewing or questioning practitioners in surveys to learn where current treatments are insufficient or non-existent. These studies help to define the types of questions that are asked in the testing of experimental drugs. The addressable market is eventually defined by the intent-to-treat patient population derived from the compendium of clinical data included in its regulatory approval package. Also, developers may conduct additional clinical studies either pre- or post-approval to grow the market and product value, hence expanding the addressable market. For products that are marketed and sold for other uses not supported by the sponsor's clinical data (not part of the original regulatory approval package) and thus used "off-label", there is no obligation for the insurers to reimburse the patient. Regardless, off-label use may contribute a premium to the overall value proposition by expanding the addressable market.

Government programs and return on investment

Another relevant consideration that may impact the overall cost of drug development involves government-sponsored programs that provide incentives to partially offset the substantial costs of bringing a product to market. Specifically, some federal laws and regulations addressing diseases and conditions that are not "blockbuster" in size or affecting millions, have evolved to stimulate companies to take on the challenge of developing treatments for these much smaller populations. Some examples are the FDA's fast track approval and

the Orphan Drug Act, among others (see Unmet Medical Need above and Chapter 10). These programs have increased the ROI in such products by reducing the overall cost and time required to move products to market to treat niche populations (medical conditions).

ADDITIONAL ELEMENTS OF DUE DILIGENCE

Competition

Competition may be defined in economic terms as a rivalry among sellers of a product or similar products seeking the same customer base with the goal of increasing profits and maximizing market share. Although this definition applies to drugs, devices and other healthcare products, understanding product competition in healthcare is more complicated. For one, treating disease isn't always based upon a single therapy or recommendation and instead there are numerous product offerings. Moreover, the current standard of care is not always the best treatment option. As such, how a new product fits into the landscape and/or pharmacopeia can be complicated, as touched upon under Unmet Medical Need, above. To understand a product's competitive landscape, a developer must comb the universe to identify products in development and currently available products. A great place to start is an examination of the pipelines of products in development from corporate sponsors and products already marketed and sold. Products in various stages of development may be found on the FDA website (*www.usfda.gov*), other worldwide regulatory agency websites, analyst reports from investment banks covering healthcare products, and websites of the companies working in the same field of interest. Some products are in programs at large drug companies and kept under the radar, not registered with the FDA. Therefore, an alternative resource that can be used to uncover competitive products is the USPTO (*www.uspto.gov*) or World Intellectual Property Organization (WIPO) (*www.patenscope.wipo*). Taken together, this information should provide a comprehensive overview of the competition.

Competitiveness, or ability to achieve significant market share, for products in the healthcare space is often based upon significant improvements in either efficacy (ability to address unmet medical need), safety (reduction of side effects), relative market exclusivity to pharmacoeconomic benefit (cost savings to the consumer and health care system) or any combination thereof. This is precisely why these are the high priority elements of due diligence as described earlier in the chapter. An example of a product displacing its competition because of achieving greater efficacy and safety is Modafinil which replaced methylphenidate and amphetamine as the first-line treatment of excessive daytime sleepiness (EDS) and sleep attacks (narcolepsy). This was largely due to the side effect profile associated with methphenidate and amphetamine (Billiard, 2008).

There are other factors to consider when analyzing whether a product has a competitive advantage. Being first-to-market is one. Additionally, products that are novel but with little to no POC data may seem to be at a competitive disadvantage because they are at a stage where they still require extensive development work and series of clinical studies. However, being novel, such products can attain significant revenue. Other products may be competitive because they enjoy quicker paths to approval based upon significant unmet medical need, such as orphan drugs, anticancer agents, anti-infectives, etc.

Basic questions that should be addressed in examining the competitive landscape include:

- *How does the product and any competing product candidate compare to current standard of care?*
  This is particularly important for a product to be successful in clinical practice. Product superiority is based upon efficacy and safety. This is the basis for insurance coverage and reimbursement. Certainly, if a product is significantly superior in terms of efficacy, or equal or better on safety, the product candidate may become the new standard of care. Often,

however, product candidates may feature a superior safety profile (e.g., fewer side effects), or greater ease-of-use but still be a worse choice for other considerations such as cost to the consumer. Prescribers are very sensitive to this calculus. As such, prescriptions and sales may never gain traction.

- *What other groups/companies are working to treat the same condition or disease and how does the product being evaluated compare?*
  This helps elucidate market share in addition to potential marketing, sales and distribution partnership opportunities.

- *Who are the experts in the field?*
  Determine who are the key opinion leaders (KOLs) or experts in the field and see to what extent they medically support the attributes of the product candidate or technology. Contracting such experts as consultants can help to better understand the overall value of the product in addressing medical need *vis à vis* the competition.

- *Are the targets and approach the same or different?*
  If the approach is novel, then the company may offer a promising therapeutic. At the same time, new approaches (e.g., mechanisms of action) also come with high risk, particularly without human POC. If the targets or approach are similar, then the due diligence analyst must understand why the product is superior and how it may fit into current clinical practice.

- *Is the product already on the market?*
  If the product is already approved, the focus turns to understanding sales generation and revenue projections. What is the upside of the product in terms of pricing, market share, exclusivity period and products in development that may take away market share? Also, if the product was recently approved, are there, potentially, any unanticipated side effects or adverse events that may diminish the commercial value of the product once introduced in commerce?

- *Where is the product being developed and where will it be marketed and sold?*
  The ability to gain access to worldwide markets offers significant upside in addressing healthcare need. While the cost to achieve regulatory approval may be significantly higher, there are reciprocal nation-to-nation memoranda of understanding, such as one with the European Medicines Agency encompassing over 32 nations that provide pan-European approvals that help lower the overall cost of development. Biotechnology/pharma companies often focus on major affluent market territories, including the US and Canada, Germany, France, the United Kingdom, Japan, Korea, Brazil and China where markets are bigger in size and economy (*https://www.ema.europa.eu/*).

- *How far along the development path is the lead product or the products?*
  In general, the closer to market a product or lead candidate is, the lower the risk of failure and the higher the probability of approval, which makes the product more attractive to an investor and therefore is another due diligence consideration (see Chapter 22 for more on risk analysis calculations). If less development effort is required to bring that product to the finish line, then less capital investment should be required. For medical devices, the regulatory path to approval is often significantly shorter, requiring only a notice of intent to market a device (a 510k filing) with the FDA (*https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm*). If the device is invasive and/or clinical endpoints are necessary to demonstrate safety and the efficacy of the device, clinical data will be required and will, therefore, take more time to reach the market. For therapeutics and diagnostics, regulatory requirements are generally more demanding and can involve multiple clinical trials ranging including Phase I, II and III clinical trials. Phase IV or post-approval studies. (To better understand these clinical trial stages of development, see table below excerpted from Corr and Williams (2009).

Preclinical studies: the medicine

Once a single compound is selected, preclinical studies are performed to evaluate a drug's safety, efficacy, and potential toxicity in animal models. These studies are also designed to prove that a drug is not carcinogenic (i.e., it does not cause cancer when it is used at therapeutic doses, even over long treatment intervals), mutagenic (i.e., it does not cause genetic alterations), or teratogenic (i.e., it does not cause fetal malformations). Because a patient's ability to excrete a drug can be just as important as the patient's ability to absorb the drug, both of these factors are studied in detail at this stage of preclinical development.

Preclinical studies also help researchers design proposed Phase I studies to be conducted with humans. For example, preclinical studies with animals help determine the initial dose to be evaluated in the clinical trial and help identify safety evaluation criteria. The latter include factors such as patient signs and symptoms that should be monitored closely during clinical trials.

The result of work at this stage is a pharmacological profile of the drug that will be beneficial long into the drug's future. Researchers can use the profile to develop the initial manufacturing process and pharmaceutical formulation to be used for testing with humans. Industry has particular strengths in these areas, and most development efforts at this stage are based in biotechnology or pharmaceutical companies. They can also use specifications assigned in this stage to evaluate the chemical quality and purity of the drug, its stability, and the reproducibility of the quality and purity during repeat manufacturing procedures. At this stage, and before testing with humans begins, an Investigational New Drug (IND) application is filed with the FDA. If the IND application is approved, then clinical trials can begin.

Phase I. Clinical Trials: Safety

Phase I trials are the first time that a drug is tested in humans. These trials may involve small numbers (20 to 100) of healthy volunteers, or they may include patients with specific conditions for which targeted pathways have been identified as potentially relevant to the disease under study. A Phase I study may last for several months. The focus of a Phase I study is the evaluation of a new drug's safety, the determination of a safe dosage range, the identification of side effects, and the detection of early evidence of effectiveness if the drug is studied in patients with disease, for example in patients with cancer. From Phase I clinical trials, researchers gain important information about

- The drug's effect when it is administered with another drug (the effect is often unpredictable and sometimes results in an increase in the action of either substance or creates an entirely new adverse effect not usually associated with either drug when it is used alone).

- The drug's pharmacokinetics (absorption, distribution, metabolism, and excretion) to better understand a drug's actions in the body.
- The acceptability of the drug's balance of potency, pharmacokinetic properties, and toxicity, or the ability of the drug to zero in on its target and not another biological process.
- The tolerated dose range of the drug to minimize its possible side effects.

Phase II. Clinical Trials: Proof of Concept

In Phase II clinical trials, the study drug is tested for the first time for its efficacy in patients with the disease or the condition targeted by the medication. These studies may have up to several hundred patients and may last from several months to a few years. They help determine the correct dosage, common short-term side effects and the best regimen to be used in larger clinical trials. This usually begins with Phase IIa clinical trials, in which the goal is to obtain an initial proof of concept. The POC demonstrates that the drug did what it was intended to do, that is, interacted correctly with its molecular target and, in turn, altered the disease. Phases I and IIa are sometimes referred to as "exploratory development". The Phase IIb trials are larger and may use comparator agents and broader dosages to obtain a much more robust POC.

Phase III. Clinical Trials: Regulatory Proof

Phase III clinical trials are designed to prove the candidate drug's benefit in a large targeted patient population with the disease. These trials confirm efficacy, monitor side effects, and sometimes compare the drug candidate to commonly used treatments. Researchers also use these clinical trials to collect additional information on the overall risk-benefit relationship of the drug and to provide an adequate basis for labeling after successful approval of the drug.

Phase III studies are conducted with large populations consisting of several hundred to several thousand patients with the disease or the condition of interest. They typically take place over several years and at multiple clinical centers around the world. These studies provide the proof needed to satisfy regulators that the medicine meets the legal requirements needed to be approved for marketing. The study drug may be compared with existing treatments or a placebo. Phase III trials are, ideally, double blinded; that is, neither the patient nor the researcher knows which patients are receiving the drug and which patients are receiving placebos during the course of the trial. Phase III trials are usually required for FDA approval of the drug. If the trials are successful, then a New Drug Application is submitted to the FDA. The process of review usually takes 10 to 12 months and may include an advisory committee review, but such a review is at the discretion of the FDA.

Phase IV. Clinical Trials: Marketing and Safety Monitoring
Phase IV trials are studies conducted after a drug receives regulatory approval from the FDA. They may be used primarily for medical marketing. In some cases, the FDA may require or companies may voluntarily undertake post-approval studies to generate additional information about a drug's long-term safety and efficacy, including its risks, benefits, and optimal use. These studies may take a variety of forms, including studies that use data from the administrative databases of health plans as well as observational studies and additional clinical trials.

Postapproval trials may also be designed to test the drug with additional patient populations (e.g., with children), in new delivery modes (e.g., as a timed-release capsule), or for new uses or indications (i.e., for the treatment of a different medical condition). Because these post approval trials are intended to provide the basis for FDA approval of further uses or delivery modes, they must meet the same standards as the Phase III trials conducted for initial approval.

FDA REGULATORY PROCESS

A due diligence analysis should examine the FDA regulatory approval process because every biotechnology product will have to be FDA approved before it can be sold on the market. A good starting place is the FDA website (*https://www.fda.gov/Drugs/DevelopmentApprovalProcess/*) which has a wealth of information on clinical development and regulatory requirements, including guidance documents, regulations and policies. Also, the Freedom of Information services website (*http://www.foiservices.com/*) is extremely useful because it lists historical precedents that show what the FDA has required from previous product developers – from investigational new drug applications to marketing submissions and approvals. Looking at precedents elucidates what the FDA finds acceptable for submissions, even those that may not exactly conform to guidance documents.

Meetings with the FDA

Meetings with the FDA are classified into three categories:

- *Type A meeting*
  A meeting that is necessary for a stalled development program. This meeting type is requested in order to proceed or to address an important safety issue. This includes dispute resolution meetings, meetings to discuss clinical holds, and special protocol assessment meetings.

- *Type B meeting*
  A routine meeting that occurs at a pre-defined milestone time point in the development program such as Pre-IND Meetings, some End of Phase I Meetings, End of Phase II Meetings, and Pre-NDA Meetings.

- *Type C meeting*
  Any meeting other than a Type A or Type B meeting regarding the development or review of a product.

These meetings are critical in moving a product closer to approval. Product developers, called "sponsors" by the FDA, who do *not* request these meetings or only follow regulatory guidance, may be taking a risk as they are left guessing as to how the FDA may respond to their application. Moreover, when the FDA makes recommendations, which are recorded in meeting minutes, the prudent sponsor will address them. Developing a good relationship with the regulatory bodies guiding product development likely increases the probability of success and is a benefit that our tax dollars provide to sponsors of new products. It is surprising to learn of companies that don't take advantage of this opportunity and a lack of meetings should be a red flag to a due diligence analyst. If there were meetings, the minutes from the meetings capture the precise guidance that the FDA has recommended to the product developer. FDA meeting minutes are typically held confidential by corporate sponsors, however, and generally not publicly disclosed.

This is primarily because unsecured disclosure to unauthorized parties could educate competitors and potentially eliminate an anticipated competitive advantage. As such, analysts must act diligently to try and gain a meaningful understanding of the regulatory requirements without actually seeing the contents of the minutes. The regulatory requirements for product submission and approval can vary from sponsor to sponsor, even for a product addressing the same condition. This is often based upon certain product characteristics that result in the regulators demanding additional testing. Therefore, questions related to regulatory requirements can often reveal product peculiarities, additional requirements, extended timelines and costs and help to facilitate an understanding of both risks and hurdles.

MANUFACTURING

The manufacture of product candidates is often an area of due diligence to which many investors and drug developers often don't necessarily pay enough attention. This is evidenced by the fact that a significant number of products fail to undergo review or get final approval due to chemistry, manufacturing and quality control (CMC) issues (*https://social.eyeforpharma.com/research-development/why-drugs-fail-get-approved*). (See Chapter 15.) Moreover, as covered in the IP section of this chapter, new manufacturing processes are a potential source of valuable IP and/or knowhow and in the current biotechnology landscape, there are more, new manufacturing processes than ever before. Traditional drug manufacturing is based on small molecules, was well developed over the history of the pharmaceutical industry and is well-defined by regulators. However, many new types of therapeutics and novel agents are not small molecules and cannot be manufactured by traditional processes. Makers of these new therapies, such as cell therapy, gene therapy, virally based therapies, antibody derivatized cytotoxins and bacterial based therapeutics and more, have had to pioneer new forms of manufacturing processes and technological platforms, all of which can be potential sources of valuable knowhow.

For commercially viable products, all of this must occur under Good Manufacturing Practices (GMP conditions). Basics of manufacturing include identification of impurities as well as stability and delineation of, and proof of, the desired quality attributes for a given drug program. Manufacturing flaws can doom a potentially life-saving drug program, for example, by not properly determining a product's shelf life. Generally, commercially viable products as a general rule should be stable for a minimum of 12 months. If the product shelf-life is too short, the cost to the GMP manufacturer of new batches of product may be too frequent in order to maintain drug supply to the market and therefore significantly impact or eliminate the profitability of a product. This, of course, varies from product to product and must be analyzed in the justification for commercial viability. Standard assays are developed and validated in order to test for stability. The newly manufactured material must fall within the original specifications as approved by the FDA. Manufacturers use these assays on an ongoing basis beyond clinical development period to quality assure new product batches of material that are intended for distribution and sales in the marketplace. If the product needs to be lyophilized or refrigerated, manufacturing costs will go up, but will not be prohibitive or a game stopper, but should be calculated into the COGs and understood as part of the overall value proposition. Any changes to a manufacturing process, including moving manufacturing from one vendor to a second vendor through a technology transfer process, may result in a product that does not entirely meet specifications. Because the cost to produce a batch of GMP material is expensive, millions of dollars can be lost if careful attention is not given to the production of a product. Therefore, understanding the risks of producing a product, such as stability is an important element of the due diligence process.

Other key manufacturing questions to address are:

- What type of manufacturing process is required?
- Is the product stable in serum or blood (particular if it is intended for i.v. administration)?

- Does the product degrade under certain conditions and require certain elements or modifications to the formulation?
  - Does the product require certain types of packaging? For example, is it light sensitive?
  - Does the product require special circumstances for storage?
- Is commercial scale-up possible and/or feasible?

Because of the importance of manufacturing in the success of a product, this area of due diligence – manufacturing cost, regulations, quality, storage, and distribution and even the potential for additional, new, valuable IP or knowhow – deserves more significant attention than is typically given by technology analysts.

FINANCIAL

A car needs gas in the tank to move. Many, if not most, start-up and emerging companies require fuel in the form of capital in order to move forward. Cash needs vary widely based upon the corporate strategy and the development plan, but are intensive for most healthcare based products. Therefore, capital needs for healthcare products should be focused on and directed at achieving value-enhancing milestones. For emerging healthcare companies, the marketplace will reward corporations that deliver on their promises. This is reflected in the ease of raising capital and the valuation of the company. For companies that overspend for any variety of reasons, access to new capital or funding is likely to become a gating item to their future success. A company in control of its financial picture will understand future value-enhancing milestones, the timing to get there and projected cash flow and future capital needs, if any. Assessing the financial picture of a private company can be difficult as it is not required to undergo an audit and disclose its finances. On the other hand, public companies are more transparent given the obligations to regularly publish audited financials. However, for any company, projecting future revenue and earnings can be complicated and unpredictable, though Wall Street analysts

nonetheless work diligently to derive models to predict probable future revenue, pricing and corporate valuations.

All businesses must model a financial strategy, from early stage ventures to more established firms. An adequate model will estimate the value of a corporation and provide sufficient information for making informed investment decisions. It should also enable the entrepreneur or analyst to deliver responsible financial projections to seek capital from outside resources (see Chapter 8). Sources of capital should be thoroughly vetted and credit reports should be included in the financial disclosures. Even for private corporations that have raised capital, third party audits can accurately reflect how capital has been deployed. Such audits also provide useful checks and balances on the corporation's accountant.

Financial models are generally used to forecast a business' financial performance into the future. The forecast is based upon a number of assumptions related to the company's past performance, anticipated future earnings and is built upon an income statement, balance sheet, cash flow statement and any supporting schedules. More complicated financial modeling may also include discounted cash flow (DCF model) data and financial data derived from market penetration and sensitivity analyses.

Drug, device and diagnostics revenue models are also derived from historical data, current trends and commercialization data, including exclusivity periods based upon IP expiration dates from territory to territory. Robust revenue models require industry benchmarks, industry datasets and assumptions related to growth and discount rates. Armed with a detailed understanding of a corporation's balance sheet and projections, valuation models can also be derived. Financial analysis often depends on many assumptions but the greater the clarity that can be derived for a given entity, the more reliable a meaningful investment may be. Strong financial datasets and revenue modeling that describes the

profitability of all its product(s) and each product's relative contribution to the overall valuation of the company serve as the basis for the financial terms underlying various transactions such as a license agreement or mergers and acquisitions. (For more information related to finance see Chapters 7 and 8.)

Non-dilutive financing is an enormously valuable contribution to a project and should be part of the due diligence process. Non-dilutive financing is defined as capital contributed to a corporation that isn't a result of the sale of the company's equity (shares of stock). Receipt of this form of funding is typically a result of a granting process or recognition of promising technology by a non-profit institution, such as a foundation, or federal agency, such as the National Institutes of Health. Typically, receiving entities have undergone peer review and attained recognition in their respective field. Non-profit institutions, the government and corporations invest heavily in research, identifying and developing curative treatments and these sources of non-dilutive financing can offset the significant cost of product development, add credibility to the program and help increase the overall value proposition.

In summary, the due diligence derived from financial analysis and financial modeling described above is important to:

- Valuing a business.
- Raising capital or personal investment.
- Selling or divesting assets or business units.
- Mergers and acquisitions.
- Corporate growth.
- Budgeting and forecasting (future planning).
- Portfolio management and capital allocation (prioritizing which project to invest in).

THE MANAGEMENT TEAM

Last but not least impacting the success of a product development program is the competency of the management team. First, the due diligence analyst must determine whether the company's management team, particularly those in charge (the executive team), has the ability, experience and track record to execute on the business plan. Where there are deficits in any of these qualifications, the analyst must see whether the company has identified capable third party consultants or vendors to assist in driving developmental and financial near term milestones based on corporate goals and objectives.

The second important element in evaluating the management team is the integrity of the information being presented. Sometimes management teams expend significant energy to raise funds and sell the corporate story, to the point that the story becomes a "tall tale" with delusions of grandeur. The keen analyst frequently uncovers this circumstance by gauging the accuracy of responses, fact checking and examining body language. One of the top performing biotechnology hedge funds, called Perceptive Advisors, LLC., based its name on this element and is known to completely drop a position where there is a sense of executive team inadequacy or hyperbole.

Information about management team members and key employees is usually readily available and is almost invariably disclosed in the company's corporate deck, business plan or website. Biographies and track records should be investigated thoroughly. Sometimes executives can turn-up with a questionable past or even a criminal record. This can be discovered through the internet and conducting a background check through a third party. CEOs that have previously built winning businesses or enterprises have a high probability to drive success again. There are no guarantees of future performance but an experienced and knowledgeable team gives investors confidence and a greater likelihood of investing. Fortunately, a management team can always be changed, certainly

more easily than the technology on which the company is based. As an experienced Venture Capitalist once said, you can always change the jockey, but you're stuck with the race horse.

WHAT DUE DILIGENCE CAN'T UNCOVER

Some information may never come to light and certain risks cannot be predicted no matter how much digging the analyst does. However, mistakes made and challenges faced by other products in the past offer at least highlight some potential issues that may arise. For example, products can negatively react with packaging, such as a rubber stopper as in the case of Dyloject™. Clinical side effects may not reveal themselves until thousands of patients have begun to use the product. A patent examiner may reject claims or even the issuance of a patent and cause a protracted prosecution period. Regulators may delay, though atypical, the development of a product(s) based upon a reviewer's bias (Miller, 2018). Due diligence analysts and biotechnology investors must be able to live with the possibility of unforeseeable risks and errors. As a former chairman, and CEO and founder of several start-up companies once stated, "the ability to tolerate ambiguity is inversely correlated with the likelihood of success."

CONCLUSION

Due diligence is a fundamental and necessary exercise prior to starting any research project, company or drug development program and should be an ongoing process, even once a product has undergone significant development and investment. Companies and investors are under enormous pressure to drive successful outcomes in understanding disease and treating patients. While both researchers and corporations have the noble goal of advancing medical knowledge and patient care, if due diligence reveals that a product or technology is unlikely to succeed, for any of the reasons discussed in this chapter, sometimes it's better to cut one's losses and focus on another, more promising area of unmet medical need.

Conducting meaningful due diligence is an essential undertaking for any savvy investor, researcher/ inventor and product developer seeking to vet something of perceived value to creating actual empirical value; in other words, to drive a product candidate from idea to the market.

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