

05 August 2004

Dockets Management Branch of FDA
HFA 305,
Room 1061
5630 Fishers Lane
Rockville MD
20852

To whom it may concern:

**RE: Suitability Petition to Request a Change from the Reference Listed Drug
(New Strength)
Methacholine Chloride
1280 mg/vial**

The purpose of this correspondence is to request approval of a suitability petition pursuant to §314.93 of the Federal Food, Drug and Cosmetic Act.

Background Information:

Provocholine® (methacholine chloride USP) powder for inhalation is indicated for the diagnosis of bronchial airway hyper-reactivity in subjects who do not have clinically apparent asthma. It is not a therapeutic agent but is used as a diagnostic agent. Provocholine® is reconstituted with 0.9% sodium chloride and 0.4% phenol (as a preservative) and serial concentrations (25 mg/mL, 10 mg/mL, 2.5 mg/mL, 0.25 mg/mL and 0.025 mg/mL) are prepared. Patient administration begins with the lowest concentration (0.025 mg/mL) and increasing serial concentrations are administered until there is a 20% reduction in FEV₁ or the highest concentration has been administered. Provocholine® is administered for oral inhalation only and not for injection.

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methapharm inc.

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The safety and efficacy of Provocholine[®] was established in NDA 19-193. The Methacholine Challenge testing has been performed worldwide for over 50 years. Provocholine[®] has been available on the US market as a 100 mg/vial powder for inhalation by Methapharm since 1998. Prior to Methapharm, Hoffman La Roche was responsible for this product from the time of market introduction in 1986.

Reference Listed Drug:

Provocholine[®] (methacholine chloride USP) 100 mg/vial powder for inhalation, is published in the “*Approved Drug Products with Therapeutic Equivalence Evaluations*” (commonly known as the Orange Book), 24th edition.

Reason for Suitability Petition:

Methapharm wishes to submit an Abbreviated New Drug Application for Methacholine Chloride 1280 mg/vial to the Office of Generic Drugs. This represents an increase in the amount of powder fill (1280 mg/vial *versus* 100 mg/vial) from the Reference Listed Drug.

In July 2004, Methapharm submitted an Abbreviated New Drug Application to the Office of Generic Drugs to obtain regulatory approval for Methacholine Chloride 100 mg/vial. The rationale for this submission is so that Methapharm can market both the approved reference listed drug product as well as the generic product.

Comparison of Provocholine[®] 100 mg/vial to Methacholine Chloride 1280 mg/vial:

The proposed generic product, Methacholine Chloride 1280 mg/vial, is the same as the reference listed drug product, Provocholine[®] 100 mg/vial, in the following ways:

- same indication (diagnosis of bronchial airway hyper-reactivity)
- same pharmacological classification (broncho-constrictor for diagnostic purposes)
- same dosage form (powder that requires reconstitution prior to administration)
- same route of administration (oral inhalation)
- same patient dosing regimen (0.025 mg/mL to 25 mg/mL)
- same active ingredient (methacholine chloride USP)
- same inactive ingredients (no excipients)
- same packaging components (20 mL amber glass vials)

Rationale for Marketing Methacholine Chloride 1280 mg/vial:

There are several reasons as to why Methapharm wishes to market a larger powder fill volume of Provocholine® (as a generic product called Methacholine Chloride 1280 mg/vial) These reasons are provided here for your consideration:

1. There are no generic products on the US market for methacholine chloride. However, several companies (e.g., Spectrum Chemical Manufacturing, Ruger Chemical, Sigma-Alerich) sell technical grade crystals directly to the end user. They provide a large volume of powder (such as 1 grams or 25 grams). This bulk chemical is used to perform the Methacholine Challenge testing in patients. As per the FDA “Guidance for FDA Staff and Industry – Compliance Policy Guides Manual, Sec. 460.200, Pharmacy Compounding”, the practice of using an unapproved chemical when a pharmaceutical product is commercially available is not permitted. However, it is the experience of Methapharm that this practice is occurring on a continual basis in the USA. The availability of a generic Methacholine Chloride powder may help to diminish the use of unapproved technical grade crystals.
2. Several distribution centers in the USA sell the technical grade crystals to facilities in the USA. Many facilities place product orders for “Methacholine Chloride”. It is unknown to the facility that the distribution center then supply the unapproved technical grade crystals instead of the FDA approved Provocholine®. When questioned about this practice, the distribution centers say that they are providing a “generic product” instead of the branded product Provocholine®. Methapharm hopes that the availability of an FDA approved generic product, in two strengths, will diminish the use of unapproved technical grade crystals.
3. The powder fill volume of 100 mg allows the testing of 2-5 patients maximum. Several larger facilities test more patients on a daily basis. In order to do this, more powder needs to be provided in the vial. It is important to note that the increase in the amount of powder in the vial **will not** result in an increase in the dosing administered to the patient. It merely allows for more patients to be tested as a larger volume of solution is prepared.

Sterility

Provocholine® 100 mg/vial powder for inhalation is *not* a sterile product. It is however, subject to stringent microbial controls. As per a voice mail message to Jane P. Costaris, Regulatory Affairs Director for Methapharm, Mr. Peter Chen, Office of Generic Drugs at FDA, said it is not an FDA requirement for a generic powder for inhalation to be sterile. Likewise, Methacholine Chloride 1280 mg/vial will be subject to the same stringent microbial controls as Provocholine® 100 mg/vial.

Environmental Considerations (§314.94(a)(9))

Methapharm requests a categorical exclusion from the requirement to prepare an environmental assessment statement.

Methapharm certifies that for the Methacholine Chloride 1280 mg/vial ANDA we are subject to the categorical exclusion from the requirement to prepare an Environmental Assessment statement, as per 21CFR25.31(a). As per the requirements, the 1280 mg/vial ANDA is for a drug product which will not be administered at a higher dosage level, for a longer duration or for different indications than were previously in effect. In addition, at the expected level of exposure, to the best of our knowledge these products are not toxic to organisms in the environment. As well, this drug product is to be used as a diagnostic agent and not a therapeutic agent.

Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.

Marketing Differentiation

In order to ensure that the generic 100 mg/vial is differentiated from the 1280 mg/vial presentation Methapharm proposes the following;

1. Use of different colored flip off seals. The color of the flip off seal for the 100 mg/vial is green whereas the color of the flip off seal for the 1280 mg/vial is black.
2. The vial labels will also be colored coded to match the color of the flip off seals.

In Canada, the Provocholine® 1280 mg/vial has been on the market since 2001. To date, there have not been any adverse events associated with the use of the 1280 mg/vial.

Labeling

The proposed labeling for the generic Methacholine Chloride 1280 mg/vial will be identical to the currently approved labeling for Provocholine® 100 mg/vial, with the following exceptions;

1. Change in powder fill sizes from 100 mg/vial to 1280 mg/vial in “Description and How Supplied” sections.
2. Change in preparation of dilutions to reflect the powder fill volume of 1280 mg *versus* 100 mg in “Dosage and Administration”. This will not result in a higher concentration to be administered to the patient.

The following sections of the package insert will remain unchanged:

1. Warnings Box
2. Indications and Usage
3. Contraindications
4. Precautions
5. Adverse Reactions
6. Overdosage
7. Reference

Supporting Documentation:

Attachment Number	Documentation
1	Approved Provocholine® 100 mg/vial Labeling
2	Proposed Provocholine® 1280 mg/vial Labeling

Conclusion:

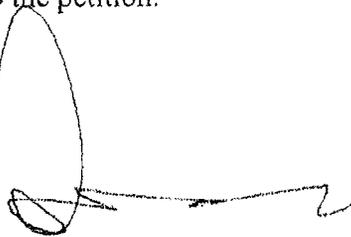
It is our position that the availability of a generic 1280 mg/vial will be beneficial to the larger volume facilities as it will allow for a single reconstitution and more patients will be able to be tested. It is also anticipated that the availability of a generic 1280 mg/vial will help to diminish the use of unapproved technical grade crystals. The availability of a 1280 mg/vial will not compromise the safety or efficacy of the Methacholine Chloride challenge testing.

Thank you for your attention to this matter. We look forward to discussing this with you. Should you have any questions, please do not hesitate to contact Andrew D. Gall, Executive Vice President, at 1.800.287.7686 extension 225 or Jane P. Costaris, Regulatory Affairs Director, at 905.857.3132.

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.

Signature:



Name of Petitioner: Mr. Andrew D. Gall, Executive Vice President

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