



**BASF** Pharma

November 9, 1999

Dockets Management Branch, HFA-305  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Re: Supplement to Citizen Petition  
on Scheduling and Procedure  
Docket No. 97N-0314/CP3

Knoll Pharmaceutical Company ("Knoll" or "KPC") submits this supplement to its Citizen Petition on Scheduling and Procedure to address two issues:

1. the unlawfulness of FDA's refusing to file, review, and approve a § 505(b)(2) application for any orally administered levothyroxine sodium drug product on the ground that FDA has previously approved one or more NDAs for an orally administered levothyroxine sodium drug product, as suggested in a recent draft guidance; and
2. the reasons why it is now imperative that FDA modify the schedule contemplated by the Notice, as requested in the Petition.

1. Section 505(b)(2) Issues

Introduction

In its Petition, Knoll requested that "FDA declare that it will not follow any . . . procedure such as approving only one or a few NDAs and treating other submissions as ANDAs." In a recent draft guidance on levothyroxine sodium, however, FDA again asserts that it may or will refuse to file, review, and approve applications submitted as § 505(b)(2) NDAs if it has already approved one or more NDAs for the product, and that it may or will require them to be resubmitted as ANDAs.<sup>1</sup> In this supplement, Knoll provides

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1. Draft Guidance for Industry on Levothyroxine Sodium, Docket No. 99D-2636, 64 Fed. Reg. 44935 (Aug. 18, 1999).

97N-0314

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further analysis of the reasons why FDA lacks authority to refuse to file and review, and to deny approval of, a § 505(b)(2) application on the ground that it has previously approved one or more NDAs for a product containing the same active ingredient.<sup>2</sup>

#### Action Requested

Knoll now specifically requests that FDA declare that it will not refuse to file, review, or approve a § 505(b)(2) application for any levothyroxine sodium product on the ground that FDA has previously approved one or more NDAs for a levothyroxine sodium product.

#### Argument

Taken together, the questions and answers in the draft guidance amount to a declaration that once the first NDA or set of NDAs is approved for levothyroxine sodium, FDA may refuse to file and refuse to review and will not approve any further § 505(b)(2) NDAs. Such a declaration is contrary to the Food, Drug, and Cosmetic Act ("FDCA" or "Act") and to the clear intent of the Congress in adopting the relevant statutory provisions.

As applied to Synthroid® levothyroxine sodium tablets, such a policy would also be both unfair and peculiar. Because Knoll responded to FDA's invitation in FDA's August 14, 1997 Federal Register notice to submit a GRAS/E Petition, an NDA is not required for Synthroid unless FDA denies Knoll's GRAS/E Petition and the courts uphold it. Thus, if an NDA is ever submitted for Synthroid,<sup>3</sup> it may not be submitted until after one or more of the other NDAs is approved, and, under the draft guidance, FDA would be free to refuse to file, review, and approve it. In so doing, FDA would, in effect, be punishing Knoll for doing what it has every right to do: accepting FDA's published invitation to submit a Citizen Petition and waiting until FDA and, if necessary, the courts reach a decision on whether Synthroid is a new drug before submitting an NDA. Importantly, because the published literature on which levothyroxine NDAs will be based consists entirely or nearly entirely of studies of Synthroid, it seems peculiar indeed to say that every company but Knoll will be allowed to rely on the published literature.

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2. This analysis was also included in Knoll's comments on the draft guidance. A copy of Knoll's comments, without attachments, is attached.

3. As stated in the text and in its GRAS/E Petition, Knoll believes that Synthroid is not a new drug and that no NDA is required for Synthroid. If, however, FDA and the courts disagree, then an NDA will have to be submitted. Knoll's discussing that possibility in these comments is not a waiver of its position that Synthroid is not a new drug.

Both the words and the structure of § 505 of the Act compel the conclusion that (except for issues of exclusivity, which are not relevant here) FDA lacks authority to refuse to file, review, and approve a new drug application merely because it has previously approved another new drug application for the same active ingredient under § 505(b)(2). Section 505(a) provides that a new drug may not be lawfully marketed unless it is the subject of either an approved New Drug Application under § 505(b) or an approved Abbreviated New Drug Application under § 505(j). Either an NDA or an ANDA is permissible; the statute expresses no preference.

That the choice of an NDA or an ANDA is the applicant's is reinforced by the wording of §§ 505(b) and 505(j). "Any person" may submit an NDA under § 505(b), and "any person" may submit an ANDA under § 505(j).<sup>4</sup> The statute imposes no duty on "any person" to refrain from submitting an NDA if an ANDA is also a possibility; the choice is left up to the applicant.

Certainly the Act does not make FDA's approval of a previous NDA a ground for denial of a later NDA submitted under § 505(b). If an NDA is submitted under § 505(b), FDA must (after a specified time period) approve it unless it finds that one or more of the grounds specified in § 505(d) is applicable. FDCA § 505(c). None of the grounds in § 505(d) has anything to do with whether one or more applications for the same drug were previously approved under § 505(b)(2), an omission which is fatal to FDA's claim of authority to deny an NDA on the ground that it had previously approved another NDA for the product containing the same active ingredient.<sup>5</sup>

There is no doubt that these provisions of § 505 apply to § 505(b)(2) applications as well as § 505(b)(1) applications. FDA has recognized as much. In the preamble to the ANDA/505(b)(2) regulations, for example, FDA stated that in all respects relevant to this issue, § 505(b)(2) applications are "subject to the same statutory provisions as full NDAs." 57 Fed. Reg. 17950, 17952 (April 28, 1992).

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4. The Act speaks of any person's "filing" an NDA. This supplement follows common usage in using the phrase "submitting" an NDA so as to avoid confusion with the actions FDA may take in "refusing to file" or "filing" a submitted NDA.

5. Nor can FDA avoid its lack of authority to deny an NDA on this ground by calling it a "refusal to file," notwithstanding FDA's regulation claiming such authority. 21 C.F.R. § 314.101(d)(9). Like the draft guidance, this regulation flies in the face of the statute, and is therefore unlawful. The agency's refusal to file certain § 505(b)(2) applications is unlawful for other reasons as well, as set forth in Knoll's Scheduling and Procedure Petition at 7-9.

The legislative history confirms that the ANDA provisions were intended to supplement - not supplant - the NDA provisions of the Act. As explained in the House Report, "Title I of the bill [the ANDA provision] allows drug manufacturers to use an abbreviated new drug application (ANDA) when seeking approval to make generic copies of drugs that were approved by the FDA after 1962." H.R. Rep. No. 98-857, pt. 2, at 11 (1984) (emphasis added) (copy attached). The ANDA procedure did not replace the NDA procedure; it "graft[ed] on the NDA procedure . . . authority for an abbreviated new drug application (ANDA) procedure . . . ." Id. Two commentators have confirmed this view:

The statute continues the availability of paper [505(b)(2)] NDAs for post-1962 drug approval, although it is expected that most applications will take advantage of the new ANDA procedures.

Allan M. Fox and Alan R. Bennett, *The Legislative History of the Drug Price Competition and Patent Term Restoration Act of 1984*, at 95 (1987) (copy attached).

The 1984 Waxman-Hatch amendments to the FDCA left intact one option for FDA approval of generic drugs that had existed previously. Approval of a generic drug can still be obtained by submitting a new drug application to the agency pursuant to FDCA Section 505(b).

Donald O. Beers, *Generic and Innovator Drugs: A Guide to FDA Approval Requirements*, at 2-2 (5<sup>th</sup> ed. 1999) (footnote omitted) (copy attached).

From a policy standpoint, FDA's attempt to remit some applicants to ANDAs once NDA(s) are approved will not save the agency any work, and could be unfair to Knoll and other applicants. In the case of levothyroxine, FDA has twice recognized, once in the Notice and once in the draft guidance, that applicants will be able to rely on published literature for proof of safety and effectiveness. Thus, each § 505(b)(2) application for levothyroxine sodium will likely contain most or all of the same published studies. Once FDA reviews those published data, it can apply its judgments on safety and efficacy to all levothyroxine products, and need not repeat the review. By contrast, it would have to review de novo each bioequivalence study in an ANDA, making more work, not less.<sup>6</sup> Equally important, the published studies are on Knoll's Synthroid.<sup>7</sup> It would be both unfair and peculiar for FDA to allow studies of Synthroid to be utilized in § 505(b)(2) applications for other products but not for Synthroid itself.

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6. See Knoll's Scheduling and Procedure Petition at 9.

7. See Knoll's GRAS/E Petition at 10-11.

The draft guidance's approach to cutoff dates for § 505(b)(2) applications is also mischievous in giving FDA far too great an opportunity to pick and choose among applicants for any reason or no reason. Because of FDA's confidentiality rules, no applicant can be sure of knowing when or whether any other applicant has submitted an NDA, when or whether FDA has filed it or refused to file it, or whether review of a particular application is progressing well toward approval or not. Thus, no applicant can gauge or even guess at when a § 505(b)(2) application needs to get submitted to avoid preclusion of its § 505(b)(2) application. But FDA can easily manipulate the process by holding up approval of one application for a day or so (or a week or a month) to allow it to file one or more other § 505(b)(2) applications, all while not filing one or more other applications before the approval. Such unbridled discretion is a recipe for unfairness, whether intentional or accidental.

## 2. Scheduling Issues

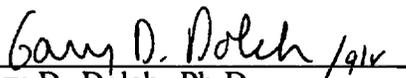
Since issuing the Notice in August, 1997, FDA has issued two draft guidances, provided advice in meetings, and sent letters which have created considerable uncertainty about the procedures it intends to use pursuant to the Notice and the design and conduct of bioavailability studies in connection with the Notice. Both draft guidances came quite late in the process; the bioavailability draft guidance was not published for comment until June, 1999, and the more general draft guidance related to the Notice was not published for comment until August, 1999, more than two years after the Notice was published. The draft guidances and other FDA communications on levothyroxine sodium have drawn criticism and expressions of concern from industry members, but even where it has had time to do so, FDA has not responded. It has not, for example, published a final guidance on bioavailability, even though the deadline for comments was August, 1999, and presumably it will not publish a final guidance on general issues until well into next year. Depending on the content of the final guidances, companies may need to conduct additional studies, which are unlikely to be completed by FDA's original proposed deadline of August, 2000. FDA's failure to provide certainty about the process and its attempt to create various unlawful and inappropriate procedures have created so much difficulty for industry members that the only appropriate remedy at this point is to modify the schedule.

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3. Conclusion

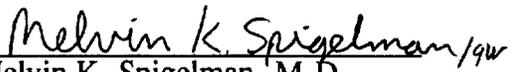
Knoll respectfully urges the agency to review its Citizen Petition on Scheduling and Procedure and take the actions requested therein to provide adequate time for industry members and FDA alike to deal with each issue implicated by the Notice.

Sincerely,

  
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BASF Pharma

October 18, 1999

Dockets Management Branch  
HFD-305  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Re: Docket No. 99D-2636  
Draft Guidance for Industry on  
Levothyroxine Sodium

Knoll Pharmaceutical Company ("KPC" or "Knoll") submits herewith its comments on this draft guidance.

The draft guidance begins with the premise that orally administered levothyroxine sodium drug products are "new drugs," and proceeds to answer questions that have arisen about the new drug applications that are to be submitted pursuant to the Food and Drug Administration's August 14, 1997 Federal Register notice (the "Notice"). As discussed in more detail below, however, FDA's initial premise is incorrect, at least as to Knoll's Synthroid<sup>®</sup> levothyroxine sodium tablets. Knoll also believes that FDA's answers to many of the questions are wrong. Any final guidance must correct these errors. In addition, FDA must recognize that it cannot by issuing a guidance avoid its obligation to respond to Knoll's Citizen Petition on Scheduling and Procedure, which raised many of the issues addressed in the draft guidance.<sup>1</sup>

#### "New Drug" Issues

Throughout the draft guidance, especially in the Introduction and the section on Regulatory Questions and Answers, FDA states that all levothyroxine sodium drug products are "new drugs" and assumes that the agency's "announcement" in the Notice disposes of the matter. In fact, the Notice itself recognized that some levothyroxine sodium drug products may not be new drugs, and invited the submission of Citizen Petitions to that effect. Knoll submitted such a Citizen Petition on December 15, 1997, demonstrating that Synthroid is

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1. Citizen Petition on Scheduling and Procedure, Docket No. 97N-0314/CP3, filed September 25, 1998 and supplemented August 4, 1999 (hereinafter "Scheduling and Procedure Petition"). A copy of the Scheduling and Procedure Petition, without attachments, is attached.

generally recognized as safe and effective and therefore not a new drug.<sup>2</sup> The agency's conspicuous omission from the draft guidance of its own invitation to submit Citizen Petitions and the fact that KPC (and one other manufacturer as well) have done so suggests once again that the agency is refusing to give Knoll's GRAS/E Petition the full and fair consideration it deserves.<sup>3</sup>

#### Cutoff Date for Section 505(b)(2) Applications

Taken together, the questions and answers in this section of the draft guidance amount to a declaration that once the first NDA or set of NDAs is approved for levothyroxine sodium, FDA may refuse to file and refuse to review and will not approve any further § 505(b)(2) NDAs. Such a declaration is contrary to the Food, Drug, and Cosmetic Act ("FDCA" or "Act") and to the clear intent of the Congress in adopting the relevant statutory provisions.

As applied to Synthroid, such a policy would also be both unfair and peculiar. Because Knoll responded to FDA's invitation in the Notice to submit its GRAS/E Petition, an NDA is not required for Synthroid unless FDA denies Knoll's GRAS/E Petition and the courts uphold it. Thus, if an NDA is ever submitted for Synthroid,<sup>4</sup> it may not be submitted until after one or more of the other NDAs is approved, and, under this draft guidance, FDA would be free to refuse to file, review, and approve it. In so doing, FDA would, in effect, be punishing Knoll for doing what it has every right to do: accepting FDA's published invitation to submit a Citizen Petition and waiting until FDA and the courts reach a decision on whether Synthroid is a new drug before submitting an NDA. Importantly, because the published literature on which levothyroxine NDAs will be based consists entirely or nearly entirely of studies of Synthroid, it seems peculiar indeed to say that every company but Knoll will be allowed to rely on the published literature.

Both the words and the structure of § 505 of the Act compel the conclusion that (except for issues of exclusivity, which are not relevant here) FDA lacks authority to refuse to file, review, and approve a new drug application merely because it has previously approved another

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2. Citizen Petition on Regulatory Status of Synthroid Orally Administered Levothyroxine Sodium USP, Docket No. 97N-0314/CP2, filed December 15, 1997 and supplemented May 29, 1998 (hereinafter "GRAS/E Petition"). A copy of the GRAS/E Petition, without attachments, is attached.

3. See Scheduling and Procedure Petition at 4-7.

4. As noted above and in its GRAS/E Petition, Knoll believes that Synthroid is not a new drug and that no NDA is required for Synthroid. If, however, FDA and the courts disagree, then an NDA will have to be submitted. Knoll's discussing that possibility in these comments is not a waiver of its position that Synthroid is not a new drug.

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new drug application for the same active ingredient under § 505(b)(2). Section 505(a) provides that a new drug may not be lawfully marketed unless it is the subject of either an approved New Drug Application under § 505(b) or an approved Abbreviated New Drug Application under § 505(j). Either an NDA or an ANDA is permissible; the statute expresses no preference.

That the choice of an NDA or an ANDA is the applicant's is reinforced by the wording of §§ 505(b) and 505(j). "Any person" may submit an NDA under § 505(b), and "any person" may submit an ANDA under § 505(j).<sup>5</sup> The statute imposes no duty on "any person" to refrain from submitting an NDA if an ANDA is also a possibility; the choice is left up to the applicant.

Certainly the Act does not make FDA's approval of a previous NDA a ground for denial of a later NDA submitted under § 505(b). If an NDA is submitted under § 505(b), FDA must (after a specified time period) approve it unless it finds that one or more of the grounds specified in § 505(d) is applicable. FDCA § 505(c). None of the grounds in § 505(d) has anything to do with whether one or more applications for the same drug were previously approved under § 505(b)(2), an omission which is fatal to FDA's claim of authority to deny an NDA on the ground that it had previously approved another NDA for the product containing the same active ingredient.<sup>6</sup>

There is no doubt that these provisions of § 505 apply to § 505(b)(2) applications as well as § 505(b)(1) applications. FDA has recognized as much. In the preamble to the ANDA/505(b)(2) regulations, for example, FDA stated that in all respects relevant to this issue, § 505(b)(2) applications are "subject to the same statutory provisions as full NDAs." 57 Fed. Reg. 17950, 17952 (April 28, 1992).

The legislative history confirms that the ANDA provisions were intended to supplement - not supplant - the NDA provisions of the Act. As explained in the House Report, "Title I of the bill [the ANDA provisions] allows drug manufacturers to use an abbreviated new drug application (ANDA) when seeking approval to make generic copies of drugs that were approved by the FDA after 1962." H. R. Rep. No. 98-857, pt. 2, at 11 (1984) (emphasis

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5. The Act speaks of any person's "filing" an NDA. These comments follow common usage in using the phrase "submitting" an NDA so as to avoid confusion with the actions FDA may take in "refusing to file" or "filing" a submitted NDA.

6. Nor can FDA avoid its lack of authority to deny an NDA on this ground by calling it a "refusal to file," notwithstanding FDA's regulation claiming such authority. 21 C.F.R. § 314.101(d)(9). Like the draft guidance, this regulation flies in the face of the statute, and is therefore unlawful. The agency's refusal to file certain § 505(b)(2) applications is unlawful for other reasons as well, as set forth in the Scheduling and Procedure Petition at 7-9.

added) (copy attached). The ANDA procedure did not replace the NDA procedure; it “graft[ed] on the NDA procedure . . . authority for an abbreviated new drug application (ANDA) procedure. . . .” Id. Two commentators have confirmed this view:

The statute continues the availability of paper [505(b)(2)] NDAs for post-1962 drug approval, although it is expected that most applications will take advantage of the new ANDA procedures.

Allan M. Fox and Alan R. Bennett, *The Legislative History of the Drug Price Competition and Patent Term Restoration Act of 1984*, at 95 (1987) (copy attached).

The 1984 Waxman-Hatch Act amendments to the FDCA left intact one option for FDA approval of generic drugs that had existed previously. Approval of a generic drug can still be obtained by submitting a new drug application to the agency pursuant to FDCA Section 505(b).

Donald O. Beers, *Generic and Innovator Drugs: A Guide to FDA Approval Requirements*, at 2-2 (5<sup>th</sup> ed. 1999) (footnote omitted) (copy attached).

From a policy standpoint, FDA’s attempt to remit some applicants to ANDAs once NDA(s) are approved will not save the agency any work, and could be unfair to Knoll and other applicants. In the case of levothyroxine, FDA has twice recognized, once in the Notice and once in the draft guidance, that applicants will be able to rely on published literature for proof of safety and effectiveness. Thus, each § 505(b)(2) application for levothyroxine sodium will likely contain most or all of the same published studies. Once FDA reviews those published data, it can apply its judgments on safety and efficacy to all levothyroxine products, and need not repeat the review. By contrast, it would have to review de novo each bioequivalence study in an ANDA, making more work, not less.<sup>7</sup> Equally important, the published studies are on Knoll’s Synthroid.<sup>8</sup> It would be both unfair and peculiar for FDA to allow studies of Synthroid to be utilized in § 505(b)(2) applications for other products but not for Synthroid itself.

The draft guidance’s approach to cutoff dates for § 505(b)(2) applications is also mischievous in giving FDA far too great an opportunity to pick and choose among applicants for any reason or no reason. Because of FDA’s confidentiality rules, no applicant can be sure of knowing when or whether any other applicant has submitted an NDA, when or whether FDA has filed it or refused to file it, or whether review of a particular application is

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7. See Scheduling and Procedure Petition at 9.

8. See GRAS/E Petition at 10-11.

progressing well toward approval or not. Thus, no applicant can gauge or even guess at when a § 505(b)(2) application needs to get submitted to avoid preclusion of its § 505(b)(2) application. But FDA can easily manipulate the process by holding up approval of one application for a day or so (or a week or a month) to allow it to file one or more other § 505(b)(2) applications, all while not filing one or more other applications before the approval. Such unbridled discretion is a recipe for unfairness, whether intentional or accidental.

### User Fees

The Act authorizes user fees for applications submitted under § 505(b)(2) only if the active ingredient "had not been approved under an application submitted under section 505(b)" or, having been so approved, is now being submitted for a new indication. FDCA § 735(1)(B). FDA acknowledges that levothyroxine sodium has been previously approved for hypothyroidism under § 505(b) in combination with triiodothyronine as Euthroid and Thyrolar. It argues, however, that because LT4 has never been approved as a single ingredient for hypothyroidism, applications will be for a new indication and a user fee will therefore be due. But nothing in the statute distinguishes between approval for a particular indication as a single ingredient or in combination. Either way, the active ingredient has previously been approved for that indication, and no user fee can be required.

FDA's interpretation of the statute is not only incorrect, it also creates considerable potential for confusion and unfairness. As FDA itself recognizes, it can collect at most one user fee in this situation, because once the first NDA is approved, no one else owes a user fee. But how will this work in practice? User fees are payable at the time NDAs are submitted, and because most applications for NDAs for levothyroxine will be submitted before the first one is approved, almost every applicant will have to send a check. Then what will FDA do? How will it decide which application to approve first, knowing that only that one applicant will have to pay? Will the unlucky loser have any right to object to having lost? Does FDA plan to cash all the checks and deprive applicants of the use of their money (a considerable sum - \$272,282 in FY1999) while review is pending? Or will it put the checks in escrow pending a decision on who owes and who doesn't? How long will it take to make refunds?

### Exclusivity

The section on exclusivity is correct in noting that five year exclusivity is not available to levothyroxine products because the active moiety has been previously approved as an active ingredient in two NDAs. The section errs, however, in leaving open the possibility that three year exclusivity may be available for applications that contain reports of "new clinical investigations" that are "essential" to the approval of the application. As the Notice stated,

and as the draft guidance reiterates, published literature supports the safety and efficacy of levothyroxine sodium. Accordingly, new clinical studies are not essential, and no three year exclusivity can attach. FDA should say so.

### Therapeutic Equivalence Issues

In suggesting that an applicant can submit as part of its NDA a bioequivalence study comparing its levothyroxine product to one previously approved, FDA seems to be creating an unlawful procedure for ANDAs. As Knoll has explained in its Citizen Petition on Scheduling and Procedure, a copy of which is attached hereto and incorporated herein by reference, the Act and FDA's implementing regulations do not permit the submission and receipt of an ANDA until there is a reference drug listed in the Orange Book, a step which can occur only after approval of an NDA for the drug. Any procedure that allows or results in simultaneous submission of an NDA and an ANDA before FDA approval of the first NDA for levothyroxine sodium contravenes these explicit statutory and regulatory requirements. FDA cannot fix this illegality by pretending that the ANDA does not exist until the time it approves the first NDA.

Perhaps this section is not intended to provide for the submission of ANDAs as such, but rather for the submission in an NDA of bioequivalence data which could result in an AB rating for two NDA-ed products. No such procedure is specified anywhere in the Act, FDA's regulations, or the Preface to the Orange Book (to which FDA generally but vaguely alludes). If Section 1.10 of the Orange Book does imply any means of making two NDA-ed drugs AB to each other (and it does not really seem to), it seems to suggest that before that can happen, both must be approved and listed in the Orange Book (as BX); only then can one of them seek an "upgrade" by submission of a bioequivalence study to the other listed drug. In any event, announcing important changes to FDA's past practice, changes which will have significant effects on the regulated industry as well as consumers, must be done by notice and comment rulemaking, not by casual assertions of authority in a guidance.

In addition, although Section 1.10 contemplates that changes in ratings of a single product from BX to AB will not ordinarily be the subject of notice and comment, the questions of bioequivalence or bioinequivalence of levothyroxine products have been so vexed for so long<sup>9</sup> that notice and comment is surely not only appropriate but necessary in this area. As FDA is aware, numerous studies have purported to show that one or more LT4 products are or are not bioequivalent or bioinequivalent. These studies are not of uniform design, and there is little or no agreement on the appropriate or desirable design of such studies. Indeed, FDA itself has been of two different minds on the subject of whether one design, the Berg-Mayor

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9. See, e.g., Leonard Wartofsky, Bioequivalence of Levothyroxine Preparations: Shortcomings and Implications of a Recently Published Study, *The Endocrinologist* 1997; 7:322-333 (copy attached).

model, is appropriate for bioinequivalence and bioavailability studies.<sup>10</sup> Many other issues have also evoked considerable debate, for example, whether it is better to study LT4 bioequivalence in athyreotic subjects or in subjects with functioning thyroids, and, if the latter, how to make sure that changes in thyroid output during the study are not confounding. And because, as FDA has recognized, levothyroxine sodium is a narrow therapeutic index drug, Notice at 43538, relatively small differences between two products that might be acceptable in other drugs could have health consequences for patients with thyroid disease. Still another important issue is the desirability of assessing individual bioequivalence using replicate designs. See FDA Draft Guidance for Industry on Average, Population, and Individual Approaches to Establishing Bioequivalence, 64 Fed. Reg. 48842 (Sept. 8, 1999), and FDA Draft Guidance for Industry on BA and BE Studies for Orally Administered Drug Products - General Considerations, 64 Fed. Reg. 48409 (Sept. 3, 1999).

Knoll believes, therefore, that FDA should not consider bioequivalence studies of levothyroxine products until some sort of iterative public process, preferably beginning with the issuance of a draft guidance for public comment, allows the medical, pharmacy, consumer, and manufacturing communities the opportunity to work with FDA to reach consensus on the considerations which should govern LT4 bioequivalence determinations and the kinds of studies which best satisfy the consensus.

### Stability

This section seems to suggest that the NDA must include 6 months' accelerated data if 24 month expiration dating is requested, or, at a minimum, 3 months' accelerated data. For products such as Synthroid which have been marketed for many years, real time stability data at 25°C, collected pursuant to FDA's GMP requirements, are available to support expiration, and FDA has in fact reviewed and accepted such data as part of its inspections, including the most recent inspection. Furthermore, accelerated stability data have not been a good predictor of room temperature stability for levothyroxine formulations because potency loss at elevated temperatures has not translated to potency loss under room temperature conditions. Knoll therefore asks FDA to confirm that real time data are acceptable, and that accelerated data are not required if real time data are available.

### Overage

In this section, FDA declares point blank that stability overages are impermissible, but cites no references and gives no reasons. Knoll does not believe that a stability overage is prohibited by the USP monograph for levothyroxine sodium, FDA's regulations on Good

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10. See Knoll's comments on FDA Draft Guidance for Industry on In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets, Docket No. 99D-1149, Letter from Nancy L. Buc to Dockets Management Branch, August 2, 1999, at 3-4. A copy of this letter, without attachments, is attached.

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Manufacturing Practices, or any other published source. USP, in fact, clearly permits overages, both as a general matter and in connection with levothyroxine in particular. Thus, in the General Notices and Requirements section, USP advises that:

Where the content of an ingredient is known to decrease with time, an amount in excess of that declared on the label may be introduced into the dosage form at the time of manufacture to assure compliance with the content requirements of the monograph throughout the expiration period.<sup>11</sup>

Likewise, the USP monograph for levothyroxine sodium tablets provides that the tablets must contain "not less than 90.0 percent and not more than 110.0 percent of the labeled amount" of LT4. FDA's own GMP regulations are not to the contrary. They provide that batches shall be formulated with "the intent to provide not less than 100 percent of the labeled or established amount of active ingredient,"<sup>12</sup> but are silent on providing over 100 percent. Knoll therefore questions the procedural permissibility of FDA's purporting to create a GMP or NDA requirement without explaining its reasons for wanting to do so and allowing an opportunity for comment. Nor does Knoll believe that the presence of a stability overage necessarily creates any problems, and it therefore questions the need for such a pronouncement.

Relationship of Draft Guidance to Knoll's Citizen Petition on Scheduling and Procedure

Many of the issues discussed in the draft guidance were raised in Knoll's Citizen Petition on Scheduling and Procedure. Knoll reminds FDA that the agency is obligated to respond to its Citizen Petition, and that even final guidances, much less draft guidances, do not obviate this requirement.

Sincerely,

*Robert W. Ashworth /qiv*

Robert W. Ashworth, Ph.D.  
Director, Regulatory Affairs

*Steven J. Goldberg /qiv*

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Associate General Counsel  
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11. United States Pharmacopeial Convention, Inc., United States Pharmacopeia 23 - National Formulary 18, at 3 (1995).

12. 21 C.F.R. § 211.101(a).

DRUG PRICE COMPETITION AND PATENT TERM  
RESTORATION ACT OF 1984

AUGUST 1, 1984.—Committed to the Committee of the Whole House on the States of  
the Union and ordered to be printed

Mr. KASTENMEIER, from the Committee on the Judiciary,  
submitted the following

REPORT

together with

ADDITIONAL VIEWS

[To accompany H.R. 3605]

[Including cost estimate of the Congressional Budget Office]

The Committee on the Judiciary, to whom was referred the bill (H.R. 3605) to amend the Federal Food, Drug, and Cosmetic Act to authorize an abbreviated new drug application under section 505 of that Act for generic new drugs equivalent to approved new drugs, and for other purposes, having considered the same, report favorably thereon with amendments and recommend that the bill as amended do pass.

The amendments (stated in terms of the page and line numbers of the bill as reported by the Committee on Energy and Commerce) are as follows:

Page 14, line 22, strike out "(i)" and strike out line 9 on page 15 and all that follows through line 4 on page 16.

Page 27, line 3, strike out "(i)", insert close quotation marks at the end of line 19, and strike out line 20 on that page and all that follows through line 21 on page 28.

Page 37, line 24, strike out "or the Secretary of Agriculture".

Page 38, strike out lines 11 through 22, and insert in lieu thereof the following:

"(1), the Commissioner shall notify the Secretary of Health and Human Services if the patent claims any human drug

was willing to compromise on the provisions of title I of the bill (relating to abbreviated new drug application procedures (ANDAs)) in exchange for some greater protection of existing human pharmaceutical patents. The generic manufacturers, on the other hand, were willing to live with an eighteen-month rule because of other provisions of the bill.

In light of the foregoing, the net effect of the Sawyer amendment would have been to substantially delay generics from getting onto the market when they seek to challenge the validity of a patent. According to the statistics of the Judicial Conference of the United States, the median time between filing and disposition of a patent suit is 36 months. Annual Report of the Director of the Administrative Office of the United States Courts—1982, at 253. Over ten percent of these cases take more than 77 months. Thus, a requirement that FDA defer generic approval until after a court decision of patent invalidity would substantially delay FDA approvals. Of course, in the event that the FDA approves a generic because of the expiration of 18 months without a court decision, and it is later determined that the patent is valid, the patent owner may still recover damages from the generic.<sup>14</sup> Therefore, in most cases the bill affords greater protection for patent holders than current law.

#### SECTIONAL ANALYSIS OF "DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984"

##### GENERAL

The Federal Food, Drug, and Cosmetic Act (hereinafter FDCA), 21 U.S.C. 355, establishes a system of premarketing clearance for drugs. Generally, the FDCA prohibits the introduction into commerce of any new drug unless a new drug application (NDA) filed with the Food and Drug Administration (FDA) is effective with respect to that drug. 21 U.S.C. 335(a). The FDA is part of the Department of Health and Human Services (HHS) and the Secretary of HHS has delegated her responsibilities under the Act to the Commissioner of Food and Drugs. 21 U.S.C. 21 CFR 5.10. A new drug is one not generally recognized by qualified experts as safe and effective for its intended use. 21 U.S.C. 321(p)(1). The Government can sue to enjoin violations, prosecute criminally, and seize and condemn articles. 21 U.S.C. 331(d), 332(a), 333 and 334.

The FDCA establishes an introduction procedure for new drugs, designed to elicit sufficient scientific information about a drug, including reports on investigations, composition, methods and precautions in manufacture, and samples of the drug, which will permit an intelligent assessment of its safety and efficacy. 21 U.S.C. 355(b).

The law provides standards under which, after notice and hearing, the FDA can refuse to allow a NDA to become effective, 21 U.S.C. 355 (c) and (d), or can withdraw a NDA in effect on the basis of new evidence that the drug was unsafe. 21 U.S.C. 355(e). Generally, the FDA must approve or disapprove an application within 180 days. The FDA is directed to refuse approval of NDA and to withdraw any prior approval of NDA if "substantial evidence" that

<sup>14</sup> See proposed section 271(e)(4) and 35 U.S.C. 271.

the drug is effective for its intended use is lacking. 21 U.S.C. 355 (d) and (e). Substantial evidence is defined to include "evidence consisting of adequate clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U.S.C. 355(d).

FDA orders refusing or withdrawing a NDA are reviewable in the court of appeals. 21 U.S.C. 355(h). Other kinds of FDA orders may be reviewed in federal district courts under the Administrative Procedure Act (APA).

The Act provides an alternative procedure for drugs intended solely for investigational use. 21 U.S.C. 355(i). Compliance with a comprehensive set of FDA regulations is required. 21 CFR 312.1 et seq.

Finally, section 355(j) requires records and reports relating to clinical experience and other data or information regarding an approved drug to be made available to the FDA which shall handle them with due regard for the professional ethics of the medical profession and the interests of patients.

#### SUMMARY OF THE BILL

The "Drug Price Competition and Patent Term Restoration Act of 1984" (H.R. 3605) consists of two titles which affect introduction procedures and patent requirements for certain kinds of generic new drugs. Title I of the bill allows drug manufacturers to use an abbreviated new drug application (ANDA) when seeking approval to make generic copies of drugs that were approved by the FDA after 1962. Title II of the bill encourages drug manufacturers to assume the increased costs of research and development of certain products which are subject to premarketing clearance by restoring some of the time lost on patent life while the product is awaiting FDA approval.

Section 1 of the bill sets out the short title: "Drug Price Competition and Patent Term Restoration Act of 1984".

#### *Title I—Abbreviated New Drug Applications*

Section 101 amends section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355, to graft on the NDA procedure previously described, authority for an abbreviated new drug application (ANDA) procedure applicable to drug manufacturers seeking approval to make generic copies of drugs that were approved by the FDA after 1962. There are "[a]n estimated 150 drug products approved after 1962 [that] are currently off patent and would become available for generic copy using the ANDA procedure proposed in this bill." H. Rept. 98-857, Part I, at 19.

The new ANDA procedure is set forth in subsection (j) of the introductory procedure provisions of current law. 21 U.S.C. 355. As a consequence, existing subsection (j), relating to records and reports which have to be made available to the FDA by manufacturers of approved drugs, is redesignated subsection (k).

Paragraph (1) of proposed subsection (j) authorizes any person to file an ANDA.

Paragraph (2)(A) of proposed subsection (j) describes the information which has to be included in the ANDA. Specifically, the ANDA must include:

(i) sufficient information to show that the conditions of use prescribed, recommended or suggested in the proposed labeling for which the applicant is seeking approval are the same as those that have been previously approved for the listed drug;

(ii)(I) if that listed drug, referred to in clause (i), has only one active ingredient, sufficient information to show that the active ingredient of the generic is the same as that of the listed drug, or

(ii)(II) if the listed drug, referred to in clause (i), has more than one active ingredient, sufficient information to show that all of the active ingredients in the generic drug are the same as those of the listed drug, or

(ii)(III) if that listed drug, referred to in clause (i), has more than one active ingredient, and if one of the active ingredients in the generic drug is different and the applicant is seeking approval under paragraph (2)(C), relating to ANDAs for drugs which are different, sufficient information to show that the other active ingredients of the generic are the same as the active ingredients of the listed drug as well as sufficient information to show that the different active ingredient is an active ingredient or a listed drug or of a drug that is not a new drug as defined by section 201(p) of the Act, 21 U.S.C. 321(p), and such other information about the different active ingredient that the ANDA may require.

(iii) sufficient information to show that the route of administration, the dosage form and the strength of the generic drug are the same as those of the listed drug, or if the generic departs from the listed drug in any one of these particulars, such information regarding that difference as the FDA may require;

(iv) sufficient information to show that the generic drug is bioequivalent<sup>15</sup> to the listed drug, except that if the applicant is seeking approval under paragraph (2)(C), relating to ANDAs for drugs which are different, sufficient information to show that the active ingredients of the generic are of the same pharmacological or therapeutic class as those of the listed drug and can be expected to have the same therapeutic effect when administered to patients for an approved condition for use;

(v) sufficient information to show that the proposed labeling for the generic drug is the same as that of the listed drug except for approved changes when approval has been obtained under paragraph (2)(C), relating to ANDAs for drugs which are different, or because the generic and the listed drug are produced or distributed by different manufacturers;

(vi) the scientific information about a generic that is required for a NDA under existing law, 21 U.S.C. 355(b)(2)-(5), as redesignated by section 103(a) of this bill (§ 355(b)(1)(B)-(F)), namely a full list of its component articles and composition, a

<sup>15</sup> The term bioequivalent is defined in section 101 of the bill.

full description of methods and precautions in manufacture, drug and component article samples, and a specimen of the proposed label;

(vii) a certification by the applicant (in the opinion of the applicant and to the best of such applicant's knowledge) of patent information applicable to the listed drug if that information has been submitted under subsections (b) and (c) of existing law as proposed to be amended by section 102(a)(1) and (a)(2) of the bill, *infra*. With respect to all product patents which claim the listed drug and all use patents which claim an indication for the drug for which the applicant is seeking approval, i.e., a controlling use patent, the applicant must certify, in the opinion of the applicant and to the best of the applicant's knowledge—

(I) that the patent information as required under subsections (b) and (c) of existing law as proposed to be amended by section 102; (a)(1) and (a)(2) of the bill, *infra*, has not been filed;

(II) that one or more of the product or controlling use patents as hereafter required to be provided for NDAs have expired;

(III) that one or more of the product or controlling use patents as hereafter required to be provided for NDAs will expire on a specified future date, and

(IV) that one or more of the product or controlling use patents as hereafter required to be provided for NDAs either are invalid or will not be infringed.

(viii) a statement when appropriate that an applicant is seeking approval for an indication not previously claimed by any use patent.

The FDA cannot require that an ANDA contain information above and beyond that required by clauses (i) through (viii), *supra*.

Paragraph (2)(B) of proposed subsection (j) requires additional patent information to be included in the ANDAs of applicants who certify pursuant to subparagraph (A)(vii)(IV), *supra*, that one or more of the product or controlling use patents either are invalid or will not be infringed. Proposed subparagraph (B)(i) provides that the ANDA in these circumstances shall state that the notice required by clause (ii) of this subparagraph has been given to the affected owner(s) of a patent which is subject to the certification requirement or their representatives and to the affected holder of an approved NDA which contains the patent information required by introduction procedures of existing law as amended by section 102(a)(1) and (a)(2) of the bill.

Clause (ii) provides that the required notice shall state that an ANDA which contains data from bioavailability or bioequivalence studies has been submitted along with a certification seeking approval for marketing a drug covered by an unexpired patent. Additionally, the notice shall explain in detail the legal and factual basis of the applicant's opinion that the relevant patent is invalid or will not be infringed.

Subparagraph (iii) requires that in the case of an ANDA which is subsequently amended so as to bring it within this notice require-

ment, notice shall be given when the amended application is submitted.

Paragraph (2)(C) of proposed subsection (j) relates to ANDAs for drugs which are different from the listed drugs. Generally, a person would be prohibited from submitting an ANDA in these circumstances unless the variance is one permitted by the law as amended by this bill and the FDA has granted a petition requesting the change. If an applicant wishes to vary one active ingredient or the route of administration, dosage form or strength of the generic drug from the listed drug, it must petition the FDA for permission to file an ANDA for the differing generic drug. The FDA has 90 days to approve or disapprove the petition from the date of its submission. The FDA shall approve a petition to submit an ANDA for a differing generic drug unless clinical studies are needed to show the safety and effectiveness of the change.

Paragraph (3) of proposed subsection (j) requires the FDA to approve an ANDA unless it finds one of the following:

(A) that the methods used in, or the facilities and controls used for; the manufacture, processing and packing of the generic drug are inadequate to assure and preserve its identity, strength, quality and purity;

(B) that the ANDA does not contain sufficient information to show that each of the conditions for use for the generic drug have been previously approved for the listed drug;

(C)(i) that the active ingredient of the generic drug is not the same as that of the listed drug and the listed drug has only one active ingredient,

(C)(ii) that the active ingredients of the generic drug are not the same as those of the listed drug and the listed drug has more than one active ingredient, or

(C)(iii) that the active ingredients of the generic drug differ from those of the listed drug and a petition permitting a change in one active ingredient has been granted but the other active ingredients of the generic drug are not the same as those of the listed drug or the different active ingredient in the generic is not a listed drug or if the different active ingredient is a new drug as defined by section 201(p) of the Act, 21 U.S.C. 321(p);

(D)(i) that an ANDA does not show that the route of administration, dosage form, or strength of the generic drug are all the same as those of the listed drug, or

(D)(ii) that an ANDA for a generic drug which has a different route of administration, dosage form, or strength from the listed drug but the petition regarding the change has not been approved under paragraph (2)(C);

(E) that an ANDA does not contain all of the information that the FDA required in previously granting a petition allowing for a difference in the generic drug from the listed drug;

(F) that an ANDA for a generic drug whose active ingredients are the same as those of the listed drug does not show that the generic drug is bioequivalent to the listed drug or, if a petition regarding a change in one of the active ingredients in a combination generic has been granted, that the ANDA does not show that the active ingredients of the generic drug are of

the same pharmacological or therapeutic class as those of the listed drug or does not show that the differing generic combination drug can be expected to have the same therapeutic effect as the listed combination product when administered to patients for an approved condition of use;

(G) that the ANDA does not show that the proposed labeling for the generic drug is the same as that of the listed drug (except for changes in the proposed labeling of the generic drug because a petition regarding a change has been granted and changes from a switch in producer or distributor);

(H) that on the basis of intrinsic or extrinsic information the inactive ingredients of the generic drug are unsafe for use under the conditions prescribed, recommended, or suggested in the proposed labeling for the generic drug or because the composition of the generic drug is unsafe under approved conditions of use;

(I) that approval of the listed drug has been withdrawn or suspended for reasons of safety or effectiveness;

(J) that an ANDA does not meet any of the requirements set forth in paragraph (2)(A), relating to ANDA's for drugs which are the same;

(K) that an ANDA contains any untrue statement of material fact.

Paragraph (4)(A) of proposed subsection (j) requires the FDA to approve or disapprove an ANDA within 180 days of the initial receipt of the application. By mutual agreement of the FDA and the applicant, that period may be extended.

Paragraph (4)(B) of proposed subsection (j) allows an ANDA approval to become effective according to relevant patent-related circumstances. Thus, under clause (i) if an applicant certifies in an ANDA that patent information has not been supplied with respect to a NDA as hereafter is required or that the relevant patents have expired, approval of the ANDA would become immediately effective. Under clause (ii), if the applicant on the basis of supplied information certifies that the patent or patents will expire on a specified future date, approval of the ANDA becomes effective on that date.

Clause (iii) would authorize a flexible schedule of ANDA approval-effectiveness dates when the applicant certifies that one or more of the product or controlling use patents are invalid or not infringed. Generally, approval of the ANDA in these circumstances could become effective after a 45-day hiatus. An approval of an ANDA would not become effective in these circumstances, however, if within 45 days of the receipt of notice of the certification an action is brought for patent infringement regarding one or more of the patents subject to that certification. In that event, approval of the ANDA could not be effective until 18 months after the notice of the certification was provided or until a court decision issues, if before the expiration of the 18 month time period a court decides such patent is invalid or not infringed the approval shall be made effective on the date of the courts order. If the court decides such patent has been infringed under 35 U.S.C. 271(e) the approval shall be made effective on the date the court orders.

Each party to a patent infringement suit is charged to reasonably cooperate in expediting the action. Failure by either party to cooperate in a reasonable manner may be used by the court to reduce or lengthen the time, as appropriate, before an ANDA approval becomes effective. No action for a declaratory judgment regarding patent infringement can be brought within the 45 days allowed for notice of certification of patent invalidity or non-infringement. An action for a declaratory judgment regarding infringement of a patent shall be brought in the judicial district where the defendant has its principal place of business or a regular or established place of business.

If an ANDA certifying patent invalidity or non-infringement is filed subsequent to an ANDA for the same listed drug that has made a similar certification, clause (iv) provides that the approval of the subsequent ANDA can be made effective sooner than 180 days after the previous applicant has begun commercial marketing, or the date on which the court rules the patent invalid or not infringed, whichever occurs first.

Paragraph (4)(C) of proposed subsection (j) provides that in the event of FDA disapproval of an ANDA, the agency shall give the applicant notice of the opportunity for a hearing on the issue of the approvability of the ANDA. In order to obtain a hearing, the applicant shall request it in writing within 30 days of the notice. The hearing may begin not later than 120 days after the notice. However, a later date may be set by mutual agreement. The hearing shall be conducted as expeditiously as possible. The FDA's decisional order shall be issued within 90 days after the date for filing final briefs.

Paragraph (4)(D) of proposed subsection (j) provides for an interim rule regarding ANDA approval effectiveness in the case of certain generic drugs whose listed drugs were originally approved between January 1, 1982 and the date of enactment of this bill. The clause provides that during this transitional period the FDA may not make effective the approval of an ANDA for a drug which includes an active ingredient (including any ester or salt of the active ingredient) until 10 years after the date of approval of the NDA.

Paragraph (5) of proposed subsection (j) relates to the consequences on an approved ANDA worked by withdrawal or suspension of approval of the listed drug. The approval of an ANDA shall be withdrawn or suspended for safety or effectiveness reasons as provided in section 505(e)(1)-(4) of the Act, 21 U.S.C. 355(e)(1)-(4). Similarly, the approval of an ANDA will also be withdrawn or suspended if it refers to a drug whose approval is withdrawn or suspended under this paragraph. Finally, the approval of an ANDA shall be withdrawn or suspended if the FDA determines that the listed drug has been voluntarily withdrawn from sale due to reasons of safety or effectiveness.

The ANDA must be withdrawn or suspended from sale for the same period as the approval of the drug to which it refers has been withdrawn or suspended. When the listed drug has been voluntarily withdrawn from the market and the FDA has determined that the listed drug was withdrawn due to safety or effectiveness reasons, the approval of the ANDA likewise must be withdrawn until

such time as the FDA determines that the listed drug was not withdrawn from sale for safety or effectiveness reasons.

Paragraph (6)(A), of proposed subsection (j) authorizes a program whereby information about listed drugs which could be copied would become available. Within 60 days after enactment of this bill, the FDA is required to publish and make available a list of drugs eligible for consideration in an ANDA. The list must include in alphabetical order the official and proprietary name of each drug which has been approved for safety and effectiveness prior to the date of enactment of this bill. If the drug was approved after 1981, the list must include the date of its approval and its NDA number. The list must specify whether in vitro or in vivo bioequivalence studies, or both, are required for ANDAs. Clause (i).

At 30-day intervals thereafter, the FDA must update the list to include drugs that have been approved for safety and effectiveness after enactment of this bill and drugs approved in ANDAs under this subsection. Clause (ii).

The FDA must include in the list patent information on listed new drugs required under section 102(a)(1) and (2) of this bill as that information becomes available. Clause (iii).

Paragraph 6(B) of proposed subsection (j) provides that a drug approved for safety and effectiveness under section 505(c) of the Act, 21 U.S.C. § 355(c) or under subsection (j) if this bill is enacted, shall be considered as published and thus eligible for approval in an ANDA on the date of its approval or the date of enactment, whichever is later.

Paragraph (6)(C) of proposed subsection (j) provides that a drug may not be listed as eligible for consideration in an ANDA if the approval of the former or pioneer drug is withdrawn or suspended for safety or effectiveness reasons under section 505(e)(1)-(4) of the Act, 21 U.S.C. § 355(e)(1)-(4), or if approval of the generic drug was withdrawn or suspended under paragraph (j)(5), supra, as authorized by this bill. Also, a drug may not be listed if the FDA determines that it has been voluntarily withdrawn for reasons of safety or effectiveness. In the event such a drug has already been listed, it must be immediately removed from the list.

A drug may not be listed so long as its approval is withdrawn or suspended. If the drug has been voluntarily withdrawn from market, it may not be listed until the FDA determines that the drug was not withdrawn from sale for safety or effectiveness reasons. A notice removing any drug from the FDA list regarding availability for copy shall be published in the Federal Register.

Paragraph (7) of proposed subsection (j) spells out the term "bioavailability" and the significance of bioequivalence for purposes of subsection (j) as authorized by the bill. The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

A drug is to be considered bioequivalent to a listed drug if the rate and extent of absorption of the generic 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 or multiple doses. Clause (1). A generic drug may also be

considered to be bioequivalent to a listed drug if the extent of absorption of the generic drug does not show a significant difference from the 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 and the difference from the listed drug in the rate of absorption of the generic drug is intentional, is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentration on chronic use, and is considered medically insignificant for the drug.

Section 102(a)(1) of the bill amends section 505(b) of the Act, 21 U.S.C. 355(b), to require certain patent related information to be filed with all new drug applications (NDAs) and with all NDAs previously filed but not yet approved. The FDA is required to publish the patent information upon approval of the NDA.

Section 102(a)(2) of the bill amends section 505(c) of the Act, 21 U.S.C. 355(c), to require that any previously approved NDA be amended within 30 days of enactment of this bill to include certain patent related information. The FDA is required to publish the patent information upon its submission. In order to accommodate these provisions, the current text of section 505(c) of the Act, 21 U.S.C. 355(c), is designated paragraph (1) and the new patent related provisions authorized by this bill would be designated paragraph (2)(A) and (B).

The patent information required includes the patent number and the expiration date of any patent which claims the drug in the NDA or which claims a method of using such drug with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engages in the manufacture, sale or use of the drug. When a patent is issued after the filing of a NDA, but before its approval by the FDA, the application would have to be amended to include the patent number and expiration date.

Section 102(a)(3)(A) of the bill amends section 505(d) of the Act, 21 U.S.C. 355(d), to provide that pending and future NDAs may not be approved unless they contain the described patent information. Appropriate redesignations of clauses of subsection (d) are authorized to accommodate this change.

Section 102(a)(3)(B) of the bill amends section 505(e) of the Act, 21 U.S.C. 355(e), to provide that a NDA may be revoked if the patent information is not filed within 30 days after receipt of a written notice from the FDA specifying the failure to provide that information.

Section 102(b)(1)-(6) of the bill amends provisions of existing law, as appropriate, in order to reconcile internal references to substantive and sectional changes that are proposed by the bill.

Section 103(a) of the bill amends section 505(b) of the Act, 21 U.S.C. 355(b), relating to the filing of a NDA, to redesignate subsection (b) as subsection (b)(1), and clauses therein presently numbered (1) through (6), as clause (A) through (F). Substantively, the changes proposed by section 103 of the bill, require an applicant filing a Paper NDA for a listed drug under subsection (j)(6) of the bill, relating to drugs that may be considered for generic treatment, to make the same certifications regarding patents as apply

to the filing of an ANDA under subsection (j) of this bill. The FDA is required to make approval of Paper NDAs under the same conditions that apply to ANDAs submitted under proposed subsection (j). Finally, section 103 would apply the 10 year transition rule and the 4 year unpatentable substances rule to Paper NDAs.

Paper NDAs are defined as any application submitted under section 505(b) of the Act, 21 U.S.C. 355(b), in which the investigations relied upon by the applicant to show safety and effectiveness were not conducted by or for the applicant and the applicant has not obtained a right of reference or use from the person who conducted the investigations or for whom the investigations were conducted. Proposed paragraph (2).

Under subparagraph (2)(A), a Paper NDA which is submitted for a listed drug under subsection (j)(6) would have to include a certification by the applicant regarding the status of certain patents applicable to the listed drug if such information has been provided to the FDA. With respect to all product patents which claim the listed drug and all use patents which claim an indication for the drug for which the applicant is seeking approval (i.e., controlling use patent), the applicant must certify, as to one of four circumstances.

First, the applicant may certify that the patent information required under section 505 (b) and (c) of the Act, 21 U.S.C. 355 (b) and (c), as amended by this bill, has not been submitted if that is the case. Second, if appropriate, the applicant may certify that one or more of the product or controlling use patents provided have expired. Third, the applicant may certify when appropriate that one or more of the product or controlling use patents will expire at some specified future date. Finally, an applicant may certify on the basis of non FDA—supplied information that one or more of the product or controlling use patents are invalid or will not be infringed. Proposed subparagraph (2)(A)(i)–(iv).

When applicable, a Paper NDA for a listed drug must also state that the applicant is not seeking approval for an indication which is claimed by any use patent for which it has not made a certification. Proposed subparagraph (2)(B).

If an applicant certifies that any product or controlling use patent is invalid or will not be infringed, paragraph (3)(A) requires that it must give notice of such certification to either the owner of the patent or the representative of the patent owner who was designated under section 505 (b) or (c) of the Act, 21 U.S.C. 355 (b) or (c), as amended by this bill.

Paragraph (3)(B) requires that such notice state that a Paper NDA has been submitted to obtain approval of the drug to engage in the commercial manufacture, use or sale of the generic drug before the expiration of the patent which has been certified as invalid or not infringed.

Paragraph (3)(C) provides that if a Paper NDA is amended after submission to include a certification that a product patent or controlling use patent is invalid, notice of such certification must be given to the appropriate parties at the time the amended application is submitted.

Section 103(b) of the bill deals with the effectiveness of approval of a Paper NDA for a listed drug. Accordingly, section 505(c) of the Act, 21 U.S.C. 355(c), as amended by section 102(a)(2) of the bill, is

further amended to require the FDA to make approval effective as appropriate in light of relevant, patent-related circumstances.

If the applicant certified in the Paper NDA that no patent information was supplied or that the relevant patents have expired, approval of the Paper NDA may be made immediately effective. If the applicant certified on the basis of supplied information that the patent would expire on a specified future date, the Paper NDA may be approved and the approval becomes effective on that date.

Generally, if the applicant certifies that one or more of the product or controlling use patents were invalid or not infringed, approval of the Paper NDA becomes immediately effective. However, if within 45 days after receipt of notice of the certification of invalidity or non-infringement, an action for patent infringement regarding one or more of the patents subject to the certification is brought, approval of the Paper NDA may not be made effective until 18 months after the notice of certification was provided or a court decision issued. If the court finds the patent is valid or not infringed, then approval shall be effective on the date of the court's order. If the court decides the patent has been infringed an order under 35 U.S.C. 271(e) shall issue. Each party to the action has an affirmative duty to reasonably cooperate in expediting the action and the court may shorten or extend the 18-month period, as appropriate, when either party breaches that duty.

No action for a declaratory judgment with respect to the patent may be brought before the expiration of the 45 day period which begins with the giving of notice of the certification of patent invalidity or non-infringement. At the end of the 45 days, a suit for declaratory judgment regarding the patent in question may be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

Subparagraph (D) denies the FDA the authority to make effective the approval of a Paper NDA for a drug which contains an active ingredient (including any ester or salt of the active ingredient) that was approved for the first time in an NDA between January 1, 1982 and the date of enactment of this bill until 10 years after the date of approval of the NDA.

Section 104 of the bill adds a new subsection (1) to section 505 of the Act, 21 U.S.C. 355, which makes hitherto undisclosed safety and effectiveness information that has been submitted in an NDA available to the public upon request. Absent extraordinary circumstances, safety and effectiveness information and data shall be disclosed in the following circumstances: (1) if the NDA is abandoned; (2) if the FDA has determined that the NDA is not approvable and all legal appeals have been exhausted, (3) if approval of the NDA under section 505(c) of the Act, 21 U.S.C.A. § 355(c), has been withdrawn and all legal appeals have been exhausted, (4) if the FDA has determined that the drug is not a new drug, or (5) upon the effective date of approval of the first ANDA which refers to the drug or upon the date which an ANDA could have been approved if an application had been submitted.

Section 104 of the bill adds a new subsection (m) to section 505 of the Act, 21 U.S.C. § 355, to define the term "patent" to mean a patent issued by the Patent and Trademark Office of the Department of Commerce.

Section 105(a) of the bill requires the FDA to promulgate rules to implement new subsection (j). These rules, which shall be issued within one year of enactment of this bill, shall be promulgated in accordance with the informal rulemaking requirements of the APA, 5 U.S.C. 553.

Section 105(b) of the bill establishes an interim procedure for approving ANDAs for post-1962 drugs until the final regulations become effective. During the year following enactment of this bill, ANDAs for listed post-1962 drugs may be submitted in accordance with the current regulations applicable to pre-1962 pioneer drugs: 21 C.F.R. 314.2. In the event of inconsistencies between current regulations and the Act as amended by this bill, FDA shall follow the latter. However, the FDA may not approve an ANDA or Paper NDA under this interim procedure for a drug which is described in section 505(c)(3)(D) or section 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act.

Section 106 of the bill amends 28 U.S.C. 2201 to insert a cross reference indicating that certain declaratory judgment actions involving patents controversies cannot be brought except as authorized by this bill.

#### *Title II—Patent Extension*

Section 201 of the bill adds a new section 156 to title 35, to extend the normal 17 year term of a product, use, or process patent in the case of a patented product which is subject to pre-marketing clearance (as defined in this Act).

Under proposed section 156(a) the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product is extended from its original expiration date if certain, specified conditions are met. The conditions that permit an extension of patent life are set forth in eight numbered paragraphs.

Paragraph (1) requires the patent to be in force at the time an application for extension is submitted to the Commissioner of Patents and Trademarks.

Paragraph (2) allows extension only if the term of the patent has never been extended. Thus, the extension authorized by the bill is a one time extension.

Paragraph (3) requires the application for extension to be submitted by the owner of record of the patent, or its agent, in accordance with the requirements of subsection (d), *infra*.

Paragraph (4), which consists of two subparagraphs, applies to product and use patents, not process patents. Subparagraph (A) permits a product or use patent to be extended if two requirements are met. First, the approved product has to be one that has not been claimed in another product patent which was issued earlier or which was previously extended. Second, the approved product and the use approved for the product may not have been identically disclosed or described in another product patent which was issued earlier or which was previously extended.

Subparagraph (B) permits a product patent to be extended notwithstanding that it would not qualify under subparagraph (A) under certain circumstances. In order to be extended in these cir-

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Paragraph (6)(C) of proposed subsection (j) provides that a drug may not be listed as eligible for consideration in an ANDA if the approval of the former or pioneer drug is withdrawn or suspended for safety or effectiveness reasons under section 505(e)(1)-(4) of the Act, 21 U.S.C. § 355(e)(1)-(4), or if approval of the generic drug was withdrawn or suspended under paragraph (j)(5), supra, as authorized by this bill. Also, a drug may not be listed if the FDA determines that it has been voluntarily withdrawn for reasons of safety or effectiveness. In the event such a drug has already been listed, it must be immediately removed from the list.

A drug may not be listed so long as its approval is withdrawn or suspended. If the drug has been voluntarily withdrawn from market, it may not be listed until the FDA determines that the drug was not withdrawn from sale for safety or effectiveness reasons. A notice removing any drug from the FDA list regarding availability for copy shall be published in the Federal Register.

## VII. STATEMENT OF LEGISLATIVE INTENT - ANDAS

THE FOLLOWING STATEMENTS HELP TO CLARIFY THE LEGISLATIVE INTENT BEHIND TITLE I OF THE STATUTE, WHICH AUTHORIZES NEW ANDA PROCEDURES. ALTHOUGH ANDAS HAD PREVIOUSLY BEEN AVAILABLE FOR PRE-1962 DRUG PRODUCTS, WHICH DID NOT REQUIRE A SHOWING OF EFFECTIVENESS TO BE MARKETED, THE STATUTE CREATED A SIMPLIFIED APPROVAL PROCEDURE FOR POST-1962 PRODUCTS AS WELL. BEFORE PASSAGE OF THIS BILL, POST-1962 DRUGS COULD BE APPROVED ONLY THROUGH A FULL NDA INCLUDING HUMAN CLINICAL TRIALS, OR THROUGH A PAPER NDA, WHICH IS A FULL NDA WHERE THE HUMAN CLINICAL TRIALS ARE SUBMITTED FROM PUBLISHED OR NON-PROPRIETARY SOURCES RATHER THAN FROM NEW CLINICAL STUDIES. THE STATUTE CONTINUES THE AVAILABILITY OF PAPER NDAs FOR POST-1962 DRUG APPROVAL, ALTHOUGH IT IS EXPECTED THAT MOST APPLICATIONS WILL TAKE ADVANTAGE OF THE NEW ANDA PROCEDURES.

### CONGRESSIONAL REPORTS:

THE FOLLOWING EXCERPTS FROM THE HOUSE REPORTS WILL HELP TO CLARIFY THE MEANING OF THESE PROVISIONS:

HOUSE REPORT PART I, AT PAGES 14-15, 16-17:

## PURPOSE AND SUMMARY

### TITLE I

The purpose of Title I of the bill is to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962. Under current law, there is a generic drug approval procedure for pioneer drugs approved before 1962, but not for pioneer drugs approved after 1962.

Title I of the bill generally extends the procedures used to approve generic copies of pre-62 drugs to post-62 drugs. Generic copies of any drugs may be approved if the generic is the same as the original drug or so similar that FDA has determined the differences do not require safety and effectiveness testing.

Title I also requires patent owners to submit information to FDA regarding produce and use patents that cover approved drugs. Generic copies of these drugs may be approved when the patents expire unless the generic company certifies that the patent is invalid or will not be infringed. In such cases, the generic company must notify the patent owner about its certification and approval of the generic drug may not be made effective until the court decides the suit for patent infringement or a period of 18 months, whichever occurs first. Notification must be given when the generic has submitted an ANDA with bioequivalence data.

In addition, Title I affords four years of exclusive market life to drugs which may not be patented and which are approved for the first time after enactment of the bill. Further, drugs which were approved for the first time between 1982 and the date of enactment received ten years of exclusive market life.

## BACKGROUND AND NEED FOR THE LEGISLATION

### TITLE I—ABBREVIATED NEW DRUG APPLICATIONS

Prior to 1962, the Federal Food, Drug and Cosmetic Act (FFDCA) required that all drugs be approved as safe before they could be marketed. The 1962 amendments required that all new drugs, generic and pioneer, must be approved as safe and effective prior to marketing.

As a result of the 1962 amendments, FDA did two things regarding pre-1962 drugs. First, the agency created the Drug Efficacy Study (DESI) to determine if all pre-1962 drugs were effective. Second, FDA established a policy permitting the approval of a generic drug equivalent to a safe and effective pre-1962 pioneer drug.

As a result of the 1962 amendments, the manufacturer of a pioneer drug must conduct tests on humans that show the product to be safe and effective and submit the results in a new drug application (NDA). A manufacturer of a generic drug must conduct tests that show the generic drug is the same as the pioneer drug and that it will be properly manufactured and labeled. This information is submitted in an abbreviated new drug application (ANDA).

The only difference between a NDA and an ANDA is that the generic manufacturer is not required to conduct human clinical trials. FDA considers such retesting to be unnecessary and wasteful because the drug has already been determined to be safe and effective. Moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective.

The FDA allows this ANDA procedure only for pioneer drugs approved before 1962. There is no ANDA procedure for approving ge-

neric equivalents of pioneer drugs approved after 1962. While the FDA has been considering since 1978 an extension of the pre-1962 ANDA policy to post-1962 drugs, it has not extended the regulation. Because of the agency's failure to act, Title I of H.R. 3605 is necessary to establish a post-1962 ANDA policy.

Some have suggested that "Paper NDAs" be used to approve generic equivalents of pioneer drugs approved after 1962. Under the Paper NDA procedure, the generic manufacturer may submit scientific reports, instead of clinical trials, to support findings of safety and efficacy. This procedure is inadequate, however, because FDA estimates that satisfactory reports are not available for 85 percent of all post-1962 drugs.

\* \* \* \*

Currently, there are approximately 150 drugs approved after 1962 that are off patent and for which there is no generic equivalent. All of these drugs could be approved in generic form if there was a procedure. Each year, more pioneer drugs go off patent and become available for approval as generics.

Among the drugs available or soon to be available for generic approval are five best sellers: valium, motrin, inderal, dyazide, and lasix. Dyazide, for example, is the most widely used diuretic for the treatment of high blood pressure. Its patent expired in 1981. Valium is a popular tranquilizer whose patent expires in 1985. Another drug whose patent has expired is indocin, an anti-inflammatory drug used in the treatment of arthritis that is the tenth highest selling drug in the United States.

The availability of generic versions of pioneer drugs approved after 1962 would save American consumers \$920 million over the next 12 years. Older Americans, in particular, would benefit because they use almost 25 percent of all prescription drugs.

Moreover, the lack of generics for post-1962 pioneer drugs will cost Federal and State governments millions of dollars. For the drug metronidazole, purchased by the Department of Defense, the taxpayers saved approximately \$1.2 million in one year as a result of the availability of a lower priced generic version. Federal and State governments will be denied comparable savings on drugs approved after 1962 because of the lack of an approval procedure.

## HOUSE REPORT PART 2 AT PAGE 5:

### SUMMARY OF H.R. 3605

H.R. 3605 contains two titles. The first title of the bill creates a new system for the approval of generic drugs by the Food and Drug Administration. This approval process for drugs approved by the FDA after 1962 has been severely criticized as too cumbersome and expensive. In essence the provisions of title I of H.R. 3605 extend the procedures for approval of generics for pre-1962 drugs to the later class of drugs.

Thus, under H.R. 3605 a general manufacturer may submit to FDA a request for approval of a generic substitute for any post-1962 drug. The generic manufacturer must establish that the proposed substitute is the same or therapeutically equivalent to the drug which has already been approved.

Under the approval process in H.R. 3605, a generic manufacturer may submit an application for approval to FDA before the so-called pioneer drug goes off patent. The generic may submit data establishing bioequivalency during this time period. In order to complete this application the generic manufacturer must conduct certain drug tests. In order to facilitate this type of testing, section 202 of the bill creates general exception to the rules of patent infringe-

ment. Thus, a generic manufacturer may obtain a supply of a patented drug product during the life of the patent and conduct tests using that product if the purpose of those tests is to submit an application to FDA for approval.

H.R. 3605 permits generic applications to be effective after a patent expires. In addition, H.R. 3605 provides that a generic manufacturer may request FDA approval to begin marketing before the patent on the drug has expired. Under current law, this situation is not an issue because of the cumbersome approval process. If the generic manufacturer seeks such an approval it must allege that the existing patent is invalid or will not be infringed. In this instance notification must be given by the generic to the patent holder concerning the application for FDA approval. In these cases the FDA may not approve the generic application until either: (1) 18 months have expired or (2) a court has determined that no infringement will take place. After the expiration of 18 months, if there has been no intervening judicial determination, the FDA will approve the generic application, even if the drug is still on patent.

Finally, title I also provides for a four year grant of market exclusivity to be granted by the Commissioner of the FDA for unpatentable substances which have been approved for use as drugs by the FDA.

# **GENERIC AND INNOVATOR DRUGS**\_\_\_\_\_

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Requirements***

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***Fifth Edition***

***Donald O. Beers***



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## § 2.01 GENERALLY

The 1984 Waxman-Hatch Act amendments to the FDCA left intact one option for FDA approval of generic drugs that had existed previously. Approval of a generic drug can still be obtained by submitting a new drug application to the agency pursuant to FDCA Section 505(b).<sup>1</sup> That application is, however, required to contain full safety and effectiveness testing of the drug, the type of testing necessary to obtain approval of a pioneer product.

Two subsequent changes apply to applications submitted pursuant to Section 505(b). First, the 1984 amendments added a new item that must be included in a 505(b) application—certification concerning the patent status of the drug covered by the application.<sup>2</sup> Second, in 1985,

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<sup>1</sup> 21 U.S.C. 355(b). The FDA interpreted that section to provide three separate mechanisms for approval of generic copies of approved drugs: full NDAs, ANDAs, and “paper NDAs.” The latter two options were available, however, only in limited circumstances, and were directly addressed by the 1984 Act. These two kinds of applications will be discussed in the next chapter.

Antibiotic drugs were, before November 20, 1997, approved under a different provision, FDCA Section 507, 21 U.S.C. 357. That section has now been repealed, but its prior existence is relevant to the applicability to antibiotics of the patent information, patent certification, and market exclusivity provisions of the Act. See Section 4.02[1] *infra*. For biologic drugs, which are otherwise covered by the FDCA, the FDA considers product licensing under Section 351 of the Public Health Service Act, 42 U.S.C. 262, to be a substitute for NDA approval under 21 U.S.C. 355. See Section 351(j) of the Public Health Service Act, 42 U.S.C. 262(j). Animal drugs are approved pursuant to FDCA Section 512, 21 U.S.C. 360b. This volume does not discuss the animal drug provisions, which parallel the human drug provisions in many respects but also deviate in important ways. (The potential for residues of animal drugs in food-producing animals produces, for example, sometimes complex legal questions.) This volume does discuss, however, the provisions of the Generic Animal Drug and Patent Term Restoration Act of 1988. That statute provides for abbreviated new animal drug applications (“ANADAs”) for generic copies of innovator drugs approved under new drug applications (“NADAs”) and permit patent term extension for animal drugs. As will be seen, it raises many of the same issues presented by the Waxman-Hatch Act.

<sup>2</sup> FDCA Section 505(b)(1), (c)(2), 21 U.S.C. 355(b)(1), (c)(2). See Section 2.01[C], *infra*.

## § 2.01

the FDA issued new regulations on the content of and procedures applicable to new drug applications.<sup>3</sup>

## § 2.02 NEW DRUG APPLICATIONS—CONTENT

### [A] Safety and Effectiveness Data

An NDA filed pursuant to Section 505(b) must contain “full reports of investigations which have been made to show whether or not [the] drug is safe for use and whether [the] drug is effective in use.”<sup>4</sup> Safety studies include studies of the pharmacologic properties of the drug relating to potential adverse reactions;<sup>5</sup> animal toxicology studies, including, as appropriate, acute, subacute, and chronic toxicity testing; carcinogenicity studies; any studies related to the drug’s particular mode of action or conditions of use;<sup>6</sup> reproduction and teratology studies;<sup>7</sup> and studies on drug absorption, distribution, metabolism, and excretion in animals.<sup>8</sup> The results of safety testing in humans must also be submitted, including pharmacokinetic and bioavailability data;<sup>9</sup> clinical pharmacology data;<sup>10</sup> and any available information on adverse reactions, drug-drug interactions, or other safety considerations.<sup>11</sup>

The effectiveness studies required for approval of an NDA must include “adequate and well-controlled . . . clinical investigations.”<sup>12</sup> Historically, FDA has interpreted the “s” on “investigations” as a statutory requirement of at least two investigations, although FDA deviated

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<sup>3</sup> 50 Fed. Reg. 7452 (Feb. 22, 1985).

<sup>4</sup> FDCA Section 505(b)(1)(A), 21 U.S.C. 355(b)(1)(A).

<sup>5</sup> 21 C.F.R. 314.50(d)(2)(i) (1997).

<sup>6</sup> 21 C.F.R. 314.50(d)(2)(ii) (1997).

<sup>7</sup> 21 C.F.R. 314.50(d)(2)(iii) (1997).

<sup>8</sup> 21 C.F.R. 314.50(d)(2)(iv) (1997).

<sup>9</sup> 21 C.F.R. 314.50(d)(3) (1997).

<sup>10</sup> 21 C.F.R. 314.50(d)(5)(i) (1997)

<sup>11</sup> 21 C.F.R. 314.50(d)(5)(vi)(a) (1997). Safety data acquired after submission of an NDA must be provided to the FDA in periodic “safety update reports,” submitted four months after initial NDA submission, following receipt of an approvable letter (*i.e.*, a letter stating that the NDA can be approved if relatively minor issues are resolved), 21 C.F.R. 314.110 (1997), and whenever else the FDA requests one, 21 C.F.R. 314.50(d)(5)(vi)(b) (1997).

<sup>12</sup> FDCA Section 505(d), 21 U.S.C. 355(d).