Guidance for Industry

Prussian Blue Drug Products — Submitting a New Drug Application

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

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Clinical Medical

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. 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 statutes and regulations.

I. INTRODUCTION

This guidance is intended to assist manufacturers wishing to submit new drug applications (NDAs) for prussian blue drug products for the treatment of internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. The *Federal Register* notice announcing the availability of this guidances explains in detail the Agency's findings regarding safety and effectiveness and includes a list of the literature on which it based those findings.

II. BACKGROUND

Prussian blue was first synthesized in 1704 by a Berlin color maker named Diesbach. It is used as an industrial and artists' pigment.[2] Since the 1960s, prussian blue also has been used investigationally as an orally ingested drug to enhance the excretion of isotopes of cesium and thallium from the body by means of ion exchange. Prussian blue has a very high affinity for cesium and thallium. Cesium and thallium ions are ordinarily excreted into the intestine, reabsorbed from there into the bile, and then excreted again into the gastrointestinal tract. Orally administered prussian blue traps thallium or cesium in the intestine, interrupts its reabsorption

[1] This document was developed in the Division of Medical Imaging and Radiopharmaceutical Drug Products in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

[2] The chemical name for prussian blue is ferric hexacyanoferrate(II). The name *prussian blue* has been used for various different, but chemically related, compounds used as a blue pigment. However, for purposes of this notice *prussian blue* refers only to insoluble ferric hexacyanoferrate (II), which has an empirical formula of $Fe_4[Fe(CN)_6]_3$ and the Chemical Abstracts Service (CAS) registry number 14038-43-8.

from the gastrointestinal tract, and thereby increases fecal excretion of thallium and cesium. Prussian blue itself is not absorbed across the intestinal wall in significant amounts.[3]
The Agency has concluded that prussian blue, when produced under conditions specified in approved NDAs, can be found to be safe and effective for the treatment of internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. As described below, our conclusion is based upon our review of published information.

III. NDAs SUBMITTED FOR PRUSSIAN BLUE DRUG PRODUCTS

A. Types of NDAs for Prussian Blue

An NDA for a prussian blue drug product may be either:

- a 505(b)(2) application, which is an NDA in which you rely for approval on studies that you did not conduct, that were not conducted for you, or for which you do not have a right of reference (described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(b)(2))

or

- a 505(b)(1) application, an NDA that relies exclusively on studies that you conducted, that were conducted for you, or for which you have a right of reference (submitted under section 505(b)(1) of the act.

After an NDA for a prussian blue drug product has been approved, abbreviated new drug applications (ANDAs) that refer to the approved prussian blue drug product can be submitted and approved (see 21 CFR part 314, subpart c). Because ANDAs cannot be submitted until an NDA is approved, we primarily discuss 505(b)(1) and 505(b)(2) applications in this guidance.

1. Submitting 505(b)(2) Applications

If you rely on published literature, including the literature we have already reviewed (see the *Federal Register* notice announcing the availability of this guidance) for approval of your application, your NDA will be a 505(b)(2) application.

A 505(b)(2) application could be considered the more direct and, probably, the quickest approach to gaining approval of an NDA for a prussian blue drug product. A 505(b)(2) application could rely entirely on the published literature that we have already reviewed for the clinical data required for approval of an NDA (see *Federal Register* notice). If you took this approach to approval, you would not need to submit copies or summaries of the reports we have

[3] Prussian blue, in 500-milligram (mg) capsules, has been distributed by the Radiation Emergency Assistance Center/Training Site (REAC/TS) under investigational new drug application (IND) number 51,700. REAC/TS is part of the Oak Ridge Associated Universities(ORAU). ORAU operates the Oak Ridge Institute for Science and Education (ORISE) under a contract with the Department of Energy. ORISE owns the IND for prussian blue. The 500-mg capsules used under the IND are manufactured by HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG (HEYL). HEYL uses the trade name Radiogardase-Cs for its 500-mg capsules of prussian blue.

cited. The clinical sections of your NDA would only have to cite the *Federal Register* notice and the listed reports we relied on in making our determination of safety and effectiveness.

2. Submitting 505(b)(1) Applications

As mentioned above, you can also submit a 505(b)(1) application. This type of NDA relies only on studies that you conducted, that were conducted for you, or for which you have a right of reference. These NDAs are sometimes called *full NDAs* and are the type of application most frequently used to gain approval for drug products whose active ingredient is not in a previously approved drug product.

We recognize the importance of continuing the development of products, such as prussian blue, to treat or prevent radiation and other types of toxicity. We also recognize that you might not be able to conduct definitive human efficacy studies for prussian blue because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic substance, and new field trials to study prussian blue's efficacy after an accidental or hostile exposure to cesium-137 or thallium might be infeasible. We encourage persons who wish to submit 505(b)(1) applications for prussian blue drug products to contact us, before starting any studies, to discuss the development of data to establish safety and effectiveness.

B. Content of NDAs for Prussian Blue

NDAs submitted to the Agency for approval must include chemistry, manufacturing, and controls information. They must also contain labeling and the appropriate patent information. These requirements are contained primarily in ' 314.50 (21 CFR 314.50).

1. Chemistry, Manufacturing, and Controls Information

In addition to the clinical data discussed in the *Federal Register* notice announcing the availability of this guidance and in section 1.A.2 of this guidance, your NDA must also include a complete chemistry, manufacturing, and controls section describing the composition, manufacture, and specification of the drug substance and drug product (section 355(b)(1) of the act and ' 314.50). You also must meet all other applicable requirements regarding the content of an NDA (section 355(b)(1) of the act and ' 314.50).

HEYL's 500-mg prussian blue capsules were used in the majority of the recent published studies. If you rely on the published literature we reviewed in making our determination about the potential safety and effectiveness of prussian blue, you should submit the results of in vitro studies showing that your product's binding to thallium and nonradioactive cesium is comparable to that of HEYL's product.

2. Labeling for Prussian Blue

We have prepared draft labeling for orally administered drug products containing 500-mg prussian blue capsules. You can use this labeling for drug products as part of a 505(b)(2) application for 500-mg prussian blue capsules. This draft labeling reflects our conclusion on the

potential safety and effectiveness of 500-mg prussian blue drug products for treatment of internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. If you wish to change the labeling to include a different or broader indication, different dosage, or make any other significant changes to the draft labeling, you should provide, as part of your 505(b)(2) application, additional literature or other studies to support your requested changes. If you submit a 505(b)(1) application for a prussian blue drug product, you cannot use this labeling because it is based on our review of the published literature. If you submit a 505(b)(1) application for prussian blue, your labeling must be based on the data contained in your NDA (section 355(b)(1) of the act and § 314.50).

The draft labeling for 505(b)(2) applications is available on the Internet.[4] You may also contact the Center for Drug Evaluation and Research's Division of Medical Imaging and Radiopharmaceutical Drug Products for a copy of the draft labeling.

3. Patent Information

If you submit an NDA (including a 505(b)(2) NDA) for prussian blue, you must file with your NDA a list of the patent numbers and expiration dates for each patent required to be submitted under section 355(b)(1)(F) of the act and § 314.50. You also must submit additional patent information within 30 days of approval of your NDA or, in the case of newly issued patents, within 30 days of issuance of the patent (section 355(c)(2) of the act and § 314.50). If your NDA is approved, we will publish the patent information in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the *Orange Book*).

We publish information regarding patents and exclusivity periods for approved drug products in the *Orange Book*. This information is important if you are considering submitting ANDAs or 505(b)(2) applications for prussian blue drug products. If a drug product listed in the *Orange Book* has listed patents, the 505(b)(2) application or ANDA seeking to rely on the finding of safety or effectiveness for that listed drug must contain certifications regarding those patents (see ' 314.50(i) for 505(b)(2) applications, and § 314.94(a)(12) for ANDAs).

C. Exclusivity

In addition to the protection provided by patents issued by the U.S. Patent and Trademark Office, prussian blue drug products approved by us may be protected from competition by periods of marketing exclusivity that are administered by us. The act provides for periods of marketing exclusivity that prevent us from filing or approving 505(b)(2) applications or ANDAs for drug products that contain the same active moiety[5] as certain previously approved drug products. The active moiety of a prussian blue drug product would be the prussian blue molecule (i.e., the ferric hexacyanoferrate (II) molecule).

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[4] See http://www.fda.gov/cder/foi/label/2003/ind51700lbl.pdf.

[5] *Active moiety* is defined in 21 CFR 314.100(a) as 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.

The following summaries of marketing exclusivity and orphan drug exclusivity are provided solely for the general information of manufacturers considering submitting an NDA for a prussian blue drug product. They should not be read as statements of our general policies regarding marketing exclusivity and orphan drug exclusivity. Our policy can be found in the regulations cited in this guidance.

1. Five-Year Marketing Exclusivity

A 5-year period of marketing exclusivity is provided by section 505(c)(3)(D)(ii) and (j)(5)(D)(ii) of the act when a sponsor obtains approval of an NDA for which no active moiety has been previously approved by the FDA. The 5-year period of marketing exclusivity generally prohibits us from filing a 505(b)(2) application or receiving an ANDA for a drug product that contains the same active moiety as the first drug product containing the active moiety to be approved.[6] The 5-year period of marketing exclusivity begins on the approval date of the first NDA approved for a drug product containing the active moiety. Both 505(b)(1) and 505(b)(2) applications may be entitled to benefit from 5-year marketing exclusivity, but only 505(b)(2) applications and ANDAs are blocked by 5-year marketing exclusivity.

Because we have never approved a drug product that contains the prussian blue molecule as the active moiety, the first NDA approved that contains prussian blue as the active moiety will likely receive 5 years of marketing exclusivity. If 5-year exclusivity is awarded for an NDA containing prussian blue, we cannot file[7] a subsequent 505(b)(2) application for 5 years after the approval date of that NDA. If you have submitted an essentially complete 505(b)(2) application before we approve the first NDA for a prussian blue drug product, review and approval of your 505(b)(2) application would not be blocked by the marketing exclusivity obtained by the first prussian blue drug product approval (54 FR 28872 at 28901, July 10, 1989). However, after we have approved the first NDA for prussian blue, 5-year marketing exclusivity would prohibit us from filing your 505(b)(2) application, no matter how soon after the first approval we received your application.

2. Three-Year Exclusivity

A 3-year period of marketing exclusivity may be applicable to prussian blue drug products sometime in the future. Three-year marketing exclusivity is provided by section 505(c)(3)(D)(iii) and (j)(5)(D)(iii) of the act. Drug products whose active moiety is the same active moiety as that in a previously approved drug product are entitled to 3-year exclusivity if a new clinical study (other than a bioavailabilty or bioequivalence study) is needed for their approval. If a drug product, or change to a drug product, is given 3 years of exclusivity, we are barred for 3 years from approving any 505(b)(2) application or ANDA for the same drug product, or change to the product, that was granted exclusivity. For example, if an applicant obtains 3 years of exclusivity for a new dosage form of prussian blue, FDA may not approve a 505(b)(2) application or an ANDA for that dosage form of prussian blue for 3 years. However,

[6] An exception to the 5-year period permits an applicant to submit a 505(b)(2) application or ANDA after 4 years if it contains a certification of invalidity or noninfringement for a patent listed for the approved drug.

[7] Our regulations regarding filing an NDA and receiving an ANDA are found at 21 CFR 314.101.

we can approve a 505(b)(2) application or an ANDA for any previously approved dosage form not protected by the exclusivity.

Our regulations in § 314.108 provide more details on marketing exclusivity. If you are interested in how marketing exclusivity could affect your NDA for prussian blue, you are encouraged to discuss the issue with the Center for Drug Evaluation and Research's Division of Medical Imaging and Radiopharmaceutical Drug Products. If you believe your drug product is entitled to marketing exclusivity, you must submit supporting information in your NDA (' 314.50(j)).

3. Orphan Drug Exclusivity

In addition to 3- or 5-year marketing exclusivity, orphan drug exclusivity may apply to prussian blue drug products approved for orphan indications. Obtaining orphan drug exclusivity is a two-step process. The regulations require that you seek orphan drug designation for the active moiety of your drug product for an orphan indication before you submit an NDA. If we designate the drug as an orphan drug and then approve it for the designated indication, the drug will receive orphan drug exclusivity. The issues involved in determining which drug products are entitled to orphan drug exclusivity and which drug products are blocked by orphan drug exclusivity are described in our regulations in part 316 (21 CFR part 316). However, we note that orphan drug exclusivity is for a 7-year period and can prohibit us from approving a 505(b)(1) application, a 505(b)(2) application, or an ANDA for the same active moiety for the same indication during the period of exclusivity. This differs from 5-year marketing exclusivity, which prohibits us from filing a 505(b)(2) application or receiving an ANDA, but would not prohibit us filing a 505(b)(1) application.

4. Waiver of Exclusivity

If your right to any type of exclusivity for a prussian blue drug product has vested, you can waive that exclusivity. Your waiver would allow one or more applicants to submit applications for the product. For example, if you obtain 5-year exclusivity with a 505(b)(2) application for a prussian blue drug product, your complete waiver of such exclusivity would enable other applicants to immediately submit 505(b)(2) applications and ANDAs for drug products containing prussian blue.

D. Innovative Prussian Blue Drug Products

We encourage the development of drug products containing prussian blue for the treatment of internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium that represent improvements in safety, effectiveness, or convenience. However, your submission of a 505(b)(2) application for such an innovative product may be blocked by marketing exclusivity if the exclusivity is not waived. If the innovative product is clinically superior to the previously approved drug product, its approval might not be blocked by orphan drug exclusivity (see ' 316.3(b)(13)). Once approved, an innovative product may qualify for 3-year marketing exclusivity. If the innovation presents a commercial advantage over the drug product that enjoys marketing exclusivity, it may be possible to reach an agreement with the person holding the exclusivity to allow marketing of the innovative drug product.