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April 15, 2003

VIA FEDERAL EXPRESS

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD, 20857

Re: Loratadine Tablets 10 mg.; L. Perrigo Company;
Petition for Rejection of Section 505(b)(2) NDA

CITIZEN PETITION

On behalf of our client Genpharm Inc. of Etobicoke, Ontario, Canada, sponsor of tentatively-approved ANDA 76-154 for loratadine tablets, 10 mg., we submit this Citizen Petition in quadruplicate pursuant to 21 U.S.C. § 355 and 21 C.F.R. § 10.30.

A. Action Requested

This Citizen Petition requests the U.S. Food and Drug Administration to send a prompt letter ruling to L. Perrigo Company ("Perrigo"), refusing to approve the Section 505(b)(2) New Drug Application ("505(b)(2) NDA") for loratadine tablets, 10 mg. which is being improperly maintained by that company.

B. Statement of Grounds

1. Perrigo recently disseminated to the pharmaceutical trade the attached promotional piece, which states on its second page that Perrigo has filed a 505(b)(2) NDA, as well as an Abbreviated New Drug Application ("ANDA"), for the same drug product: loratadine tablets, 10 mg. (hereafter "Perrigo's loratadine product").

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Perrigo's 505(b)(2) NDA for its loratadine product cannot be approved because:

(a) a 505(b)(2) NDA can only be approved for a drug product which is a new chemical entity, or which includes a change from a previously approved drug product requiring submission of new clinical data or information;

(b) the approval of an ANDA is mandatory for a duplicate of an already approved drug; and

(c) Perrigo's loratadine product is a duplicate of Claritin® brand of loratadine 10 mg. tablets, does not include any change from Claritin®, and therefore must be approved via an ANDA.

2. **Perrigo's loratadine product is ineligible for approval via a 505(b)(2) NDA.** In this regard, FDA's guidance document entitled *Guidance for Industry: Applications Covered by Section 505(b)(2)* ("505(b)(2) Guidance," copy attached) provides in pertinent part:

> **"What kind of application can be submitted as a 505(b)(2) application?**
>
> *1. New chemical entity (NCE)/new molecular entity (NME)*
>
> A 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and as to which the applicant has not obtained a right of reference...
>
> * * * *
>
> *2. Changes to previously approved drugs*
>
> For changes to a previously approved drug product, an application may rely on the Agency's finding of safety and effectiveness of the previously approved product, coupled with he information needed to support the change from the approved product. The

additional information could be new studies conducted by the applicant or published data. This use of Section 505(b)(2), described at 21 CFR 314.54, was intended to encourage innovation without creating duplicate work...

* * * *

What are some examples of 505(b)(2) applications?

Following are examples of changes to approved drugs for which 505(b)(2) applications should be submitted...

- Dosage form
- Strength [lower or higher]
- Route of Administration
- Substitution of an active ingredient in a combination product
- Formulation [different quality or quantity of an active ingredient]
- Dosing regimen
- Active ingredient [different salt, ester, complex, chelate, clathrate, racemate, or enantiomer]
- Combination [new]
- Indication [new]
- Rx/OTC switch..."

Here, from the face of Perrigo's attached promotional piece, and upon information and belief, Perrigo's loratadine product is not an NCE, and does not incorporate any change from the previously approved drug Claritin®. [1] Thus, Perrigo's loratadine

[1] According to Perrigo's attached piece, its loratadine product has the same active ingredient and strength as Claritin®, and is bioequivalent to Claritin®. It is virtually certain that the loratadine product in Perrigo's 505(b)(2) NDA is a duplicate of Claritin®. (It should also be noted that Perrigo's attached piece appears to constitute pre-approval promotion, in violation of FDA regulation 21 CFR § 312.7).

product is nothing more than a generic formulation of Claritin® brand of 10 mg. loratadine tablets, with none of the permissible changes from Claritin® that would permit utilization of the 505(b)(2) NDA approval mechanism. Accordingly, there is no valid regulatory basis upon which Perrigo can be allowed to maintain its 505(b)(2) NDA for its loratadine product.

A possible pretext for Perrigo's 505(b)(2) NDA was that at the time the application was filed, Claritin® was still on prescription status, and Perrigo's application may have sought approval of 10 mg. loratadine tablets as an OTC product.[2] However, FDA approved a supplemental NDA filed by Schering switching Claritin® to OTC status in November, 2002 while Perrigo's application was still under review, thereby eliminating any valid basis for Perrigo to maintain a 505(b)(2) NDA for its loratadine product. Perrigo's loratadine product must have the same OTC condition of use as Claritin®.

3. **The proper FDA pre-market approval mechanism for Perrigo's loratadine product is an ANDA**. This is clear from FDA's 505(b)(2) Guidance, which states in pertinent part:

> **What can't be submitted as 505(b)(2) applications?**
>
> - An application [for a drug] that is a duplicate of a listed drug and eligible for approval under section 505(j) (see 21 CFR 314.101(d)(9)); or
>
> - An application [for a drug] in which the *only* difference from the reference listed drug is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the

[2] Schering Corporation, manufacturer of Claritin®, announced in March, 2002, that it would seek OTC status for the drug, and an FDA advisory panel had recommended a year earlier that FDA approve such a switch.

site of action is less than the listed drug (21 CFR 314.54(b)(1)); or

- An application [for a drug] in which the *only* difference from the reference listed drug is that the rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is *unintentionally* less than that of the listed drug (21 CFR 314.54(b)(2))[emphasis in the Guidance].

These requirements of FDA's 505(b)(2) Guidance are amply supported by FDA regulation 21 C.F.R. § 314.101(d)(9), which requires the agency to refuse to accept an application for filing if:

> "[t]he application is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act."

Again, based on Perrigo's attached promotional piece and upon information and belief, Perrigo's loratadine product is a duplicate of Claritin 10 mg. loratadine tablets (see note 1, *supra*). Clearly, **Perrigo itself** recognized that an ANDA is the appropriate approval mechanism in this situation, since the first application Perrigo filed for its loratadine product was ANDA 76-301, filed on February 22, 2002.

4. Perrigo's motivation for attempting to gain approval of its loratadine product via a 505(b)(2) NDA can be gleaned from a brief summary of generic drug company filings for 10 mg. loratadine tablets. In September, 1997, Geneva Pharmaceuticals, Inc. ("Geneva") filed the first ANDA for this drug containing a Paragraph IV certification against one of the pertinent listed Orange Book patents, thereby making Geneva eligible for 180 days of generic market exclusivity. Thereafter, ANDAs with paragraph IV certifications were filed by nine other applicants (including Teva Pharmaceuticals USA, Inc., Zenith Goldline Pharmaceuticals, Inc., Andrx Pharmaceuticals, Inc., Mylan Pharmaceuticals, Inc., American Home Products Corp., Impax Laboratories, Inc., Ranbaxy Laboratories

Ltd., Genpharm and Perrigo, in that order). The paragraph IV certifications in all of these ANDAs constituted the basis for infringement actions commenced by Schering, the patent owner, consequently subjecting these ANDAs to automatic 30-month stays of approval. None of the ANDAs following Geneva's could be approved until the expiration of Geneva's 180-day exclusivity period, and until either the 30-month stay expired for the particular ANDA or an appellate court found the patent invalid or not infringed. [3]

Perrigo, clearly realizing that it was the last of the above-noted ten ANDA applicants for 10 mg. loratadine, and that the above-noted restrictions would preclude approval of its ANDA until expiration of Geneva's 180-day exclusivity period and the expiration of its own 30-month stay (not slated to expire until August 25, 2004), evidently decided to filed a separate 505(b)(2) NDA, in addition to its ANDA, for the purpose of circumventing these restrictions.

Perrigo's motive is laid out in its attached promotional piece:

> "In the case of Perrigo's Loratadine 10mg tab product, for which we have filed an NDA, the 30-month stay period will not affect our launch timing. With an NDA, the 30-month stay terminates once there is a decision in the lower court that is adverse to the innovator, unlike an ANDA which requires a final decision after all appeals are exhausted. Since there was an adverse lower court ruling in the Schering-Plough case in August 2002, the 30-month stay has already terminated for Perrigo's NDA, and Perrigo's launch will not be affected by the 30-month stay period rule.

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[3] Because Geneva's ANDA was filed prior to March, 2000, the decision of an appellate court holding the relevant patent invalid or not infringed is the governing judicial event for approval of all such ANDAs sooner than expiration of each 30-month stay. 21 U.S.C. § 355(j)(5)(B)(iii)(I); "Guidance for Industry -- Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act," March 30, 2000.

> ...We filed our NDA (in addition to an ANDA) **specifically so we could get approval early, regardless of what happens in the patent case**. Perrigo is confident enough in our position that we have purchased raw materials and are about to begin packaging product in preparation for launch. (Emphasis added).

Perrigo's "gaming" of the system via its concomitant 505(b)(2) approach, if permitted to succeed, would have the practical effect of moving Perrigo's expected approval date ahead of all ANDA applicants for generic loratadine who have followed the proper ANDA procedure, even though the other applicants had filed their applications months or even years earlier than Perrigo. Allowing Perrigo to move to the head of the line in this fashion -- when it was the last company to file its application -- is demonstrably unfair.

5. Significantly, however, the governing Hatch-Waxman provision and pertinent FDA regulations make it clear that Perrigo's 505(b)(2) NDA, even if it were allowed to be maintained, could not be approved until the end of the 30-month stay, or a court decision of invalidity or non-infringement, in Schering's separate Paragraph IV action against Perrigo based on Perrigo's 505(b)(2) NDA. [4]

Under 21 U.S.C. § 355(c)(3)(C)(i), approval of a 505(b)(2) NDA containing a paragraph IV certification against a listed Orange Book patent must await expiration of an applicable 30-month stay effected by the commencement of a timely infringement action commenced by the patent owner, except that:

> "if before the expiration of such period **the court** decides that such patent is invalid or not infringed, the approval may be made effective on the date of **the court decision**" (emphasis supplied).

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[4] Schering filed another Paragraph IV infringement action against Perrigo based on the paragraph IV certification in Perrigo's 505(b)(2) NDA. Upon information and belief, the 30-month stay in this action will not expire until June, 2005.

Similarly, FDA regulation 21 CFR § 314.107(b)(3)(ii) provides in pertinent part:

> "If before the expiration of the 30-month period...**the court** issues a final order that the patent is invalid, unenforceable or not infringed, approval may be made effective on the date **the court** enters judgment (emphasis supplied).

Manifestly, these provisions mandate that there be a judicial decision of invalidity, unenforceability or non-infringement, **in Schering's action against Perrigo based on the paragraph IV certification in Perrigo's 505(b)(2) NDA,** in order for Perrigo's said application to be approvable prior to expiration of the pertinent 30-month stay in June, 2005. Neither FDA, nor any court, has ever ruled that a judgment of invalidity, unenforceability or non-infringement in another applicant's case will truncate a 505(b)(2) applicant's 30-month stay. [5]

8. Perrigo's 505(b)(2) NDA should be summarily refused approval, for all the reasons set forth above. FDA should issue this ruling to Perrigo before May 1, 2003, the date when Perrigo has announced that it expects a decision on its 505(b)(2) NDA under a PDUFA timetable.

C. Environmental Impact

Petitioner believes that this petition does not require the preparation of an environmental analysis, pursuant to 21 C.F.R. § 25.31(a).

D. Economic Impact

An economic impact statement is required only when requested by FDA,

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[5] This result is not altered by the statement in FDA's above-noted March, 2000 Guidance that the first court decision finding the patent invalid or not infringed will shorten a 30-month stay for approval purposes. That Guidance, by its own terms, applies solely to ANDAs, not to 505(b)(2) NDAs.

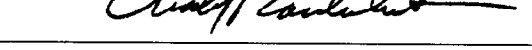
pursuant to 21 C.F.R. § 10.30(b).

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By 

Charles J. Raubicheck

Attorneys for Petitioner GENPHARM INC.

Loratadine 10mg Tab Launch Timing
Perrigo, Leiner/Genpharm and Ranbaxy/Ohm

The intent of this letter is to clarify the launch timing for Perrigo, Leiner and Ranbaxy/Ohm, particularly in regard to how we believe it is affected by the 30-month stay issue.

What is a 30-month stay?
When a company files an ANDA for a product with an existing patent, they are typically sued by the innovator (national brand) company. The FDA will not give final approval to an ANDA if there is patent litigation in process. However, by law, the FDA provides the courts 30 months to settle any patent disputes. If the case is not resolved by the end of the 30-month stay period, the FDA will approve the ANDA (assuming all other filing issues are resolved to the satisfaction of the FDA) and the ANDA holder can launch at risk. The ANDA holder is at risk because the final judgment in the lawsuit may be adverse to the ANDA holder, who would then be exposed to a damage award to the innovator for sales made since the end of the 30-month stay period. The 30-month stay period begins around the time when the ANDA holder files its ANDA, so each applicant's 30-month stay begins and ends at different times.

Ranbaxy/Ohm
Ranbaxy/Ohm has filed an ANDA and has been sued by Schering-Plough. Based on publicly available documents, we believe Ranbaxy/Ohm's 30-month stay expires in November 2003. Therefore, they can not launch until the earlier of either the final decision of the court (after all appeals are exhausted) or November 2003.

Leiner/Genpharm
Genpharm has filed an ANDA and has been sued by Schering-Plough. Based on publicly available documents, we believe Genpharm's 30-month stay expires in December 2003. Therefore, Leiner/Genpharm can not launch until the earlier of either the final decision of the court (after all appeals are exhausted) or December 2003.

Patent Case Status
Schering-Plough lost on Summary Judgment at the lower court and has appealed. We believe the appellate court hearing will be scheduled in April or May. After the hearing, the appellate court will likely take 6 to 12 months to issue a ruling (the average length of time for an appellate court to issue a ruling in a patent case). After the appellate court issues a ruling, Schering-Plough will have 3 months to decide whether to appeal to the Supreme Court. Therefore, even if Schering-Plough loses the appeal and decides not to petition to the Supreme Court, the appellate court decision case will not be "final" three months after it is issued. Of course, the decision could take even longer if Schering-Plough decides to appeal to the Supreme Court or wins in the appellate court (in which case the case will be sent back to the lower court for trial).

Because the 30-month time period expires for Ranbaxy/Ohm in November 2003 and for Leiner/Genpharm in December 2003, we believe that these companies will not receive final approval of their ANDAs until November and December respectively. Their respective

product launches cannot commence until after they receive the final approval. However, even if the appellate court acts with unusual swiftness and rules within two to three months after the oral hearing, the decision will not be "final" until the three month time period for taking the case to the Supreme Court expires with no petition for review being filed. So, even on an expedited basis, the Ranbaxy/Ohm and Leiner/Genpharm ANDAs would not receive final approval until sometime in September or October.

Perrigo

In the case of Perrigo's Loratadine 10mg tab product, for which we have filed an NDA, the 30-month stay period will not affect our launch timing. With an NDA, the 30-month stay terminates once there is a decision in the lower court that is adverse to the Innovator, unlike an ANDA which requires a final decision after all appeals are exhausted. Since there was an adverse lower court ruling in the Schering-Plough case in August 2002, the 30-month stay has already terminated for Perrigo's NDA, and Perrigo's launch will not be affected by the 30-month stay period rule.

Perrigo paid a substantial application fee with our NDA per the Prescription Drug User Fee Act, and with that, the FDA has set an action date of May 1, 2003 for our approval. Perrigo has had no indication to date that the NDA will not be approved on the May 1 action date. A May 1 approval will lead us to a May/June launch date. We filed our NDA (in addition to an ANDA) specifically so we could get approval early, regardless of what happens in the patent case. Perrigo is confident enough in our position that we have purchased raw materials and are about to begin packaging product in preparation for launch.

Bottom Line

Our customers will be best positioned if they plan to launch with Perrigo in May/June. We are confident we will receive approval on May 1 (the FDA action date). Because of the 30-month stay, Ranbaxy/Ohm and Leiner/Genpharm will probably not be able to launch until November/December, respectively. At best, they could launch in September/October if (1) the appellate court acts with unusual swiftness in this several hundred million dollar patent lawsuit by ruling in 2-3 months, and (2) Schering-Plough decides not to appeal (both unlikely). Since Perrigo's action date is at least 4-6 months prior to Leiner/Genpharm and Ranbaxy/Ohm's launch dates, our customers will have adequate time to plan a launch with these companies even under the unlikely scenario that Perrigo doesn't receive approval of its NDA on May 1.

National Brand Equivalency

In a recent customer letter, Ted Green, Vice President of Marketing for Leiner, claimed that Perrigo's Loratadine 10 mg tablet "will **not** be national brand equivalent and **cannot** carry a 'compare to' statement". Mr. Green is incorrect on both counts. Perrigo's product has the same active ingredient, is the same strength, and is bioequivalent (same availability of the drug in the blood stream) to Claritin 10 mg tabs, and received Shuster's highest "VERY GOOD" rating. In addition, during a recent conference with the FDA, they confirmed our ability to use a "compare to" statement with our NDA Loratadine

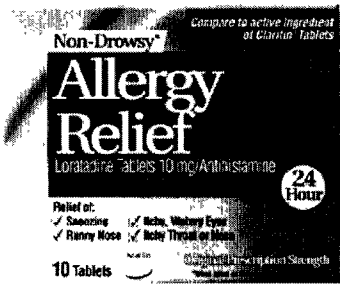
As with most major Switches, it is a confusing time for retailers who must choose their store brand partner. While no company can provide a 100% guarantee, Perrigo is best positioned to provide retailers a timely, cost-friendly 10 mg Loratadine product that is supported by a full marketing plan.

- Launch Timing: May/June 2003
- Complete line with all 5 forms of Loratadine (10mg tabs, D-24, D-12, Redi-Tabs, and Syrup)
- Competitive pricing
- Ability to launch with complete promotional and pharmacy marketing programs

If you or your customers have any further questions on Loratadine plans, please call me.

Sincerely,

Tom Cotter
Category Manager—Cough/Cold/Allergy/Sinus
Perrigo Company
(269) 686-1689
tcotter@perrigo.com



Guidance for Industry

Applications Covered by Section 505(b)(2)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Khyati Roberts, (301) 594-6779.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 1999

Guidance for Industry

Applications Covered by Section 505(b)(2)

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 1999

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Table of Contents

I. WHAT IS THE PURPOSE OF THIS GUIDANCE? 1

II. WHAT IS A 505(B)(2) APPLICATION? 2

A. WHAT TYPE OF INFORMATION *CAN* AN APPLICANT RELY ON?.. 2

B WHAT KIND OF APPLICATION CAN BE SUBMITTED AS A 505(B)(2) APPLICATION?..... 3

III. WHAT ARE SOME EXAMPLES OF 505(B)(2) APPLICATIONS? 4

IV. WHAT CAN'T BE SUBMITTED AS 505(B)(2) APPLICATIONS? 6

V. WHY DOES IT MATTER IF AN NDA IS A 505(B)(2) APPLICATION?..... 6

VI. PATENT AND EXCLUSIVITY PROTECTIONS THAT COULD AFFECT A 505(B)(2) APPLICATION.. 7

A. WHAT TYPE OF PATENT AND/OR EXCLUSIVITY PROTECTION IS A 505(B)(2) APPLICATION ELIGIBLE FOR? 7

B. WHAT COULD DELAY THE APPROVAL OR FILING OF A 505(B)(2) APPLICATION?..... 7

VII. WIIAT SHOULD BE INCLUDED IN 505(B)(2) APPLICATIONS? 7

REFERENCES 10

GLOSSARY..... 11

Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Applications Covered by Section 505(b)(2)

I. WHAT IS THE PURPOSE OF THIS GUIDANCE?

This guidance identifies the types of applications that are covered by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act). A 505(b)(2) application is a new drug application (NDA) described in section 505(b)(2) of the Act. It is submitted under section 505(b)(1) of the Act and approved under section 505(c) of the Act. This guidance also provides further information and amplification regarding FDA's regulations at 21 CFR 314.54.

Section 505 of the Act describes three types of new drug applications: (1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); (2) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and (3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j)). Note that a supplement to an application is a new drug application.

Section 505(b)(2) was added to the Act by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). This provision expressly permits FDA to rely, for approval of an NDA, on data not developed by the applicant. Sections 505(b)(2) and (j) together replaced FDA's *paper NDA policy*, which had permitted an applicant to rely on studies published in the scientific literature to demonstrate the safety and effectiveness of duplicates of certain post-1962 pioneer drug products (see 46 FR 27396, May 19, 1981). Enactment of the generic drug approval provision of the Hatch-Waxman Amendments ended the need for approvals of duplicate drugs through the paper NDA process by permitting approval under 505(j) of duplicates of approved drugs (listed

[1]This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the types of applications that may be submitted pursuant to section 505(b)(2) of the Act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

drugs) on the basis of chemistry and bioequivalence data, without the need for evidence from literature of effectiveness and safety. Section 505(b)(2) permits approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on an Agency finding of safety and/or effectiveness for an approved drug product.

Definitions for specific terms used throughout this guidance are given in the Glossary.

II. WHAT IS A 505(B)(2) APPLICATION?

A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)).

A. What type of information *can* an applicant rely on?

What type of information can an applicant rely on in an application that is based upon studies "not conducted by or for the applicant and for which the applicant has not obtained a right of reference?"

1. Published literature

An applicant should submit a 505(b)(2) application if approval of an application will rely to any extent on published literature (a *literature-based* 505(b)(2)). If the applicant has not obtained a right of reference to the raw data underlying the published study or studies, the application is a 505(b)(2) application; if the applicant obtains a right of reference to the raw data, the application may be a full NDA (i.e., one submitted under section 505(b)(1)). An NDA will be a 505(b)(2) application if any of the specific information necessary for approval is obtained from literature or from another source to which the applicant does not have a right of reference, even if the applicant also conducted clinical studies to support approval. Note, however, that this does not mean ***any*** reference to published general information (e.g., about disease etiology, support for particular endpoints, methods of analysis) or to general knowledge causes the application to be a 505(b)(2) application. Rather, reference should be to specific information (clinical trials, animal studies) necessary to the approval of the application.

2. The Agency's finding of safety and effectiveness for an approved drug

An applicant should submit a 505(b)(2) application for a change in a drug when approval of the application relies on the Agency's previous finding of safety and/or effectiveness for a drug. This mechanism, which is embodied in a regulation at 21 CFR 314.54, essentially makes the Agency's conclusions that would support the approval of

a 505(j) application available to an applicant who develops a modification of a drug. Section 314.54 permits a 505(b)(2) applicant to rely on the Agency's finding of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions at section 505(j). This approach is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug.

It is possible that an applicant could submit a 505(b)(2) application that relies both on literature and upon the Agency's finding of safety and effectiveness for a previously approved drug product (e.g., to support a new claim).

B. What kind of application can be submitted as a 505(b)(2) application?

1. New chemical entity (NCE)/new molecular entity (NME)

A 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference. For an NCE, this data is likely to be derived from published studies, rather than FDA's previous finding of safety and effectiveness of a drug. If the applicant had a right of reference to all of the information necessary for approval, even if the applicant had not conducted the studies, the application would be a considered a 505(b)(1) application.

2. Changes to previously approved drugs

For changes to a previously approved drug product, an application may rely on the Agency's finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product. The additional information could be new studies conducted by the applicant or published data. This use of section 505(b)(2), described in the regulations at 21 CFR 314.54, was intended to encourage innovation without creating duplicate work and reflects the same principle as the 505(j) application: it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug. The approach was described in a letter to industry dated April 10, 1987, from Dr. Paul D. Parkman, then Acting Director of the Center for Drugs and Biologics. This guidance helps to clarify and amplify the approaches stated in the April 10, 1987, letter and in the regulations.

An applicant should file a 505(b)(2) application if it is seeking approval of a change to an approved drug that would not be permitted under section 505(j), because approval will require the review of clinical data. However, section 505(b)(2) applications should

not be submitted for duplicates of approved products that are eligible for approval under 505(j) (see 21 CFR 314.101(d)(9)).

In addition, an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration pursuant to a suitability petition under Section 505(j)(2)(C) of the Act. In the preamble to the implementing regulations for the Hatch-Waxman amendments to the Act, the Agency noted that an application submitted pursuant to section 505(b)(2) of the Act is appropriate even when it could also be submitted in accordance with a suitability petition as defined at section 505(j)(2)(C) of the Act (see 57 FR 17950; April 28, 1992).

III. WHAT ARE SOME EXAMPLES OF 505(B)(2) APPLICATIONS?

Following are examples of changes to approved drugs for which 505(b)(2) applications should be submitted. Please note that in particular cases, changes of the type described immediately below may not require review of information other than BA or BE studies or data from limited confirmatory testing.[2] In those particular cases, approval of the drug may also be sought in a 505(j) application based on an approved suitability petition as described in section 505(j)(2)(C) of the Act. The descriptions below address the situation in which the application should be filed as a 505(b)(2) application because approval of the application will require review of studies beyond those that can be considered under section 505(j). Some or all of the additional information could be provided by literature or reference to past FDA findings of safety and effectiveness for approved drugs, or it could be based upon studies conducted by or for the applicant or to which it has obtained a right of reference.

- *Dosage form.* An application for a change of dosage form, such as a change from a solid oral dosage form to a transdermal patch, that relies to some extent upon the Agency's finding of safety and/or effectiveness for an approved drug.

- *Strength.* An application for a change to a lower or higher strength.

- *Route of administration.* An application for a change in the route of administration, such as a change from an intravenous to intrathecal route.

- *Substitution of an active ingredient in a combination product.* An application for a change in one of the active ingredients of an approved combination product for another active ingredient that has or has not been previously approved.

Following are additional examples of applications that may be accepted pursuant to section 505(b)(2) of the Act. Some or all of the additional information could be provided by the literature or reference to

[2] Limited confirmatory testing is explained in further detail in 54 FR 288872, 28880 (July 10, 1989) and 57 FR 17950, 17957-58 (April 28, 1992)

past FDA findings of safety and effectiveness for approved drugs, or it could be based on studies conducted by or for the applicant or to which it has obtained a right of reference.

- *Formulation.* An application for a proposed drug product that contains a different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application.

- *Dosing regimen.* An application for a new dosing regimen, such as a change from twice daily to once daily.

- *Active ingredient.* An application for a change in an active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety.

- *New molecular entity.* In some cases a new molecular entity may have been studied by parties other than the applicant and published information may be pertinent to the new application. This is particularly likely if the NME is the prodrug of an approved drug or the active metabolite of an approved drug. In some cases, data on a drug with similar pharmacologic effects could be considered critical to approval.

- *Combination product.* An application for a new combination product in which the active ingredients have been previously approved individually.

- *Indication.* An application for a not previously approved indication for a listed drug.

- *Rx/OTC switch.* An application to change a prescription (Rx) indication to an over-the-counter (OTC) indication.

- *OTC monograph.* An application for a drug product that differs from a product described in an OTC monograph (21 CFR 330.11), such as a nonmonograph indication or a new dosage form.

- *Naturally derived or recombinant active ingredient.* An application for a drug product containing an active ingredient(s) derived from animal or botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug.

- *Bioinequivalence.* Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the Act and the proposed product must be shown to be bioequivalent to the reference listed drug (21 CFR 314.101(d)(9)). Applications for proposed drug products where the rate (21 CFR 314.54(b)(2)) and/or extent (21 CFR 314.54(b)(1)) of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence compared to a listed drug may be submitted pursuant to section 505(b)(2) of the

Act. Such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery. Generally, the differences in rate and extent of absorption should be reflected in the labeling of the 505(b)(2) product. The proposed product does not need to be shown to be clinically *better* than the previously approved product; however, a 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application (21 CFR 314.101(d)(9)).

For example, a 505(b)(2) application would be appropriate for a controlled release product that is bioinequivalent to a reference listed drug where:

1. The proposed product is at least as bioavailable as the approved pharmaceutically equivalent product (unless it has some other advantage, such as smaller peak/trough ratio); or

2. The pattern of release of the proposed product, although different, is at least as favorable as the approved pharmaceutically equivalent product.

IV. WHAT CAN'T BE SUBMITTED AS 505(B)(2) APPLICATIONS?

- An application that is a duplicate of a listed drug and eligible for approval under section 505(j) (see 21 CFR 314.101(d)(9)); or,

- An application in which the *only* difference from the reference listed drug is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than the listed drug (21 CFR 314.54(b)(1)); or,

- An application in which the *only* difference from the reference listed drug is that the rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is *unintentionally* less than that of the listed drug (21 CFR 314.54(b)(2)).

V. WHY DOES IT MATTER IF AN NDA IS A 505(B)(2) APPLICATION?

Unlike a full NDA for which the sponsor has conducted or obtained a right of reference to all the data essential to approval, the filing or approval of a 505(b)(2) application may be delayed due to patent or exclusivity protections covering an approved product. Section 505(b)(2) applications must include patent certifications described at 21 CFR 314.50(i) and must provide notice of certain patent certifications to the NDA holder and patent owner under 21 CFR 314.52.

VI. PATENT AND EXCLUSIVITY PROTECTIONS THAT COULD AFFECT A 505(B)(2) APPLICATION

A. What type of patent and/or exclusivity protection is a 505(b)(2) application eligible for?

A 505(b)(2) application may itself be granted 3 years of Waxman-Hatch exclusivity if one or more of the clinical investigations, other than BA/BE studies, was essential to approval of the application and was conducted or sponsored by the applicant (21 CFR 314.50(j); 314.108(b)(4) and (5)). A 505(b)(2) application may also be granted 5 years of exclusivity if it is for a new chemical entity (21 CFR 314.50(j); 314.108(b)(2)). A 505(b)(2) application may also be eligible for orphan drug exclusivity (21 CFR 314.20-316.36) or pediatric exclusivity (section 505A of the Act).

A 505(b)(2) application must contain information on patents claiming the drug or its method of use (21 CFR 314.54(a)(1)(v)).

B. What could delay the approval or filing of a 505(b)(2) application?

Approval or filing of a 505(b)(2) application, like a 505(j) application, may be delayed because of patent and exclusivity rights that apply to the listed drug (21 CFR 314.50(i), 314.107, and 314.108 and section 505A of the Act). This is the case even if the application also includes clinical investigations supporting approval of the application.

VII. WHAT SHOULD BE INCLUDED IN 505(B)(2) APPLICATIONS?

The Act (sections 505(b)(1) and (b)(2)) and FDA regulations (21 CFR 314.54) distinguish between 505(b)(1) and (b)(2) applications. Although the two types of applications must meet the same standards for approval (see section 505(b) and (c) of the Act), they differ in source of information to support safety and effectiveness, the patent certification requirements, BA/BE evidence, exclusivity bars, and processing within the FDA. The requirements for 505(b)(1) and 505(b)(2) applications are described at 21 CFR 314.50. Additional requirements for certain 505(b)(2) applications are described at 21 CFR 314.54.

A 505(b)(2) application should include the following:

- Identification of those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference (for example, for reproductive toxicity studies).

- If the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy for a listed drug or drugs, identification of any and all listed drugs by established name, proprietary name (if

any), dosage form, strength, route of administration, name of the listed drug's sponsor, and the application number (21 CFR 314.54(a)(1)(iii)). Even if the 505(b)(2) application is based solely upon literature and does not rely expressly on an Agency finding of safety and effectiveness for a listed drug, the applicant must identify the listed drug(s) on which the studies were conducted, if there are any. If the 505(b)(2) application is for an NCE and the 505(b)(2) applicant is not relying on literature derived from studies of an approved drug, there may not be a listed drug. If there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.

- Information with respect to any patents that claim the drug or the use of the drug for which approval is sought (21 CFR 314.50(h)). This patent information will be published in the Orange Book when the application is approved.

- Information required under 314.50(j) if the applicant believes it is entitled to marketing exclusivity (21 CFR 314.54(a)(1)(vii)).

- A patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)).

  If there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug. Patent certifications should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.

- If an application is for approval of a new indication, and not for the indications approved for the listed drug, a certification so stating (21 CFR 314.54(a)(1)(iv).

- A statement as to whether the listed drug(s) identified above have received a period of marketing exclusivity (21 CFR 314.108(b)). If a listed drug is protected by exclusivity, filing or approval of the 505(b)(2) application may be delayed.

- A Bioavailability/Bioequivalence (BA/BE) study comparing the proposed product to the listed drug (if any).

- Studies necessary to support the change or modification from the listed drug or drugs (if any). Complete studies of safety and effectiveness may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s).

Before submitting the application, the applicant should submit a plan to the appropriate new drug evaluation division identifying the types of bridging studies that should be conducted. The applicant should also identify those components of its application for which it expects to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The division will critique the plan and provide guidance.

REFERENCES

April 10, 1987, letter from then Acting Director of the Center for Drugs and Biologics to all NDA and ANDA holders and applicants.

"Abbreviated New Drug Application Regulations; Proposed Rule," *Federal Register.* Vol. 54, No. 130, Monday, July 10, 1989, page 28872.

"Abbreviated New Drug Regulations; Final Rule," *Federal Register.* Vol. 57, No. 82, Tuesday, April 28, 1992, page 17950.

"Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule," *Federal Register.* Vol. 59, No. 190, Monday, October 3, 1994, page 50338.

GLOSSARY

505(b)(2) application: an application submitted under section 505(b)(1) of the Act for a drug for which one or more of the investigations relied on by the applicant for approval of the "application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)).

Active ingredient: "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or of animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect" (21 CFR 60.3(b)(2)).

Active moiety: "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance" (21 CFR 314.108(a)).

Investigations relied on for approval: those without which the application cannot be approved (i.e., animal and human safety tests as well as clinical investigations of effectiveness).

Listed drug: "a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product" (21 CFR 314.3(b)).

Literature: published reports of well-controlled studies that support safety or effectiveness; proposed and final monographs published in the *Federal Register*; the data supporting a *Federal Register* notice announcing a product's safety and/or effectiveness.

Orange Book: *Approved Drug Products with Therapeutic Equivalence Evaluations* and any current supplement to the publication.

Pharmaceutical equivalent or duplicate: "drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and,

where applicable, content uniformity disintegration times and/or dissolution rates" (21 CFR 320.1(c)). Products with different mechanisms of release can be considered to be pharmaceutical equivalents or duplicates.

Referenced listed drug: "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3(b)).

Right of reference or use: "the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary" (21 CFR 314.3(b)).

Sponsors have the right of reference to any studies: (1) they conduct, (2) that are conducted for them, or (3) for which they formally obtain a documented *right of reference*.

An applicant is not considered to have a *right of reference* to published studies, because the applicant does not have access to the raw data. However, if the raw data are in the public domain, a right of reference is unnecessary.

Suitability petition: A citizen petition submitted to the Agency seeking permission to file an abbreviated new drug application for a change from a listed drug in dosage form, strength, route of administration, or active ingredient in a combination product. (See section 505(j)(2)(C) of the Act)

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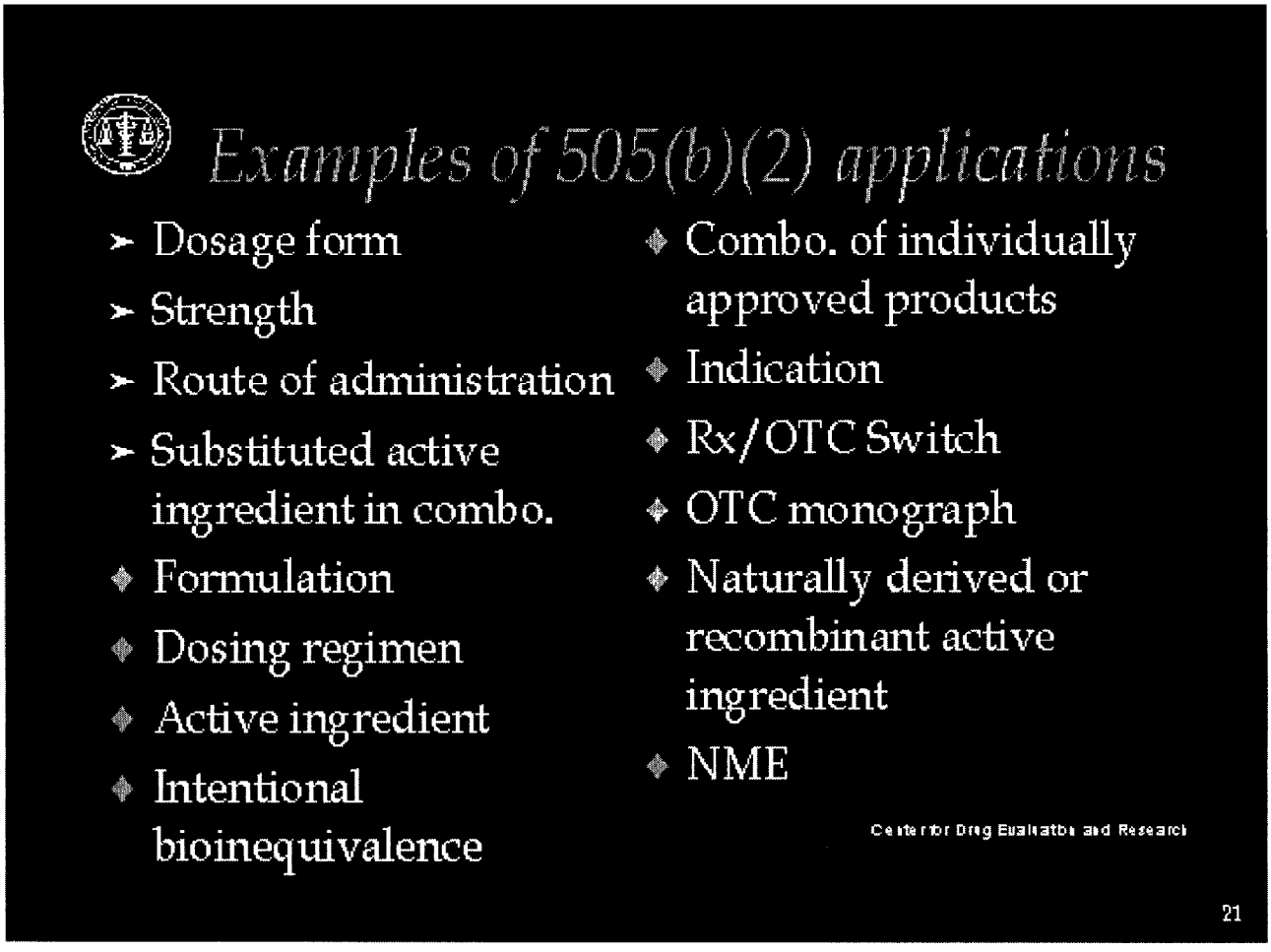
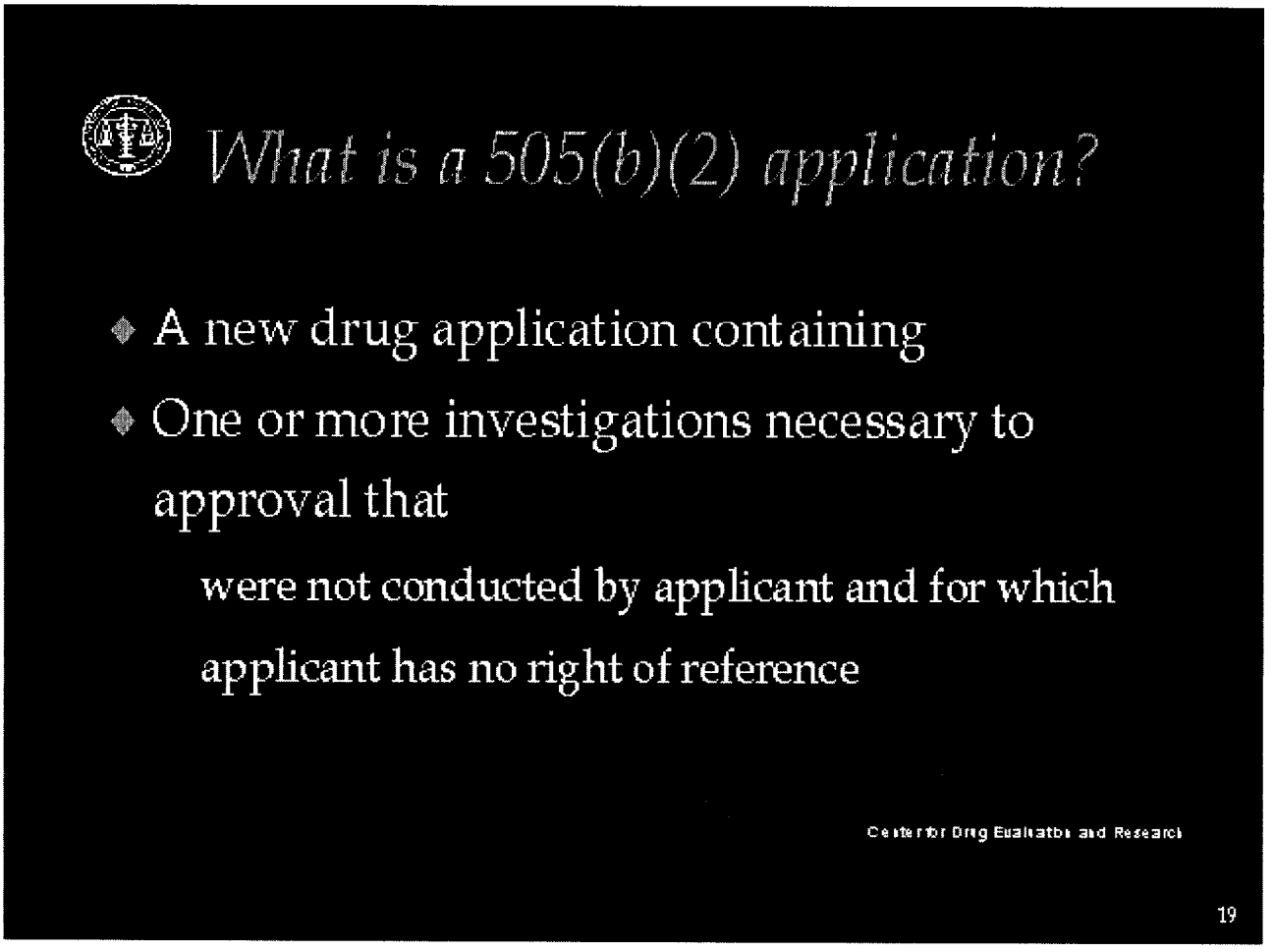


Slide 21 of 24

First Previous Next Last Index Text



Slide 19 of 24