



# Bringing Your Pharmaceutical Drug to Market

*Edited by Neil P. DiSpirito, Ralph F. Hall, and Matthew J. Hill*



**BRINGING YOUR  
PHARMACEUTICAL DRUG  
TO MARKET**

EDITED BY  
NEIL P. DISPIRITO  
RALPH F. HALL  
MATTHEW J. HILL

© 2015 FDLI. All rights reserved.

ISBN 978-1-935065-75-3

Authorization to photocopy items for internal or personal use of specific clients is granted by the Food and Drug Law Institute, provided that the base fee of US \$.75 per page is paid directly to the Copyright Clearance Center (CCC), 222 Rosewood Drive, Danvers, MA 01923, USA.

For those organizations that have been granted a photocopy license by CCC,  
a separate system for payment has been arranged.

The fee code for users of the Transactional Reporting Service is: 978-1-935065-75-3/02.75.



1155 15th Street NW  
Ste. 910  
Washington, D.C. 20005  
Tel: (202) 371-1420; Fax: (202) 371-0649  
[www.fdpi.org](http://www.fdpi.org)

# Generics

## **I. INTRODUCTION**

The development of the generic pharmaceutical industry after the Drug Price Competition and Patent Term Restoration Act of 1984 (informally known as the Hatch-Waxman Act) brought about huge savings for patients and healthcare payors and provided further incentive for innovation as branded products lost patent protection and became subject to competition from generic products. The success of the Hatch-Waxman amendments to the Federal Food, Drug, and Cosmetic Act (FDCA) prompted Congress to adopt a similar framework for an abbreviated application for approval of “biosimilar” products that are highly similar to already approved biological products.

There are many factors to consider when developing a generic pharmaceutical product for market, including product identification, patent strategies, options of regulatory pathways, and studies necessary to gain approval. In this chapter, we aim to give a brief overview of the process for bringing a generic drug product through the regulatory process and to commercialization.

## **II. PRODUCT IDENTIFICATION AND SELECTION**

The first step in bringing a generic drug product to market is product identification and selection. When evaluating whether to choose to invest resources in developing any given generic drug product you should consider both the market landscape and your company’s technical capabilities. You should evaluate the market landscape including the total size of the market; the number of other generic competitors, current or anticipated, for the same brand product; and whether there are other branded drug competitors for a particular drug product. It can also be helpful to consider the future direction of the market for a drug product. For example, does the brand company have line extensions in development or perhaps the brand company has already launched a line extension and begun converting some sales of the reference listed drug. Also,

consider whether the market for this particular class of drugs is well developed with many branded and generic competitors, or whether this particular drug product fits a more unique niche.

Once the market landscape has been evaluated, you will need to consider that market in the context of your company's technical capabilities. Does the company have manufacturing capacity to make the product once it gets approval? Will this product require capital investment in new facilities or equipment? Do you have the resources available to perform the necessary development studies? If your company has produced only solid oral dosage forms in the past, it will require more detailed consideration before jumping into the market with an ophthalmic solution product. Perhaps your company is ready to make that jump and invest in the facilities, equipment, and know-how to market ophthalmic products, but that evaluation should always happen early in the process of product selection.

As explained more fully below, the product classification will determine the development and regulatory requirements, mechanism of sale to consumers, and type or extent of marketing and promotion that may be necessary. Over-the-counter (OTC) products often have less voluminous requirements for regulatory submissions than prescription products, but are marketed differently with sale directly to consumers instead of requiring the doctor or pharmacist as an intermediary. Traditional small molecule products have an entirely different regulatory scheme than biosimilars, but traditional generic small molecule products are often automatically substituted at the pharmacy, while biosimilars may require some amount of promotion and advertising. All of these factors will have to be taken into account when determining which generic product or products make the most sense for your company to add to its pipeline for development.

### **III. STRATEGY FOR ADDRESSING PATENT AND REGULATORY EXCLUSIVITIES**

Regardless of the type of generic product under consideration for development, you must develop a strategy for addressing any issues with patent or regulatory exclusivities. The patent strategy, along with any applicable regulatory exclusivity, may limit when you may launch the product. For a generic product of a new drug application (NDA)-approved reference listed drug or an OTC medication, information on patent and regulatory exclusivity is available in the Orange Book: Approved Drug

---

Products with Therapeutic Equivalence Evaluations. The electronic Orange Book is available online and updated daily. The Food and Drug Administration (FDA) just published the Purple Book for biosimilar products.

### **A. Strategies for Addressing Patents Related to the Proposed Drug Product**

Any applicant who submits an NDA or amendment to an NDA must submit for listing in the Orange Book each patent that claims the drug or method of using the drug that is the subject of the NDA, and which could reasonably be asserted against a person who makes, uses, or sells that drug product without a license.<sup>1</sup> For each product, there is a separate page showing all of the listed patents for that product as well as the patent expiration date.

The patents required to be listed in the Orange Book may not be the only patents about which you should be concerned when developing a generic drug product. Oftentimes there are additional patents not listed in the Orange Book that a branded company may assert during litigation. Before you invest the time and resources in developing a product and preparing an application for approval to FDA, you should have a strategy for dealing with these patents as well as any Orange Book listed patents.

For a generic version of a biologic product, FDA now publishes the Purple Book. It, however, is not as straightforward as the patents listed in the Orange Book. Instead, for generic biologics products, sometimes generally called “biosimilars,” the company holding the approved biologics license application (BLA) for the brand product is not required to provide a list of patents for which it believes a claim of patent infringement could be asserted until 60 days after receiving the biosimilar application from the proposed generic manufacturer.<sup>2</sup> Thus it will be important when considering pursuing a biosimilar to undertake a freedom-to-operate analysis to identify all relevant patents and pending patent applications.

Once the relevant patents have been identified—by reference to the Orange Book and by evaluation of any patents not listed in the Orange Book as well as pending patent applications—those patents should be evaluated for the scope and strength of patent protection, as well as the duration of patent life. If any patents expire before, or even just shortly after, expiration of all applicable regulatory exclusivities, it may not make sense to challenge those particular patents. On the other hand, for any patents that

extend for a significant period of time beyond regulatory exclusivities, you should consider potential avenues to challenge those patents. For narrowly drafted patent claims, your generic drug product can often be designed in a manner that avoids infringement of the claims. Broadly drafted patent claims may be susceptible to an invalidity challenge based on prior art pre-dating the patent application. Sometimes claims are structured in such a way as to be susceptible to both invalidity and non-infringement challenges.

Developing a clear patent strategy early will help evaluate how quickly you expect to be able to launch the product and to determine the commercial viability of deciding to invest in the development of a product. An invalidity strategy or a non-infringement strategy may provide for earlier market entry. A unique non-infringement position unlikely to be shared with other generic applicants may provide for market entry sooner than other competing generic products. In addition to assisting with evaluation of whether it makes business sense to pursue a particular generic drug product, developing a clear patent strategy early will inform the development strategy and regulatory strategy for the product. If you have invested the time and resources to develop a non-infringement strategy that may get your product on the market several years before a patent is set to expire, make sure that strategy is carried through to the development of the product and accurately reflected in all regulatory submissions and correspondence.

As part of a full patent strategy, remember also to consider possibilities to file for your own patent protection. As the research and development of the generic drug product gets underway, there may be opportunities to protect novel methods for making the drug substance or drug product, novel polymorphs of the drug substance, or perhaps even novel formulations of the drug product. While having your own patent portfolio can be a valuable tool, again always make sure that any patents for which you apply stay consistent with the overall patent strategy for defending against any allegations of infringement of the brand company's patents.

## **B. Strategies for Addressing Any Potential Issues with Regulatory Exclusivities**

Unlike patents, which are often susceptible to challenge on grounds of non-infringement or invalidity, regulatory exclusivities tend to be more straightforward and generally less susceptible to challenge. Regulatory exclusivities are determined by



---

statute. Like listed patents, the expiration date for applicable regulatory exclusivities for a given product are listed in the Orange Book. New chemical exclusivity is five years from the date of approval of the NDA.<sup>3</sup> Orphan drug exclusivity is seven years from the date of approval.<sup>4</sup> New clinical investigation exclusivity (for a product that does not contain a new chemical entity) is three years from the date of approval.<sup>5</sup> Pediatric exclusivity extends any other relevant exclusivity period by six months.<sup>6</sup> For biologic products regulatory exclusivity is 12 years from the date of approval of the BLA for the reference product.<sup>7</sup>

Regulatory exclusivities are difficult to challenge unless FDA has made an error in applying the statute with respect to any given drug product. If you believe FDA has made an error, challenging FDA's grant of exclusivity for a drug product requires petitioning FDA through a Citizen Petition to change the exclusivity granted. If FDA denies the petition, the next avenue of recourse would be to sue FDA to convince a court that FDA was wrong in the way it applied the statute in granting exclusivity.

To this point, we have been mostly concerned with evaluating regulatory exclusivities of the branded product, but there are regulatory exclusivities that are also available for generic products. The first abbreviated new drug application (ANDA) for a given reference listed drug that includes a certification that one or more of the Orange Book listed patents are invalid, unenforceable, and/or not infringed is entitled to 180 days of exclusivity before any other later-filed ANDA can be approved.<sup>8</sup> If multiple ANDAs are filed on the same day, then each of those ANDA applicants are considered "first-filers," and they jointly share the 180 days of first-filer exclusivity. For biosimilar applications under 42 U.S.C. § 262(k), one year of marketing exclusivity is available for the first commercial marketing of the first biosimilar product determined to be *interchangeable* with a reference product.<sup>9</sup> As we will see later, there is a big difference between approval of a biosimilar application under section 262(k) and a determination of interchangeability.

The availability of marketing exclusivity for your proposed generic drug product may put you on a specific timeline for development and preparation of an application. If you are later in the process to start development of a given product, it may be that others are likely to get an application on file before you and beat you to available regulatory exclusivities. Knowing where you are at in the process, and whether others may likely be ahead of you, are all important factors to consider to honestly evaluate the commercial landscape for any generic product under consideration for development.



## **IV. FORMING A DEVELOPMENT STRATEGY AND REGULATORY STRATEGY**

Once you have selected a specific generic drug product to add to your company's pipeline, the development strategy and regulatory strategy will go hand-in-hand. There may be multiple regulatory pathways to approval from which to select, and the pathway you choose will determine the type and amount of data necessary to generate in the development program to gain FDA approval.

### **A. OTC Drug Monographs for Over-the-Counter Products**

Many OTC products represent probably the simplest path to market. For many therapeutic classes of drugs FDA has developed OTC drug monographs, which FDA considers akin to a recipe book of acceptable ingredients, doses, formulations, and labeling. As long as the OTC product complies with the specifications of the monograph, no prior approval from FDA is necessary to start marketing the product.<sup>10</sup> OTC products that do not conform to a monograph must go through the NDA approval process.<sup>11</sup> Alternatively, any person or company can petition FDA to amend an OTC monograph or to establish a new monograph.<sup>12</sup> FDA has established standardized format and content requirements for labeling OTC products, for ease of use to the consumer and ease of implementation for manufacturers.<sup>13</sup>

### **B. Abbreviated New Drug Application**

An abbreviated new drug application is an option for generic versions of previously approved NDA products. The Hatch-Waxman amendments to the FDCA established this abbreviated pathway for approval of generic drug products. Instead of having to conduct clinical trials to prove safety and efficacy, like an NDA, an ANDA need only show bioequivalence of the proposed generic drug product to a reference drug product from a previously approved NDA.<sup>14</sup> By statute, "bioequivalence" requires showing that

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.<sup>15</sup>

---

Bioequivalence can be shown by either 1) including a full bioequivalence study in the ANDA, or 2) including information in the application sufficient to allow FDA to waive the requirement for a bioequivalence study.<sup>16</sup> FDA prefers pharmacokinetic measurements as the method to show bioequivalence, with C<sub>max</sub> and AUC indicating rate and extent of absorption, respectively.<sup>17</sup> FDA has provided relatively detailed guidances on the design of studies sufficient to show bioequivalence, and the most efficient path to approval will adhere to these guidances as closely as possible.<sup>18</sup>

Pharmacokinetic studies are the gold standard for bioequivalence for oral dosage forms or any other dosage forms in which systemic exposure in the blood is sufficient to be a suitable method for determining bioequivalence. For example, immediate release tablets typically require two studies: 1) a single-dose fasting study and 2) a single-dose fed study.<sup>19</sup> A proposed generic drug product is generally considered to be bioequivalent when the 90 percent confidence interval for both C<sub>max</sub> and AUC is fully within 80 percent to 125 percent of the C<sub>max</sub> and AUC of the reference listed drug. Typically, only the highest dosage form needs to be tested for bioequivalence when there are multiple dosage levels included in the ANDA.<sup>20</sup>

While pharmacokinetic measures, most typically C<sub>max</sub> and AUC, are the gold standard for showing bioequivalence, other measures including pharmacodynamics, clinical, and in vitro studies can be acceptable in an appropriate situation to show bioequivalence. Different types of dosage forms have different requirements for showing bioequivalence. Applicants can often get a waiver of the requirement for bioequivalence studies for dosage forms such as oral solutions, where for example, the proposed generic product contains the same active ingredient in the same concentration, and does not contain any excipient likely to affect absorption or bioavailability. For dosage forms such as ophthalmic solutions or topical ointments where systemic exposure is not expected to be significant in action of the drug product, the applicant must resort to other methods besides pharmacokinetic studies to show bioequivalence, or provide information to show that FDA can grant a waiver of the requirement for bioequivalence studies.

One of the key benefits of the ANDA pathway is the opportunity for the proposed generic product to be “AB-rated” as a therapeutic equivalent to the reference product. While FDA is responsible for rating of generic products as therapeutic equivalents, most state pharmacy laws permit substitution when there is a generic product available that is rated by FDA as a therapeutic equivalent, e.g., AB-rated.<sup>21</sup> Thus, AB-rated

generic products typically do not require promotion and marketing to consumers to achieve sales. FDA generally gives a product an AB-rating when the generic product has identical active ingredients, dosage form, and route of administration and the same dosage strength as a reference listed product and a study demonstrates that the generic product is bioequivalent to the reference product.<sup>22</sup> Thus, a well-designed bioequivalence study not only satisfies the requirements for approval of an ANDA but also generally qualifies the product to be AB-rated.

The ANDA pathway is generally available where the active ingredient, the route of administration, the dosage form, and the dosage strength are not different from those in an approved NDA. If any of these are different from the approved reference listed product, FDA may still accept an ANDA. First, however, you will need to get permission from FDA to submit an ANDA by way of submitting an ANDA suitability petition.<sup>23</sup> Use of ANDA suitability petitions has dropped substantially over the last several years.<sup>24</sup> Choosing to submit an ANDA suitability petition will likely delay the time to approval, as the ANDA itself cannot be submitted until FDA rules on the suitability petition. Also, having to rely on an ANDA suitability petition may mean that the approved generic product will not be AB-rated, and thus not eligible for automatic substitution. Nevertheless, the ANDA suitability petition is a viable option when the proposed generic product differs from the reference listed drug in one of the above four areas, and in the appropriate circumstances may be the most efficient regulatory pathway for a product that has only minimal changes from a previously approved reference product.

### **C. Section 505(b)(2) New Drug Application (Paper NDA)**

Another alternative to preparing and submitting a full NDA when an ANDA may not be appropriate is to submit an NDA under section 505(b)(2) of the FDCA, also known as a “paper NDA.” In instances where the proposed drug product represents a change from a previously approved product, section 505(b)(2) allows an applicant to rely on studies that were not conducted by the applicant or on the applicant’s behalf. These include situations where some of the preclinical and clinical studies required for an NDA have previously been submitted to, and reviewed by, FDA as part of another NDA. In these instances, the applicant may rely in part on these earlier studies and provide FDA with enough further studies to show the safety and efficacy of the change from the reference listed drug. A paper NDA may be an appropriate pathway where the listed drug product is the same as a previously approved product but differs in

---

dosage form, dosage strength, route of administration, is a combination product, or has a lightly altered active ingredient. For example, a different salt form of the same active ingredient as a previously approved application may be a good candidate for a 505(b)(2) application.

#### **D. Section 351(k) Application (Biosimilar)**

While the Hatch-Waxman Act has provided an abbreviated pathway to approval of generic small molecule drug products since the mid-1980s, until very recently there was no abbreviated pathway for approval of generic biologic products, or biosimilars. In response to a perceived need for an abbreviated pathway for approval of biosimilars, in 2010 Congress passed the Biologics Price Competition and Innovation Act (BPCIA). In concept, the BPCIA is similar to the Hatch-Waxman Act in that it allows an applicant to gain approval for a biologic drug product without submitting a full BLA, but instead by referencing a previously approved BLA for a similar product. The abbreviated biologics applications are often referred to as a “351(k) application” making reference to section 351 of the Public Health Service Act.

Section 351(k) applications replace bioequivalence with the concept of biosimilarity. A 351(k) application will be approved based on data showing the proposed product is at least highly similar to the reference listed product. A 351(k) application requires information sufficient to show the proposed product is “biosimilar” to a reference biologic product based on data from 1) analytical studies demonstrating that the proposed product is highly similar to the reference product, 2) animal studies including assessment of toxicity, and 3) a clinical study or studies to demonstrate safety, purity, and potency in one or more conditions of use for which the reference product is licensed.<sup>25</sup>

FDA’s approach to biosimilarity is somewhat more nebulous than the standard for bioequivalence, because of the differences between traditional small molecule drug products and biological products. Also because biosimilar applications are new to FDA, the process and procedures for submitting a biosimilar application are still being developed and refined. FDA recommends a stepwise approach to demonstrate biosimilarity, and will evaluate a biosimilar application under a risk-based, totality-of-the-evidence standard evaluating all available data and information.<sup>26</sup> The stepwise approach starts with structural and functional characterization of the proposed biosimilar product and the reference.<sup>27</sup> With a stronger and more comprehensive

presentation of data for this initial characterization, FDA is more likely to allow a more streamlined and targeted approach for later animal and clinical studies. If the initial characterization leaves questions open regarding the proposed product, FDA is likely to require more extensive animal and clinical testing.<sup>28</sup>

While many biosimilars applications are in process of being prepared, the first application was accepted for filing by FDA in July 2014. As both FDA and product sponsors become more familiar and more comfortable with the biosimilar application process, and as biological products continue to become more widely used in the practice of medicine and treatment of disease, the regulatory pathway under section 351(k) for biosimilars will become more and more important for development of generic products.

## **V. SUBMITTING APPLICATION TO FDA**

Once the appropriate regulatory pathway has been determined, and all the necessary development work been finished and all of the necessary data for the selected application gathered, it is time to compile the application. When compiling the application, the number one purpose at every stage should be to clearly communicate to FDA how the proposed product meets the regulatory requirements for approval. The story that you tell throughout all the various required sections of the application should make clear to FDA the degree to which the proposed generic product is bioequivalent, or biosimilar as the case may be, to the reference product.

### **A. Checklists**

FDA has a multitude of applications to review with a large amount of substantive data in each. FDA has prepared checklists of the necessary information to be included in an application to make your job (and its own job) easier.

For ANDAs, FDA provides an ANDA Filing Checklist that you can (and should) use to make sure that the application includes everything FDA is looking for to accept and eventually approve the application. This is the same document that FDA will use to determine if an application has all the necessary components and to provide internal comments on each specific section of the ANDA. FDA provides this form on its website, so that applicants can use it to better prepare their ANDAs prior to submission. For both section 505(b)(2) applications and section 351(k) biosimilars

---

applications, the application form, Form FDA 365h, will be used when filing the application and can serve as a checklist for preparation of the application.

## **B. Patent Certifications**

One section of the ANDA or 505(b)(2) application requires patent certifications for any Orange Book-listed patents. The two most common certifications are so-called “paragraph III” and “paragraph IV” certifications.<sup>29</sup> A paragraph III certification means that the applicant certifies that approval is not being sought until after the date on which the listed patent will expire. A paragraph IV certification means that the applicant believes the listed patent is “invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.”<sup>30</sup> Each listed patent requires its own certification, and an applicant can choose to provide a different certification for different patents. The patent certification is just to let FDA know the applicant’s position with respect to each of the listed patents. There is no need for a detailed statement as part of the application itself. For 351(k) biosimilars applications, the procedure for resolving patent disputes differs from the procedure for ANDAs or 505(b)(2) applications. Without the equivalent of an Orange Book for biological products, there is no need for certification on patents for a biosimilars application.

There is an additional option for any method of use patents in the Orange Book. If the method of use patent does not claim a use for which the applicant is seeking approval, an ANDA applicant can include a “section viii statement” that the method of use patent does not claim a use for which the applicant is seeking approval.<sup>31</sup> An ANDA applicant is not required to apply for approval for every indication for which the reference listed drug is approved. In some circumstances, an ANDA applicant may want to “carve out” a particular indication for which the brand product has been approved. In those instances, if there is a method of use patent covering that carved-out indication, the applicant should include a section viii statement in the ANDA. There is a similar procedure for carving out indications from a 505(b)(2) application.<sup>32</sup>

## **C. Labeling**

The application will also need to include proposed labeling. Not only will FDA want to see the proposed labeling for the proposed generic product, it will also want to see side-by-side labeling of the proposed product with the labeling for the approved reference listed product. For ANDAs, the labeling for the proposed generic product

will have to be essentially identical to the label for the reference listed product, with justification for any deviations from the reference listed drug, such as a section viii carve-out. How much labeling for a 505(b)(2) product will differ from the labeling for the reference product will depend largely on what the differences are between the proposed 505(b)(2) product and the reference product, but again any differences must be justified to FDA based on the differences between the two products. As the first section 351(k) biosimilars application wasn't even accepted for filing until July 2014, there are not yet any approved labels for biosimilar products approved under section 351(k). Somewhat similar, to a 505(b)(2) application, however, any differences between the label for the proposed biosimilar and the reference listed product will depend on the differences between the two products as determined by FDA during the course of reviewing the application.

#### **D. Fees**

FDA does not review your application for free. And without the necessary fees associated with each application, FDA will not even accept the application for filing. If FDA receives your application submission fee within 20 days of receiving the application, it will still consider the day it actually receives the application as the date of filing. If the fees aren't paid within 20 days, however, the filing date is adjusted to the date the fees are actually paid.<sup>33</sup> A delayed date of filing could be the difference between having a first-to-file market exclusivity and missing out and having to wait until another ANDA applicant has reaped the benefits of 180 days of market exclusivity. Another note of caution: not only are there fees associated with new drug product applications, but there are fees with Drug Master File (DMF) applications as well for manufacture of an active drug substance. If the DMF holder has not paid its fees, then that DMF is not available to rely on for purposes of an ANDA or other new drug application. Accordingly, failure of the DMF holder to pay its fees puts the filing date of your application in just as much jeopardy as failure to pay the ANDA fee or 505(b)(2) fee itself. Needless to say, it is worthwhile getting your money in on time.

### **VI. SUBSTANTIVE REVIEW AND EXCHANGES OF PATENT INFORMATION AFTER FILING THE APPLICATION**

Once the application is submitted, FDA will go through its checklist to make sure that all of the required sections are included, and that all of the fees have been paid. FDA does not begin substantive review of the application until it has ensured that



---

the application includes all of the necessary information. This process can take several months, but once FDA is satisfied that the application includes the required components, it will send a notice of acceptance for filing. Acceptance for filing marks the beginning of FDA's substantive review of the application. FDA will most surely have questions and may request certain amendments to the application.

Once you receive notice of acceptance for filing from FDA, not only will FDA's substantive review begin but also, to the extent there are any patents in play, certain pre-litigation exchanges of information are required with the NDA-holder/reference product sponsor. While the overall concept is the same for ANDA/505(b)(2) applications and for section 351(k) biosimilars applications, the mechanics of those exchanges differ significantly.

#### **A. Sending Notice Letter After Receiving Acceptance for Filing of ANDA or 505(b)(2) Application**

Once an ANDA applicant or 505(b)(2) applicant receives notice of acceptance for filing, if the application included a paragraph IV certification for any patents, the applicant has to send a letter to the NDA holder and the patent owner(s) to provide notice that the application they have filed includes a paragraph IV certification.<sup>34</sup> This notice letter must be sent within 20 days from the date of the postmark on FDA's notice of acceptance for filing.<sup>35</sup> The notice letter must state that the application seeks approval to engage in commercial manufacturing, use, or sale of the drug before the expiration of the patent (or patents) referred to in the certification, and include a detailed statement of the factual and legal basis for the opinion that the patent is invalid or will not be infringed.<sup>36</sup> The notice letter should also be accompanied by an offer of confidential access, offering to provide a copy of the application to the NDA holder and patent owner for the purposes of determining whether they are going to bring a patent infringement action alleging infringement of those patents that the applicant challenged by a paragraph IV certification.<sup>37</sup>

The NDA holder and patent owner have 45 days from the date the notice letter has been received by both the NDA holder and the patent owner to file a patent infringement lawsuit.<sup>38</sup> If they do file a patent infringement lawsuit within that 45-day time period, FDA cannot give final approval to the ANDA or 505(b)(2) application until 30 months from the date of receipt of the notice letter, or the date of a final court decision finding the patents either invalid or not infringed.<sup>39</sup> In the event neither the patent owner nor

the NDA holder files a patent infringement lawsuit within the 45-day time period after receiving the notice letter, the ANDA applicant or 505(b)(2) applicant may bring a declaratory judgment action, to the extent they have standing and jurisdiction as allowed under the Constitution.<sup>40</sup>

## **B. The Section 351(k) Biosimilars Application Exchange of Information**

For biosimilars applications under section 351(k), the information exchange is set up slightly differently. As there is no Orange Book, and thus no patent certifications, there is no notice letter to be sent with a detailed statement of an opinion why any given patent is invalid or not infringed. Instead, when the application is submitted to FDA, the applicant must provide confidential access to certain attorneys for the reference product sponsor patent owner.<sup>41</sup> While the BPCIA provides for the exchange of information described below, the first district court to address the exchange under section 351(l) held that a biosimilar applicant has the option not to engage in the statutory exchange, and instead face a potential infringement lawsuit sooner and without the benefit of pre-suit dialogue and negotiation with the reference product sponsor.<sup>42</sup>

Under the BPCIA exchange, the applicant provides the application to the reference product sponsor within 20 days of receiving notice of acceptance for filing.<sup>43</sup> At the same time, the applicant provides “other information that describes the process or processes used to manufacture the biological product that is the subject of such application.”<sup>44</sup>

Within 60 days after receipt of the application, the reference product sponsor provides a list of the patents they believe a claim of patent infringement could reasonably be asserted and an identification of the patents on that list they would be prepared to license to the applicant.<sup>45</sup> Within 60 days after receipt of this list of patents, the biosimilars applicant provides either 1) a detailed statement of the factual and legal basis for an opinion that the patent is invalid or not infringed, or 2) a statement that the applicant does not intend to begin marketing the biosimilar product before the date the patent expires.<sup>46</sup> The applicant can also add patents to the list that was initially provided by the reference product sponsor.<sup>47</sup> In addition, the applicant provides a response with respect to any patents the reference product sponsor indicated a willingness to offer a license.<sup>48</sup> Within 60 days of receiving the applicant’s detailed statement, the reference product sponsor provides a detailed statement of the factual and legal basis for an

---

opinion that any of the patents will be infringed, and a response to any assertions of invalidity and enforceability.<sup>49</sup>

After all of these required exchanges, the parties negotiate in good faith regarding which, if any, of the listed patents, may be included in a patent infringement lawsuit, subject to certain limitations if the parties are not able to reach agreement.<sup>50</sup> Once it has been determined which patents may be asserted in a patent infringement lawsuit, the reference product sponsor has 30 days to bring an action for patent infringement.<sup>51</sup>

As the section 351(k) biosimilar application progresses to approval, the applicant provides the reference product sponsor 180 days' notice before the date of first commercial marketing of the biosimilar product.<sup>52</sup> Upon receiving such notice, the reference product sponsor may seek a preliminary injunction to prevent marketing of the biosimilar product until the court decides the issue of patent validity, enforceability, and infringement for certain patents.<sup>53</sup>

## **VII. APPROVAL AND LAUNCH**

Once your application has made it through FDA's substantive review process you are primed for approval. If there are any outstanding exclusivities, FDA will grant tentative approval. If all outstanding exclusivities have expired, you should receive final approval, which is the go-ahead to start selling the generic or biosimilar product you have worked so hard to develop. If the patent litigation has not yet been resolved, you will have to weigh the risks and potential benefits of launching at risk. If the court later finds that the generic product infringes any of the brand company's patents, your company may be liable for damages. If either the court finds that each of the patents are invalid, unenforceable, or not infringed or if the relevant patents have expired, there is nothing standing in the way of launching the FDA-approved generic product.

Now that the product has been launched, one note about products liability. A full discussion of products liability for generic drug products is beyond the scope of this chapter. It is worth noting briefly, however, that because generic drug manufacturers are required to copy the labeling of the branded product, the United States Supreme Court has held that federal law preempts certain state-law products liability claims.<sup>54</sup> This does not insulate generic drug manufacturers from all products liability claims, but in certain instances, where the claim is based on the label such as in a failure-to-warn claim, the generic manufacturer should not be liable under current law.

## ENDNOTES

1. 21 C.F.R. § 314.53.
2. 42 U.S.C. § 262(l)(3)(A).
3. 21 U.S.C. § 355(c)(3)(E)(ii).
4. 21 U.S.C. § 360cc(a).
5. 21 U.S.C. § 355(c)(3)(E)(iii), (iv).
6. 21 U.S.C. § 355a(b), (c).
7. 42 U.S.C. § 262(k)(7)(A).
8. 21 U.S.C. § 355(2)(j)(D)(iv).
9. 42 U.S.C. § 262(k)(6).
10. *See* 21 C.F.R. § 330.1.
11. 21 C.F.R. § 330.11.
12. 21 C.F.R. § 330.10(a)(12).
13. 64 Fed. Reg. 13,254 (Mar. 17, 1999).
14. 21 U.S.C. § 355(j)(2)(iv).
15. 21 U.S.C. § 355(j)(8)(B).
16. 21 C.F.R. § 320.21(b).
17. Center for Drug Evaluation and Research (CDER), FDA, Draft Guidance, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (December 2013), at 2-3, *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf> (last visited Mar. 29, 2015) [hereinafter Bioequivalence Draft Guidance (2013)].
18. *See, e.g.*, Bioequivalence Draft Guidance (2013).
19. Bioequivalence Draft Guidance (2013) at 8-9.
20. Bioequivalence Draft Guidance (2013) at 6, 8, 11, 17.
21. In some instances, state law may require substitution absent a specific physician order to the contrary. For example, many states require substitution if Medicaid is the payor.
22. *See* Orange Book, Preface.
23. 21 U.S.C. § 355(j)(2)(C).
24. *See* B. Pollock, *The 505(j)(2)(C) ANDA Suitability Petition – Has Its Utility Diminished?* (May 23, 2013) *available at* <http://www.lachmanconsultants.com/the-505j2c-anda-suitability-petition-has-its-utility-diminished.asp>.
25. 42 U.S.C. § 262(k)(i)(I).
26. *See* Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), FDA, Draft Guidance, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (February 2012), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf> (last visited Mar. 29, 2015) [hereinafter Scientific Biosimilars Guidance (2012)].
27. *Id.* at 7.
28. *Id.*
29. *See* 21 U.S.C. § 355(j)(2)(vii); 21 U.S.C. § 355(b)(2)(A).
30. 21 U.S.C. § 355(j)(2)(vii)(IV).
31. 21 U.S.C. § 355(j)(2)(viii).
32. 21 U.S.C. § 355(b)(2)(B).

- 
33. FDA, Generic Drug User Fee Amendments of 2012: Questions and Answers, Draft Guidance (August 2012), at 10.
  34. 21 U.S.C. § 355(j)(2)(B); 21 U.S.C. § 355(b)(3).
  35. 21 U.S.C. § 355(j)(2)(B)(ii)(I); 21 U.S.C. § 355(b)(3)(B)(i).
  36. 21 U.S.C. § 355(j)(2)(B)(iv); 21 U.S.C. § 355(b)(3)(D).
  37. 21 U.S.C. § 355(j)(5)(C)(i)(III); 21 U.S.C. § 355(c)(2)(D)(i)(III).
  38. 21 C.F.R. § 314.107(f).
  39. 21 U.S.C. § 355(j)(5)(B)(iii); 21 U.S.C. § 355(c)(2)(C).
  40. 21 U.S.C. § 355(j)(5)(C); 21 U.S.C. § 355(c)(2)(D).
  41. 42 U.S.C. § 262(l)(1)(B).
  42. *Amgen Inc. v. Sandoz Inc.*, Case No. 14-cv-4741-RS, 2015 U.S. Dist. LEXIS 34537, at \*16-\*23 (N.D. Cal. March 19, 2015).
  43. 42 U.S.C. § 262(l)(2).
  44. *Id.*
  45. 42 U.S.C. § 262(l)(3)(A).
  46. 42 U.S.C. § 262(l)(3)(B)(ii).
  47. 42 U.S.C. § 262(l)(3)(B)(i).
  48. 42 U.S.C. § 262(l)(3)(B)(iii).
  49. 42 U.S.C. § 262(l)(3)(C).
  50. 42 U.S.C. § 262(l)(4).
  51. 42 U.S.C. § 262(l)(6).
  52. 42 U.S.C. § 262(l)(8)(A).
  53. 42 U.S.C. § 262(l)(8)(B).
  54. *See* PLIVA, Inc. v. Mensing, 131 S. Ct. 2657, 2572-73 (2011); *Mutual Pharm Co. v. Bartlett*, 133 S. Ct. 2466, 2472 (2013).

