

Pre-ANDA LITIGATION

Strategies and Tactics for Developing
a Drug Product and Patent Portfolio

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chapter 18

ANDA Preparation (with an Eye toward Approval and Litigation) and the FDA Review¹

I. Introduction

As a manufacturer of generic drug products, undoubtedly one of your goals is to prepare an Abbreviated New Drug Application (ANDA) that will pass regulatory scrutiny efficiently. Your ANDA submission is a culmination of time, money, and effort by many in your organization: from those responsible for identifying target products to those responsible for developing those products and, finally, to those responsible for filing the application. This effort can take several years, and even the smallest missteps can result in months of delay and possibly millions in lost revenue and sunk costs. Keeping your goal in mind, every communication that you have with the Food and Drug Administration (FDA) should be made with an eye toward making the FDA's job of reviewing your ANDA easier so that you can get your approval faster.

But as you probably already know, your ANDA can be a technical act of patent infringement that triggers a patent infringement lawsuit from your adversary under the Hatch-Waxman Act. Let's face it: the ANDAs with the most potential reward are the ones most likely to be sued on. Your ANDA filing, therefore, should be made with an eye not only toward regulatory compliance and approval but also toward the litigation that will likely follow. If your team has devoted the effort to developing a Paragraph IV

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strategy, make sure that the entire ANDA submission accurately portrays the proposed ANDA product in light of the potential patent obstacles.

With that in mind, this chapter digs into the ANDA itself—the required components in the initial filing and post-filing submissions you may need to make—and discusses the FDA’s review of your application. In the context of this discussion, we will provide some insight on the FDA’s review of your application. We also will discuss how to craft certain parts of your submissions with the knowledge that your audience is not only the FDA but also a future litigant, and a federal judge or jury.

Let’s begin with a discussion of the driving force behind most business decisions—cost. Specifically, we begin our discussion with the Generic Drug User Fee Act (GDUFA) and how much filing an ANDA will cost.

II. A Fistful of Dollars: The Generic Drug User Fee Act (GDUFA)

Unfortunately, the costs do not stop once you have completed developing your product and preparing your ANDA. An ANDA applicant is also required to pay certain fees associated with filing its ANDA. The types of fees are identified in the Generic Drug User Fee Act, which is commonly known as GDUFA, and the amount of each fee is published annually in the *Federal Register*. GDUFA fees are just one cost component of your ANDA application process, but it is important enough to merit this brief, initial discussion.

The stated purpose of GDUFA is to speed the entry of safe and effective generic drugs to the market and to reduce costs to the industry.² In that respect, GDUFA shares a common goal with the Hatch-Waxman Act. For the purpose of this chapter, we will focus on only two of the GDUFA fees: the generic drug submission fee and the facility fees. The backlog fee—a one-time fee applied to ANDAs pending on October 1, 2012, to reduce the FDA’s backlog of applications—and the Drug Master File (DMF) fee are outside the scope of this chapter.

A. Generic Drug Submission Fee

The generic drug submission fee can be thought of as your application fee. The submission fee is a one-time fee due on the date of submission of the application. There are two components to the submission fee: a base

2. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, GENERIC DRUG USER FEE AMENDMENTS OF 2012: QUESTIONS AND ANSWERS 2 (Revision 1, Sept. 2013) [hereinafter GDUFA 2013 GUIDANCE].

submission fee and a fee calculated with reference to active pharmaceutical ingredient (API) manufacture. For fiscal year 2013, the base submission fee was \$51,520. The ANDA submission fee for 2014 is \$63,860.³ The base submission fee is adjusted annually for inflation and is based on the number of projected ANDAs that will be filed in the given year. The base submission fee for the year is published in the *Federal Register* no later than 60 days before the start of each fiscal year (i.e., no later than 60 days before October 1 of each year).

1. Base Submission Fee

The FDA will not consider your application received unless the submission fee is paid at the time of the application or within 20 calendar days after filing the ANDA. If you pay the submission fee after 20 calendar days, the FDA will consider the day it receives the submission fee as the “received” date of your application.⁴ This delayed received date could mean that your ANDA goes from being a “first-filed application,” which could be entitled to 180 days of marketing exclusivity, to an application that is not entitled to “first-filer” status. In other words, missing the payment date by just one day can mean a loss of millions of dollars in revenue and significant market share. If the FDA refuses your application for a reason other than failure to pay fees associated with the ANDA, you are entitled to a refund of 75 percent of the submission fee.

The submission fee also applies to Prior Approval Supplements (PASs) to ANDAs. PASs are supplements to an approved ANDA and will be dealt with in greater detail in Section IV.B.2.b., “Applicant-Initiated Changes,” of this chapter. Briefly, a PAS is a major change to an approved ANDA that could have a substantial adverse effect on the identity, strength, quality, purity, or potency of the drug product.⁵ A PAS may include a change in manufacturing site or manufacturing process.⁶ Importantly, because generic drug product labels must be the “same as” the product label of the appropriate Reference Listed Drug (RLD),⁷ a PAS may also include a change to your approved product label as a result of a labeling change by

3. *Abbreviated New Drug Application (ANDA) and Prior Approval Supplement (PAS) Fees*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm319568.htm> (last updated Feb. 5, 2014); *see also* Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, Drug Master File, Final Dosage Form Facility, and Active Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2014, 78 Fed. Reg. 46,977, 46,978 (Aug. 2, 2013).

4. GDUFA 2013 GUIDANCE, *supra* note 2, at 11.

5. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, CHANGES TO AN APPROVED NDA OR ANDA 3 (Apr. 2004); *see also* 21 C.F.R. § 314.70(b).

6. GDUFA 2013 GUIDANCE, *supra* note 2, at 10–13.

7. 21 U.S.C. § 505(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iii).

that brand RLD.⁸ The PAS fee for fiscal year 2013 was \$25,760, and the PAS fee for fiscal year 2014 is \$31,930.⁹

2. API-related Fee

The API-related fee involves some calculation, which might be painful if you dislike math. But we'll get through this together. GDUFA requires that an ANDA applicant pay a one-time fee for each API manufactured in its own facility *for which the applicant has not previously paid an API-related fee* (i.e., payment as part of its DMF submission). This API-related submission fee is calculated based on the number of APIs referenced in the ANDA and the number of additional facilities identified in the ANDA in which those APIs will be manufactured. It is important to note that this one-time fee is different from the annual facility fee that must be paid for each API-manufacturing facility, which will be discussed in more detail later in this chapter. Roughly, the equation for figuring out the API-related submission fee is:

$$\begin{aligned} & ((n)\text{APIs referenced in ANDA} + (n)\text{Additional facilities for each API}) \\ & \quad \times \text{DMF fee} \end{aligned}$$

Remember, the fee is paid only once per API and only once per facility manufacturing that API, but you will have to pay an additional facility fee if you have a different drug product using the same API that is manufactured in a different facility. See, not so bad.¹⁰

So, with that taken care of, let's move on to facility fees.

B. Facility Fees

Anyone who owns a facility that is identified or intended to be identified in at least one ANDA to produce a finished dosage form or an API is required to pay a facility fee.¹¹ GDUFA defines a finished dosage form (FDF) facility as one that makes drug products—tablets, capsules, solutions, topicals, or drug products requiring reconstitution.¹² GDUFA defines an API facility as one that makes drug substances that are (1) intended to be used as a component of a drug and that furnish pharmacological activity, diagnosis, cure, treatment, or prevention of a disease, or (2) intended for final crystallization, purification, or salt formation to become a substance described in (1).¹³ A facility that manufactures both FDFs and APIs will incur *both*

8. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, CHANGES TO AN APPROVED NDA OR ANDA 24–25 (rev. 1 Apr. 2004).

9. GDUFA 2013 GUIDANCE, *supra* note 2, at 5.

10. For further discussion from the FDA, see GDUFA 2013 GUIDANCE, *supra* note 2, at 11–13.

11. *Id.* at 14.

12. *Id.* at 16.

13. *Id.* at 16–17.

an annual FDF fee and an annual API fee.¹⁴ The facility fee is an annual fee. For 2013, the domestic FDF facility fee was \$175,389, and the domestic API facility fee was \$26,458. For 2014, the domestic FDF facility fee is \$220,152, and the domestic API facility fee is \$34,515.¹⁵

A company may have to pay separate facility fees if its facilities are in two different geographic locations. Two locations will not be considered geographically distinct for the purposes of the facility fee, however, so long as the separate buildings are within close proximity, have closely related activities, are under the same local management, and are capable of being inspected by the FDA during a single inspection.¹⁶ Facilities located outside the United States and its territories will be charged a fee not less than \$15,000 and not more than \$30,000 more than the amount of the fee for a domestic facility.¹⁷ Thus, where you manufacture your FDFs and APIs is an additional component of the total cost analysis.

C. Drug Master File (DMF) Fees and Additional Information

A full discussion of DMF fees is outside the scope of this article. However, a word of caution is in order for those companies filing ANDAs that rely on a DMF of a separate company. If a DMF holder has not paid its GDUFA fees, the DMF will be deemed not available for reference, and no ANDA will be accepted for filing or reviewed unless the fee is paid.¹⁸ There is a 20-calendar-day grace period after the FDA has provided notification of delinquency to pay any late DMF fee.¹⁹ It should go without saying that any failure to timely pay a DMF fee could jeopardize your status as a first-filer ANDA and your place in the exclusivity line. More information on DMF fees, and other GDUFA fees, can be found at the FDA's draft *Guidance for Industry—Generic Drug User Fee Amendments of 2012: Questions and Answers*, Revision 1, September 2013.

D. Some Helpful Hypotheticals

Consider the following hypotheticals to help get the feel of the GDUFA costs associated with filing an ANDA. Assume you own Staley Generic Pharmaceuticals and you intend to file an ANDA seeking approval to market a generic version of helpamide tablets. You are a vertically integrated company and will be making the API for the helpamide tablets in both your Illinois and New Jersey facilities and the tablets in your Illinois

14. *Id.* at 17.

15. *Id.* at 5.

16. *Id.* at 18–19.

17. *Id.* at 18.

18. *Id.* at 9.

19. *Id.*

facility. Using 2013 numbers, here is your cost of filing the ANDA for helpamide tablets:

ANDA base submission fee:	\$ 51,520
API submission fee (1(API + 1(Additional API facility)) × \$21,340 (DMF fee):	\$ 42,680
Facility fee \$26,458 (NJ API) + \$175,389 (IL FDF):	<u>\$201,847</u>
Total	\$296,047

If Staley Pharmaceuticals did not make its own API but, instead, simply referenced another company's DMF, it would only pay the ANDA submission fee and the FDF facility fee for its helpamide tablet ANDA (a total of \$226,909).

Now let's say that instead of manufacturing its API in New Jersey, Staley Pharmaceutical's API facility is located in India, while the FDF is still manufactured in Illinois. In this situation, the ANDA base submission fee and the API submission fee would remain the same (\$51,520 and \$42,680, respectively), but, as a result of employing a foreign API facility, the facilities fees will increase an additional \$15,000 to \$30,000:

ANDA base submission fee:	\$ 51,520
API submission fee (1(API + 1(Additional API facility)) × \$21,340 (DMF fee):	\$ 42,680
Facility fee: (India API) \$26,458 + (\$15,000–\$30,000):	\$ 31,458–56,458
Facility fee: (IL FDF):	<u>\$175,389</u>
Total	\$311,047–326,047

III. The Initial ANDA Filing

With an understanding of the fees associated with an ANDA filing, we can now move to the nuts and bolts of actually compiling and filing the ANDA.

Before actually filing your ANDA, you should obtain a pre-assigned application number. In fact, you are required to obtain a pre-assigned application number before filing an electronic copy of your ANDA, which, as discussed in the following section, is the FDA's preferred method for receiving applications. You can request a pre-assigned electronic application number by contacting the Office of Generic Drugs (OGD) at the Center for Drug Evaluation and Research (CDER). The FDA's website provides instructions on how to request an electronic application number and lists the information that will be required when making the request. The FDA will provide a pre-assigned application number within three business days after receiving a request, but plan ahead so that you don't miss out on a filing deadline because you are waiting for an application number. Because your six-digit application number ties your entire submission together, it should be included throughout your ANDA submission and on any correspondence with the FDA regarding the application.

A. Paper or Plastic?

The FDA allows you to file your initial ANDA application in paper form or in electronic form, but you should choose to file in electronic form. Myriad are the pleas from the FDA in speeches, presentations, guidance documents, and the like to file in electronic form. Do not ignore these pleas. Like most branches of the federal government, the FDA is seeking to reduce the volume of paper it has to deal with. Additionally, the electronic form makes it easier for the FDA to review and to "share" your ANDA or portions of your ANDA among the departments responsible for reviewing your submission. The federal government is so serious about wanting submissions in electronic, as opposed to paper, format that Congress enacted Section 745A(e) of the Federal Food, Drug, and Cosmetic Act, which requires (among other things) NDAs and ANDAs to be filed in electronic format beginning 24 months after the FDA finalizes its guidance on providing regulatory submissions in electronic format. The FDA issued Revision 3 of the draft guidance in January 2013.²⁰

The format for your electronic submission should be in what is called an XML-based eCTD (electronic Common Technical Document). The XML format helps to organize your application by allowing the user to set up folders and subfolders as well as use hyperlinks to navigate the submission.

20. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, PROVIDING REGULATORY SUBMISSION IN ELECTRONIC FORMAT—CERTAIN HUMAN PHARMACEUTICAL PRODUCT APPLICATIONS AND RELATED SUBMISSIONS USING THE ECTD SPECIFICATIONS (Draft Guidance, rev. 3 Jan. 2013).

It goes without saying that, because the FDA is the body responsible for approving your ANDA, your goal should be to make the FDA's job easier. If you do so, you will be that much closer to getting your approval quickly. To that end, consider the following general tips for your electronic submission.

- Hyperlink your sections and use bookmarking so that the FDA can more easily navigate your submission.
- Use hyperlinks for cross-referencing to other documents in your submission. (Make sure you are hyperlinking to the correct document and the correct page of the document.)
- Provide a table of contents (hyperlinked, of course) with headings arranged hierarchically.
- Use easy-to-recognize directory and file names so that the reviewers can quickly and easily find the exact section or document that they are looking for.
- Use searchable PDF documents or, if you cannot use a PDF, create scanned searchable text or OCR (optical character recognition) documents rather than documents that are not searchable. Again, this makes it easier for the FDA to find relevant information, and the format allows the FDA to cut and paste materials from your submission into deficiencies, requests for information, or other correspondence.

One last note on electronic submissions: have an additional copy of your electronic submission for your outside counsel handling the notice letter and patent litigation, and make sure that the copy is in the same format that you provided to the FDA. Your outside counsel needs to know the contents of the application on which the notice letter and subsequent litigation are based, and your ANDA (or portions of it) will need to be offered to the NDA holder and patent owner(s) (on a confidential basis) during the 45 days after receipt of your notice letter. From a practical standpoint, you do not want your outside counsel to have to explain to a judge any delay (absent failure to agree on portions of the ANDA that will be disclosed or individuals who can review the ANDA) in providing your ANDA to the other side during that 45-day period.

B. The ANDA Checklist—Managing Your Modules

Now that you have figured out how much the filing fees will be for your ANDA and that you will file in electronic format, it is time to focus on the component parts of the ANDA that you will need to include for your submission. Fortunately, the FDA has made this part easy. The FDA provides an ANDA checklist—the very document that the FDA will use

to determine if you have provided all the necessary components for your ANDA and to provide internal comments on the specific ANDA sections. The ANDA checklist is available at the FDA's website as a PDF link from its generic drug user's page.²¹ Use it.

Keep in mind, as discussed further in the following sections, that the FDA does not start its substantive review of your ANDA until it has determined that your ANDA is technically complete (i.e., it includes all of the required portions). This determination can typically take around two to three months, but it can take as long as five to six months.

When it comes to small-molecule products, the FDA knows exactly what it wants to see in an ANDA submission. For the most part, the decision of what to include in your ANDA is not an opportunity for creativity. If you do have a unique aspect to your filing, be upfront with the FDA and provide a short but detailed explanation for your deviation. Do not make the FDA search for or question any new or missing aspect. And, if needed, file an appropriate suitability petition. We address specific modules and what they should contain in the following sections.

1. Module 1: Administrative Materials (and the Patent Certification(s))

For the most part, Module 1 is the simplest module, and there are few excuses for having any issue with this module. The required portions for electronic versions of Module 1 include:

- 1.1 Signed Application form 356h
- 1.2 Cover letter
 - 1.2.1 Form FDA 3674
 - 1.3.2 Field Certification Form (21 C.F.R. § 314.94(d)(5))
 - 1.3.3 Debarment certification
 - 1.3.4 Financial certification
 - 1.3.5 Patent information
- 1.4.1 References
- 1.12.4 Request for comments
 - 1.12.11 Basis for submission
 - 1.12.12 Product comparison
 - 1.12.14 Environmental impact analysis

21. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/>.

- 1.12.15 Request for waiver of in vivo BA/BE (bioavailability/bioequivalence) studies
- 1.14.1 Draft labeling
- 1.14.3 Listed drug labeling

Of these required components, each of which is important, we will focus on the Form 356h (but only briefly), the cover letter (also briefly), the patent information and certifications, and the labeling sections. It should go without saying that it is imperative to be candid with respect to all sections of your application, including the debarment and financial certifications.

First, Form 356h is used for many different types of submissions to the FDA, including for original ANDA submissions, 505(b)(2) submissions, supplements to pending applications, annual reports, and more. The FDA provides a fillable PDF version of Form 356h at the “Forms” section of its website along with instructions regarding use of the form. You must sign and complete Form 356h.

Every submission to the FDA should also contain a cover letter. If there is anything that is atypical about your submission, use the cover letter to briefly explain the situation to the FDA. Do not bury any issues that your application may have, but instead get your story out front to facilitate conversation with the FDA. Make the FDA’s job as easy as possible.

The next major component of Module 1 is the patent information and certification section. In this section, you must include the patent number and expiration date of all of the patents listed in the Orange Book (OB patents) for the appropriate RLD. The patent numbers and expiration dates associated with the appropriate RLD can be found in the FDA’s electronic Orange Book.

You must also include a certification for each OB patent. The certification is simply a one- or two-page document that lists the patent number(s), the type of certification (Paragraph I–IV or Section viii), and the date of expiration of the patent(s). Briefly, a Paragraph I Certification states that no patent information is listed in the Orange Book. A Paragraph II Certification states that any OB patents have now expired. With a Paragraph III Certification, the ANDA applicant is certifying that it will not market its product before the expiration of that particular patent or patents identified in the certification. Finally, with a Paragraph IV Certification, the ANDA applicant is certifying that it intends to market its product before expiration of the OB patent(s) and that the patent certified against is invalid and/or will not be infringed by the ANDA applicant’s product. With respect to the Paragraph IV Certification, the short certification is not the same as the notice letter that you are required to send to the NDA

holder and patent owner detailing why your product, if approved, will not infringe an OB patent or why the OB patent is invalid. Those are two different submissions made to two different entities. Moreover, the decision as to the type of certification you will make has downstream implications that occur after submission of your application and should be made jointly with legal counsel.

The final section of Module 1 we will discuss, the labeling section, requires multiple copies of your proposed draft product label (packaging, product insert, and a side-by-side comparison of labeling of the RLD with annotations) as well as the RLD's labeling and packaging. From a submission standpoint, this section is quite simple. With some exceptions, the generic product's labeling must be the "same as" the approved labeling for the RLD or else the FDA will refuse to approve the ANDA.²² The exceptions to the "same label" requirement are changes as to the identity of the manufacturer and distributor, the use of the generic name of the product instead of the brand name, changes in the identity of certain inactive ingredients,²³ and "Section viii" carve-outs of additional indications for which the ANDA sponsor is not seeking to market its product.²⁴ The "same label" requirement allows the FDA to assume that bioequivalent generic drugs are safe and effective without having to demand and review minor changes in product labeling, thus fulfilling the statutory goal of getting lower-cost generics on the market quickly.²⁵

The proposed product labeling should be a consideration early in product development. Increasing are the number of ANDA cases involving patent claims that involve information in the product label, including many cases involving method-of-use claims. For example, patent holders argue that the label instructs or "induces" a doctor or patient to infringe a method-of-use claim and that the ANDA applicant is therefore responsible for that infringement. It is therefore imperative to know the product label for the RLD during the development stage of your product to determine whether there are indications from the label that are not covered by the patent claims or that can be carved out.

It is also important to know what kinds of changes you can make to your product label. Although frequently asserted during litigation, it is untrue that a generic company should simply petition the FDA to change its label if, for example, the generic product has a "different" pharmacokinetic

22. 21 C.F.R. §§ 314.105(d), .127(a)(7).

23. *Id.* § 314.94(a)(8)(iii), (iv).

24. 21 U.S.C. § 355(j)(2)(A)(viii); 21 C.F.R. § 314.94(a)(8)(iv).

25. *SmithKline Beecham Consumer Healthcare LP v. Watson Pharm. Inc.*, 211 F.3d 21 (2d Cir. 2000).

profile than the Reference Listed Drug. Putting aside changes to the label as to the manufacturer of the product, excipients that are used, or where there is a Section viii statement, the FDA will not approve an ANDA if the generic product label is different from the RLD's label except where such differences are approved after a petition under 21 C.F.R. § 314.93.²⁶ Although a separate section of the regulations seems to indicate that an ANDA applicant can petition for labeling changes with respect to aspects of its product like its pharmacokinetic profile, that section only allows for differences that are approved under a Section 314.93 petition.²⁷ And the *only* differences in labeling that are permitted by a Section 314.93 petition are differences in which the ANDA product “is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug.”²⁸ Most ANDA products have the same active ingredients, “route of administration, dosage form, and strength” as the RLD. Therefore, according to the regulations, an ANDA applicant would not receive permission for a labeling change with respect to, for example, a “different” pharmacokinetic profile.

The label is typically a primary document in any subsequent patent litigation. It is important to recognize what the label says, what can and cannot be changed in the label, and implications for patent infringement arguments in litigation. While there is little merit in the litigation argument that an ANDA applicant can make all sorts of changes to its label, an ANDA applicant must be aware of the information required to be in its product labeling and the potential implications for litigation.

2. Module 2: Quality Overall Summary (QOS) and Clinical Summary

As the title indicates, Module 2 provides summary information for the reviewers and allows for a high-level understanding of an ANDA application and the product described therein. While the documents that comprise Module 2 are summary documents, an applicant still must be careful to properly describe and cross-reference its product and supporting data in this section because even these summary documents will find their way into a subsequent ANDA litigation. Thus, the individual tasked with drafting these summary documents should work with the author of the primary sections (as well as with counsel, if possible) to ensure both completeness and accuracy.

26. 21 C.F.R. § 314.127(a)(7).

27. *Id.* § 314.94(a)(8)(iv).

28. *Id.* § 314.93(a), (b).

a. *Quality Overall Summary (QOS)*

The QOS is the summary or Cliff Notes version of the Chemistry Manufacturing and Controls (CMC) section of Module 3. In fact, a great deal of the information provided in the QOS is put verbatim into the CMC section. So, you may ask, what is the rationale for having a QOS at all? The primary reason for a QOS is to summarize pertinent information about the drug substance and drug product of the ANDA, such as how it is characterized and how it is made, so reviewers (including reviewers that need the information but are not CMC experts) can quickly access certain information about your product without digging into the more detailed CMC section.

The QOS is separated into information regarding the drug substance (Section 2.3.S, with the “S” standing for “substance”) and information regarding the drug product (Section 2.3.P, with the “P” standing for “product”). The FDA elicits information regarding the drug substance and the drug product in these sections through a series of standing questions that should be answered by the applicant. As you should now come to expect, the FDA provides these questions on the website of the Office of Generic Drugs and has a sample QOS with answers.

I. 2.3.S Drug Substance (Active Pharmaceutical Ingredient)

In the section on the drug substance, the applicant is asked to provide information on the molecular structure, formula, and weight; the manufacturer of the drug substance and manufacturing controls; characterization of the drug substance; test specifications for the drug substance, including a discussion of any analytical methods that are used; discussion of the certification of reference standards; an explanation of the container closure system used to package and store the drug substance; and stability testing information on the drug substance. Many of the questions in the drug substance section are answered by referring the FDA to the Drug Master File upon which the applicant is relying.

II. 2.3.P Drug Product

In the drug product section of the QOS, the applicant must provide a summary of the components of the drug product and their respective functions; any potential concerns that may be raised from any differences from the RLD; a summary of the development of the product, including alternative formulations and a rationale for the current formulation; the manufacture of the product and scale-up plans; control of excipients and the drug product; reference standards; the container closure system; and stability testing.

As with other sections of your ANDA, draft these summaries cognizant of the way the drug product was developed and with an eye toward possible litigation. While the QOS provides a helpful summary for the ANDA

reviewers, if it is not artfully drafted, it could also be useful for a future adversary who takes poorly worded statements out of context in litigation. For example, Section 2.3.P.1 requests information regarding the function of each excipient in your drug product. Many patent claims are drafted such that a certain excipient is functioning in a specific manner in the claimed formulation. If the excipient in your formulation is not functioning in the same way that excipient functions in the RLD (e.g., not acting as an extended-release excipient or extending release in a substantially different way), then you should not characterize it this way merely because the RLD does.

b. Clinical Summary (Bioequivalence)

The information provided in Module 2.7—the clinical summary section—should be primarily in tabular form based on the data from Module 5. The tables should provide highlights of the data, with brief summaries to make the most pertinent information readily accessible to the reviewer. The more detailed information and reports should be reserved for Module 5.

3. Module 3: Drug Substance and Drug Product Information— The Pharmaceutical Development Report (PDR)

Module 3 will contain detailed information regarding the drug product and drug substance relevant to your ANDA. Here, the FDA wants to know about testing specifications and procedures, validation methods, and stability protocols, as well as how the drug substance and drug product are made and will be made on a large scale. From a safety perspective, the FDA will be focusing on controls, validation, and stability. From a manufacturing perspective, the FDA will be focusing on the description of the manufacturing process and process validation for the drug product (Sections 3.2.S.2 and 3.2.P) and the executed batch records for the drug product (Section 3.2.R). But the full story of your product and how it came before the FDA is told in the pharmaceutical development report found at Section 3.2.P.2. That is the story that you will eventually be recounting during litigation, and it should be consistent with your litigation strategy developed at the outset of the project.

a. 3.2.S Drug Substance

The first part of Module 3 contains information about the drug substance—the active pharmaceutical ingredient (API)—in your ANDA product. For much of this information you will be referring to the DMF for the drug substance used in your ANDA product. For certain sections, however, the FDA does not want you to merely refer to the ANDA product. This includes Section 3.2.S.1 with general information about nomenclature, structure, and general properties of the API and Section 3.2.S.5 regarding reference

standard or materials. Otherwise, much of the information concerning characterization of the drug substance, identification of impurities, analytical procedures, batch analyses, and stability will likely come from the DMF.

b. 3.2.P Drug Product

The second part of Module 3 contains information about the drug product—the finished dosage form that will be sold to customers. In this section, the FDA will want all of the information concerning development, manufacture, specifications, controls, and analysis for the finished drug product.

c. Pharmaceutical Development Report (PDR)

The pharmaceutical development report is your opportunity to present to the FDA the knowledge that you have gained through the development of the product and its manufacturing process. Your goal in drafting your pharmaceutical development report is to demonstrate to the FDA the scientific rigor that went into developing a bioequivalent drug product that can be reliably manufactured. You should convey an intimate understanding of your drug product and manufacturing process, while explaining any aspect that is unusual or atypical. Again, getting out in front of any potential issues is key to expedient approval. In addition, familiarity with the patent claims covering the formulation of the branded product is important. You may want to stress that the design of your product was deliberately chosen to meet patients' needs and to perform in a particular manner. More on that later.

The following are the key sections of the pharmaceutical development report:

The components of the drug product: This section includes a discussion of properties of the drug substance that can affect performance of the drug product (e.g., solubility, particle size, and biological activity) and information regarding the excipients in the drug product, including any compatibility issues with the drug substance.

The drug product: This section should contain a description of the formulation development, including identifying attributes that are *critical to the quality* of the drug product, and should highlight the “evolution of the formulation design from initial concept up to the final design.”²⁹ In this section, you will also want to include information from any comparative in vitro or in vivo studies (with hyperlinked cross-referencing to the actual studies) and any attempts to establish an in vitro/in vivo correlation.

29. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: Q8(R2) PHARMACEUTICAL DEVELOPMENT 5 (Nov. 2009).

Manufacturing process development: This section should include information on the selection, control, and improvement of the manufacturing process, as well as a discussion of any critical process parameters. You should clearly but succinctly explain any differences between the manufacturing process for batches used in pivotal clinical trials or stability studies and the manufacturing process described in Section 3.2.P.3.3.

Container closure system: This section should provide information regarding the choice and rationale for the selected container closure system for the commercial product.

Microbiological attributes: Where applicable, this section should provide justification for aspects relating to the microbiological aspects of the drug product.

Compatibility: This section should provide supportive information for product labeling, including recommended storage conditions.

While many pharmaceutical development reports tell the story of the drug products described in an ANDA, those same reports can serve as cautionary tales. The pharmaceutical development report is part of your ANDA and will, at some point, be produced to your adversary in litigation. Because the FDA requires so much information regarding the rationale for chosen steps or components and so much information about the results of such steps and components with respect to the performance of your product, care should be taken with how you draft this document. Draft your pharmaceutical development report with the patents that may likely be asserted against you in mind.

The pharmaceutical development report must tell the accurate and complete scientific development story for the proposed ANDA product. All members of the development team should be aware of and on board with any design-around strategies for potential patent noninfringement positions. Sometimes you will develop design-around strategies at the outset of development. Other times, potential noninfringement positions will come about during the development process by finding a better way of making the product using different excipients or different methods of manufacture. Regardless, if you have designed around a patent, and have a potential noninfringement position for a patent, the scientific facts underlying that position should be contained in the pharmaceutical development report. Of course, this report tells a scientific story, not a legal argument. But it is important that the scientific facts underlying that design around are included in the report. At the end of the day, explain the differences between your ANDA product or its components and the RLD, because that

is the story that is going to be told in litigation, and it should be a consistent story.

If you are not considering the future patent lawsuit awaiting you when drafting the pharmaceutical development report, you could find yourself fighting against your own written words. In contrast, a well-written pharmaceutical development report not only will assist in obtaining regulatory approval but can also be used as both a shield and a sword in litigation—protecting you from accusations of patent infringement and, at the same time, providing your litigation expert with support from your internal documents for the expert's scientific opinions.

4. Module 5:³⁰ Clinical Study Reports

Module 5 contains information regarding the supporting clinical studies associated with your ANDA product. This section will include tables, reports, calculations, protocols, and other associated information regarding your bioequivalence studies. Most importantly, this section will provide data supporting the fact that your proposed ANDA product meets the bioequivalence criteria established by the FDA (AUC and possibly C_{\max} mean results that are within 80 to 125 percent of those of the RLD at a 90 percent confidence interval), so that the FDA can presume that your ANDA product is safe and efficacious.

IV. All Hands on Deck: Filing Your ANDA

Compiling various sections of the ANDA will be a cross-disciplinary effort. That effort should be shepherded by someone with regulatory experience who can be responsible not only for making sure that all of the technical aspects are present but also for coordinating review of the final components by each department that has main responsibility for each section. After all the time, money, and effort spent to compile your ANDA, now is not the time for shortcuts. Even generally mundane tasks, such as checking spelling or page numbering, are important and should be done with care and attention to detail. Again, these details make the FDA's job easier, which will hopefully bring your approval more quickly with fewer bumps along the road.

Once your ANDA is compiled and reviewed, you are almost ready for filing. The last review of your ANDA, if you are going to submit in electronic form, should be to check all electronic aspects of the file, such as verifying hyperlinks and file names. Many of the FDA reviewers have

³⁰. Module 4 is not applicable to ANDAs.

expressed frustration at small errors in such electronic aspects of the ANDA submissions. These errors are easily found and fixed, and you do not want these errors to be taken by the FDA as a sign of sloppiness or an indication of larger issues with the application.

Remember that ANDA checklist that we discussed in Section III.B of this chapter? The first thing that the FDA will do when it receives your ANDA is to go down that checklist and make sure you have included all of the required sections of the ANDA. Accordingly, the last thing you should do before filing the ANDA is to go through the checklist with the electronic disc that you will be sending to the FDA and make sure that when the FDA opens the disc it will find every item on the checklist in the place it is supposed to be.

Finally, you are ready to file your application. For electronic submissions, you can send a disc containing your ANDA to the OGD's electronic document room.

A. Start the Clock: Acceptance for Filing and Refusal to File

When the FDA receives your ANDA, the reviewer will go through the ANDA checklist to make sure you have included all of the required sections of the ANDA. This is the acceptance for filing review, and the FDA will not substantively review your ANDA until it is satisfied that it meets the technical requirements and has all the required components. The reasons that the FDA will refuse to accept your ANDA for filing are specifically enumerated at 21 C.F.R. § 314.101(d)–(3) and in the FDA's draft *Guidance for Industry, ANDA Submission—Refuse-to-Receive Standards*, October 2013, and include failure to include the required components of an ANDA, failure to properly organize and format an ANDA, failure to pay required GDUFA fees, lack of a U.S. agent, inadequate bioequivalence or stability information, and so forth.

If your ANDA is missing any required components, or if any component is facially deficient, the FDA will refuse to accept the ANDA. That refusal may result in your losing your filing date. One of the purposes in having an initial acceptance for filing review by the FDA is to deter companies from filing incomplete ANDAs as placeholders with the goal of fleshing out issues and fixing them during the course of a complete review. That practice wastes the FDA's time and resources. Acceptance for filing should be an easy hurdle for your application if you provide the FDA what it is looking for or clearly explain any variances at the outset.

Typically, it takes two to three months from the date of filing for the FDA to issue an acceptance for filing or refusal to file letter, but we have heard from companies that are reporting a full five to six months to receive their acceptance for filing. Once the FDA sends you the letter accepting

your ANDA for filing, you have 20 days from the date of the postmark on the FDA's letter to send a notice letter to the NDA holder and patent owner(s) with respect to any patents for which you have filed a Paragraph IV Certification.³¹

B. Post-filing Submissions

There are a variety of required and optional submissions that are made after the initial submission of the ANDA, many of which are outside the scope of this chapter. Here, we will focus on the notice letter (which is submitted not to the FDA but to other parties), certifications that must be made with respect to later listed patents, and certain amendments to the ANDA.

1. The Notice Letter

Prudent companies start working on their notice letters before they even start compiling their ANDAs. The notice letter provides the detailed basis for your assertion to the FDA that the OB patents are invalid and/or that your product will not infringe those patents. To be sure, it may take around four months from the time you first file your ANDA until you actually have to send your notice letter. That may seem like sufficient time to develop invalidity and noninfringement arguments, and it may well be. But because you must make the actual noninfringement and invalidity assertions in Module 1 of your ANDA, it is advisable to have a good-faith basis for such a certification at that time. The time between filing your ANDA and serving your notice letter is best spent revising and focusing the arguments in your notice letter.

We will not burden this chapter with a detailed discussion of notice letters. We will, however, provide you with two important practice points. First, recall that the statute requires a detailed basis for your certifications of noninfringement and invalidity, but it does not require that you provide every such basis that you might raise in the context of litigation. In fact, several cases have expressly held that ANDA applicants are not limited to the defenses raised in their notice letter, but may raise additional defenses during the course of the lawsuit.³² Second, it is important to stay apprised of the Orange Book entry for the RLD applicable to your ANDA, as the sponsoring company may list additional patents for that drug even after you file your ANDA. While those additional patents, in most cases, will not create any additional 30-month stays of approval of your ANDA, you

³¹ 21 U.S.C. § 355(j)(2)(B)(ii)(I).

³² See, e.g., *Abbott Labs. v. Apotex Inc.*, No. 09 C 7968, 2010 U.S. Dist. LEXIS 68452 (N.D. Ill. July 9, 2010).

are still required to certify to any “later listed” patents³³ as an amendment to your ANDA. You must also send your notice letter with respect to the patent(s) on the same day you send your certification. To avoid being surprised by “later listed” patents, monitor the U.S. Patent and Trademark Office for patents relating to the RLD applicable to your ANDA.

2. Changes: Amendments and Supplements to ANDAs

There are two main situations that may cause you to make changes to your ANDA. First, there are pre-approval changes that you are compelled to make with respect to your ANDA based on a deficiency from the FDA. Second, there are postapproval changes that you make yourself with respect to your ANDA. As in any dealings with the FDA, the key is to be accurate—here, about the category and nature of the change—and to communicate clearly what the change is and why you are making it.

a. Amendments in Response to a Deficiency

It is difficult to pitch a perfect game in baseball; it is nearly impossible to submit an ANDA that is approvable without comment from the FDA. And when the FDA finds fault with your ANDA, you will receive a deficiency letter from the FDA. The various reviewing departments of the FDA have the ability to send deficiencies regarding your ANDA, and often an ANDA will receive deficiencies from multiple departments in one letter. These deficiencies can relate to incomplete information or additional questions regarding chemistry, manufacturing, controls, microbiology, labeling, or bioequivalence. Sometimes the deficiency will request additional information or require additional testing. When responding to a deficiency letter from the FDA, directly address the issue or issues identified in the deficiency letter. Otherwise you risk delaying approval of your application. In other words, answer the question you have been asked, or the FDA will likely just ask it again.

Your response to an FDA deficiency letter will often require an attendant amendment to your ANDA. The FDA will identify in the deficiency letter whether the responding amendment should be categorized as a major, minor, or telephone amendment. Major amendments are required, for example, if the applicant needs to manufacture a new batch of drug product (and with it, new supporting information), if the applicant has to perform a new bioequivalence study, or if the applicant is required

33. There is a distinction between patents that are listed after you file your ANDA, which would be “later listed” as to your ANDA or any other ANDA already on file, and late-listed patents, which are patents for which the sponsor requests listing in the Orange Book more than 30 days after the patent has issued. With respect to the latter, there is no obligation to certify to late-listed patents, but also nothing prohibiting anyone from asserting position on those patents.

to provide new analytical methods or validation data.³⁴ Minor amendments—where most amendments fall—are for those issues more easily addressed than with a major amendment, including issues where the FDA needs more information or where resolution of the deficiency is outside the control of the applicant.³⁵ Finally, telephone amendments are reserved for issues of limited complexity that can be resolved more expeditiously.³⁶

Review timelines and review priority vary depending on the type of amendment. Because major amendments are the most complex, they usually have the longest review time frame and have a lower priority than minor amendments or telephone amendments.³⁷ Major amendments are given the same priority as an original, unreviewed ANDA and, like original ANDA filings, are reviewed on a “first in, first reviewed” basis.³⁸ The OGD attempts to review major amendments within 180 days.³⁹

With minor amendments, the OGD tries to complete its review within 30 to 60 days, but the review can take longer.⁴⁰ A categorization of an amendment as minor usually means that the application is closer to approval, and thus such amendments are given higher priority.⁴¹

Telephone amendments are a reviewer’s highest priority, as such amendments typically mean that the application is on the verge of approval with only clarification or postapproval commitments needed.⁴² Sometimes a postapproval commitment will be in the form of an update in an annual report or submission of a Changes Being Effected or Changes Being Effected in 30 Days commitment, which are discussed in greater detail in the following section. With a telephone amendment, the FDA and the applicant discuss the issue by phone and agree on the proper resolution. When the FDA requests a telephone amendment, the applicant should respond within ten calendar days of the telephone call.⁴³ The applicant’s response to the telephone amendment is reviewed “upon receipt.”⁴⁴

b. Applicant-initiated Changes

The FDA must be informed of any postapproval changes that you make to your product, the process for making your product, or the labeling for your

34. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: MAJOR, MINOR, AND TELEPHONE AMENDMENTS TO ABBREVIATED NEW DRUG APPLICATIONS 2–3 (rev. 2 Dec. 2001).

35. *Id.* at 3.

36. *Id.* at 4.

37. *Id.* at 2.

38. *Id.*

39. *Id.* at 4.

40. *Id.*

41. *Id.* at 2.

42. *Id.*

43. *Id.* at 4.

44. *Id.*

product. You must, therefore, report any changes that you are making to your ANDA to the FDA, and you must properly categorize your changes so that the FDA can properly evaluate and approve (or disapprove) your changes. Thus, it is important to know the types of changes that can be made to ANDAs and the expected review times for such changes.

Broadly, the changes that can be unilaterally made to an ANDA by the applicant are categorized as major changes, moderate changes, and minor changes.⁴⁵ It is imperative that you know the full effect of your proposed changes before implementing them. Accordingly, testing is crucial. Although the title of each category is telling, we provide a bit more substance on each.

Major changes: A major change is one that “has a *substantial* potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.”⁴⁶ Major changes include changes to components and composition of the drug product or drug substance, manufacturing sites, manufacturing processes, testing specifications, container closure systems, and labeling. A major change is made through a supplement called a Prior Approval Supplement (PAS).⁴⁷ Expedited review of a PAS is available, but the requester must show a public health reason or hardship on the applicant absent expedited review.⁴⁸ The applicant cannot make the change requested in the PAS unless the FDA approves the change. Only with approval can the applicant sell any product made using the change requested in the PAS.

Moderate changes: A moderate change is one that “has a *moderate* potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.”⁴⁹ Moderate changes can include the same type of subject matter as major changes. A moderate change is effected through either a Supplement—Changes Being Effected in 30 Days (CBE 30) or a Supplement—Changes Being Effected (CBE).⁵⁰ A CBE 30 is used for changes that the applicant intends on making in 30 days unless the FDA informs the applicant

45. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED NDA OR ANDA: QUESTIONS AND ANSWERS 3–4 (Jan. 2001).

46. *Id.* at 3.

47. *Id.*

48. *Id.*

49. *Id.*

50. *Id.*

that a PAS is required in order to make the change. A CBE is for moderate changes that are being made immediately. If the FDA ends up disapproving a CBE 30 or CBE after review, the FDA may order that the applicant cease distributing any product using the disapproved change(s). The less potential there is for the change to have an adverse effect on the drug product, the more likely that the moderate change is a CBE as opposed to a CBE 30. Alternatively, if you are looking for some assurance from the FDA that your moderate change is appropriate before actually implementing it, you should use a CBE 30.

Minor changes: It is not surprising that a minor change is one that “has *minimal* potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.”⁵¹ A minor change is made in the context of an annual report and does not require pre-approval from the FDA. Like major and moderate changes, minor changes can be made with respect to any aspect of the manufacturing process or components of the drug product or its labeling.

When implementing one of the preceding changes, whether through a supplement or an annual report, provide the FDA with a list of all proposed changes in a cover letter (for supplements) or in a summary section (in an annual report).⁵² The supplement or annual report should clearly and completely describe the change or changes so that the FDA can quickly determine whether you have used the proper reporting category and can efficiently evaluate the change.

V. Conclusion

Your ANDA should be the result of the collaborative efforts of your scientists, your regulatory affairs professional, your attorneys, and other key decision makers. And at the end of the day, compliance is the key to obtaining swift FDA approval—provide the FDA with what it is looking for in the form it has outlined for you. But compliance with an eye toward preparation for litigation will mean that all of the effort expended in obtaining the FDA approval will not be wasted when the patent lawsuit is filed.

51. *Id.* at 4.

52. *Id.*