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September 19, 2005

Via FedEx

Andrew G. Rozycki, Esq.
Senior Intellectual Property Counsel
Cardinal Health, Inc.
7000 Cardinal Place
Dublin, OH 43017

Re: Paragraph IV Notification Letter for ANDA No. 77-271

Dear Mr. Rozycki:

We write in response to your September 13, 2005 letter notifying Medi-Flex Hospital Products, Inc. ("Medi-Flex") that Cardinal Health, Inc. ("Cardinal") has submitted an Abbreviated New Drug Application ("ANDA") for a generic version of Medi-Flex's drug product ChloroPrep® One-Step (chlorhexidine gluconate 2%, isopropyl alcohol 70%). Cardinal's ANDA, which was assigned No. 77-271, identifies ChloroPrep® One-Step as the reference listed drug and contains paragraph IV certifications for all seven of the patents listed for ChloroPrep® One-Step.

Medi-Flex believes that Cardinal may have identified the wrong reference listed drug and provided certifications for the wrong patents. As you know, on November 18, 2004, Cardinal submitted a suitability petition to the U.S. Food and Drug Administration ("FDA") with respect to Cardinal's ANDA 77-271 requesting approval for a change in ChloroPrep® One Step's applicator volume from 10.5 ml to 26 ml and adding a tint ingredient (i.e., FD&C Red. No. 40) (attachment 1). As indicated in the suitability petition, ANDA 77-271 seeks approval for a generic product with tint. However, the ANDA relies on ChloroPrep® One-Step, which does not contain tint, as the reference listed drug. ChloroPrep® One-Step is not the FDA's designated reference listed drug for such tinted products. Rather, the FDA has specifically designated Medi-Flex's product ChloroPrep® with Tint (chlorhexidine gluconate 2%, isopropyl alcohol 70%) as the reference listed drug for such tinted products. FDA intentionally designates a single

Andrew G. Rozycki, Esq.

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Page 2

reference listed drug for a product to avoid variations between generic products.¹ Cardinal's ANDA for a generic tinted product should have relied on the only reference listed drug identified by FDA for such tinted products, ChloroPrep® with Tint.²

Cardinal's apparent reliance on the wrong reference listed drug seems to be an attempt to circumvent patent protection and Hatch-Waxman exclusivity that would otherwise apply to Cardinal's ANDA. Medi-Flex expended significant resources to perform clinical trials essential to the approval of ChloroPrep® with Tint. Consequently, Medi-Flex was awarded three years of Hatch-Waxman exclusivity, which prohibits FDA from approving any ANDA for such a tinted product until May 3, 2008. Moreover, ChloroPrep® with Tint contains a listed patent directed specifically to tinted products. Complying with FDA rules, Medi-Flex listed that patent only with respect to its tinted product and not with its untinted product. If Cardinal's ANDA is for a tinted product, then Cardinal's suitability petition and designation of the wrong reference listed drug appear to be an attempt to get around the tint patent and Medi-Flex's three-year exclusivity. The FDA has specifically stated that such gamesmanship is not acceptable.

Indeed, as FDA recently explained:

[I]f a tablet and a capsule are approved for the same moiety with patents listed for the tablet and none listed for the capsule, an ANDA applicant seeking approval for a tablet should cite the approved tablet as the reference listed drug. It should not circumvent the patents on the tablet by citing the capsule as the reference listed drug and filing a suitability petition under section 505(j)(2)(C) of the Act and 21 CFR 314.93 seeking to change to a tablet dosage form.

Letter from Galson to Beers and Cavanaugh at 9 fn 13 (Nov. 30, 2004) (attachment 2). In addition to preventing an end-run around patent and exclusivity protections, FDA's requirement that an ANDA rely on the appropriate reference listed drug serves the policy goals of ensuring that ANDA applicants do not re-prove established findings and that the FDA does not re-review previously submitted data.

As the issues detailed above have significant regulatory and patent consequences, please clarify whether Cardinal's ANDA is for a generic product with tint. If Cardinal's ANDA is for a

¹ See FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") 25th Ed. at xi. (2005).

² Medi-Flex acknowledges that ChloroPrep® with Tint was approved on May 3, 2005, several months after Cardinal submitted its suitability petition requesting permission to file an ANDA for a product with tint. However, once approved, Cardinal should have relied on ChloroPrep® with Tint as the reference listed drug or at least resolved the outstanding patent and exclusivity issues related to the tint product (as discussed in this letter). If Cardinal's ANDA is for a tinted product, then Cardinal's actions may indicate an intent to end-run such protections.

Andrew G. Rozycki, Esq.
September 19, 2005
Page 3

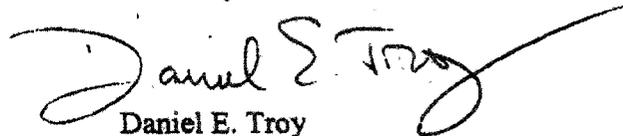
product with tint, then Medi-Flex requests that Cardinal immediately withdraw its paragraph IV notification letter and certify to the correct reference listed drug and patents. In an effort to facilitate a quick resolution and avoid any unnecessary litigation, we also invite Cardinal to contact us to discuss a mutually agreeable solution to this situation.

Additionally, if Cardinal's generic product does not contain tint and the notice letter is deemed appropriate, Medi-Flex believes that the letter is legally deficient. FDA's regulation governing notice requirements specifically states that every notice must contain "[a] statement that FDA has received an abbreviated new drug application submitted by the applicant containing any required bioavailability or bioequivalence data or information." 21 C.F.R. § 314.95(c)(1) (emphasis added). *See also* 21 U.S.C. § 355(j)(2)(B)(iv) (requires the notice letter to reference bioavailability or bioequivalence data). Contrary to FDA's requirements, Cardinal's paragraph IV notice letter does not contain a statement concerning any required bioavailability or bioequivalence data or information. Please amend Cardinal's notice letter to meet the requirements of § 314.95(c)(1).

In the meantime, Medi-Flex is continuing to evaluate its regulatory and patent options, including its analysis of whether Cardinal infringes any of the seven patents identified in the paragraph IV notification letter. Towards that end, Medi-Flex also requests that Cardinal provide additional information concerning its product, including the product's qualitative and quantitative composition, to assist Medi-Flex in determining whether any patent infringement action is warranted. As contemplated by the new amendments to the Hatch-Waxman Act, Medi-Flex requests that Cardinal provide Medi-Flex with confidential access to Cardinal's ANDA for the sole purpose of evaluating potential infringement by Cardinal. Additionally, Medi-Flex requests that Cardinal provide samples of Cardinal's product for an infringement evaluation by Medi-Flex. To ensure the confidentiality of this material, Medi-Flex is willing to enter into an appropriate confidentiality agreement and has provided a proposed confidentiality agreement with this letter (attachment 3).

As noted in your September 13th letter, Medi-Flex has 45-days from the date of receipt of that letter to bring suit under the Hatch-Waxman Act. Therefore, we request that Cardinal respond to this letter by September 30, 2005.

Sincerely,


Daniel E. Troy

cc: Jeffrey E. Fine, Esq.
Michael J. Gross, Esq.
Linda McBride, R.Ph.

ATTACHMENT 1



Cardinal Health

1500 Waukegan road
McGaw Park, IL 60085
847-473-1500

11/18/04

Mr. Gary Buehler
Food and Drug Administration
Office of Generic Drugs
Document Mail Center (HFD-600)
7500 Standish Place
Rockville, MD 20855

Dear Mr. Buehler:

Cardinal Health is submitting this Suitability Petition to the FDA requesting permission to file an ANDA for a preoperative prep containing a chlorhexidine gluconate (CHG) / isopropyl alcohol (IPA) solution with tint. More specifically, the intent of this petition is to address the change in applicator volume from 10.5 ml to 26 ml.

A. Action Requested:

As indicated above, Cardinal Health proposes to file an ANDA based upon the reference listed drug (RLD) ChloroPrep® One-Step chlorhexidine gluconate 2% (w/v) and isopropyl alcohol 70% (v/v) antiseptic patient preoperative skin preparation (10.5 mL) (hereinafter referred to as ChloroPrep) manufactured by Medi-Flex, Inc., (NDA 20-832) and the recent ANDA submission by Cardinal Health for a similar product (ANDA 77-271). The marketing exclusivity of the reference listed drug expired July 14, 2003. The specific intent of this petition is to request approval for a change in applicator volume from 10.5 ml to 26 ml.

B. Statement of Grounds:

The active ingredients in the proposed Cardinal Health drug product, CHG and IPA, are the same as those of the reference listed drug approved in NDA No. 20-832. The dosage form and strength of the proposed product are also the same as those of the reference listed drug approved in NDA No. 20-832. The inactive ingredients in Cardinal Health's Prevail-CHG and ChloroPrep are presented in the following table.

Inactive Ingredients in Prevail-CHG and ChloroPrep	
Prevail-CHG	ChloroPrep ^a
Purified Water, USP	Purified Water, USP
FD&C Red No. 40	
^a Inactive ingredients listed on ChloroPrep labeling are provided	

There is considerable commercial experience with one-step preoperative prep products containing alcohol. As summarized in the following table, the widespread use of Povidone Iodine-plus-alcohol based products, such as 3M's Dura-Prep (26 ml) and Cardinal Health's Prevail (59 ml) and Prevail-FX (40 ml) represent an estimated 70% of the entire preoperative prepping market.

2004P-0528

CPI

Currently Marketed Patient Preoperative Prepping Solutions Containing Alcohol		
DuraPrep[®], 26 ml	Iodophor and IPA (0.7% Available Iodine and 74% IPA w/w)	6,000,000 units est. sold annually.
Cardinal Large Applicators (Prevail[®], 59 ml; Prevail-FX, 40 ml)	Povidone Iodine USP and Alcohol (Prevail: 0.5% Available Iodine and 62% v/v Ethanol) (Prevail-Fx: .83% Available Iodine and 72.5% IPA w/w)	1,000,000 units est. sold annually.
ChloraPrep[®], 10.5 ml	Chlorhexidine Gluconate and IPA (2% CHG w/v and 70% IPA v/v)	1,500,000 units est. sold annually.

It is speculated that the reason for the relatively high use of products containing more than 10.5 ml of solution is that a majority of surgical procedures require larger volumes of solution to prep the area of concern. The surface area of a typical human body is approximately 2800 square inches, (referencing Cornell University website <http://www-users.med.cornell.edu/~spon/picu/calc/bsacalc.htm>). The 10.5 ml applicator covers an area of about 8.4 square inches. It is evident that preparing a patient for typical procedures such as laparoscopies would normally require more than a single applicator. Through clinical observation and discussion with practitioners, it has been determined that a full-body prep commonly uses 80 ml of antimicrobial solution in the preparation of skin for surgery. Eight (8) separate containers of the 10.5 ml RLD would have to be opened in this case, significantly increasing the time for prepping as well as negatively impacting the cost of the procedure. Using Cardinal Health products as a case study, the packaging and sterilization costs are approximately half of the total product cost. In addition, it would take practitioners extra time and effort to obtain and open the units without improving patient or clinician safety. The proposed Cardinal Health product has been developed in consideration of cost and convenience.

Cardinal is aware that there is concern with OR fires associated with prepping solutions containing a high percentage of alcohol. This concern, as well as customer safety, was taken into consideration during the design of the Cardinal applicator. With many products on the market, notably DuraPrep and ChloraPrep, the container holding the fluid is a glass ampoule, which is broken during applicator activation. Once broken, there is no means of controlling fluid flow through the sponge of the applicator and onto the surgical site. With the Cardinal Health applicator system, the container for the fluid is an HDPE bottle. Once the foil seal on the neck of the bottle is punctured, fluid can be expelled through the neck of the bottle by squeezing or, conversely, fluid flow will be slowed significantly by merely holding the bottle without squeezing. This applicator is the same as that of Cardinal's currently sold prep products, i.e., Prevail and Prevail-Fx.

The proposed prep contains 70% isopropyl alcohol, which provides fast and broad-spectrum antimicrobial kill. Additionally, this alcohol allows for quick dry time (2-3 minutes). Combined with CHG, this system yields an extremely fast-acting, persistent preoperative skin preparation.

Based on investigations, published figures, and searches of the U.S. Food and Drug Administration's (FDA) medical device reporting databases, ECRI estimates that 100 surgical fires per year occur in the United States each year (Risk Management Reporter, Oct 2003). In conversations with Mark E. Bruley (ECRI Vice President, Accident and Forensic Investigation), roughly 5-15% of these surgical fires are attributed to alcohol-based preps.

It has been well established that for a fire to occur, an ignition source, fuel and oxidizer must be present. Alcohol and alcohol-based preps are flammable until all liquid has evaporated (Health Devices, November 2003). Once dry, the solution is no longer flammable. It is important to note that the OR fires are easily prevented through education and training of proper application methods and dry times.

In conjunction with the concern of excess fluid being applied to the area being prepped, there is also a concern that hospital linens or drapes will become saturated and will not be removed or replaced prior to coming in contact with an ignition source. The proposed product label clearly warns of the concerns with use of a flammable solution. It also provides instructions on removal of soaked materials and advises users to allow for sufficient drying of solutions prior to surgery. Please refer to correspondence between the 3M Corporation and the FDA, docket Management Branch (HFA-305), dated June 15, 1995 Docket No. 75N-183H, where a detailed review of cause and corrective action, notably awareness and training of the professional OR staff.

In conclusion, Cardinal Health's proposed prep product has been developed to address cost, convenience and the safety concerns of the OR staff. It is our opinion that the proposed Cardinal product with a change in packaging size to 26 ml as compared to the 10.5 ml packaging size of the RLD is suitable to be filed as an ANDA.

C. Environmental Impact Statement:

By providing a single applicator containing 26 ml of solution, the end user is cutting in half the amount of waste generated during patient preoperative prepping with use of the RLD.

D. Economic Impact Statement:

Not required at this time.

E. Certification:

The undersigned certified 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 that are unfavorable to the petition.



Michael L. Groesbeck

Vice President, Quality Operations, Infection
Infection Prevention, Cardinal Health

1500 Waukegan Rd., Bldg. WM
McGaw Park, IL 60085
(847) 785-3267

Attachments:

Label copy for Prevail-CHG2: Bottle, Pouch, Case Label
Label copy for ChloroPrep® Bottle, Pouch, Dispenser



Cat. 4VAIL-CHG2

NDC 63517-015-26

Prevail CHG
One Step Topical Preoperative Prep Solution and Applicator

Contains Chlorhexidine Gluconate 2% (w/v) and Isopropyl Alcohol 70% (w/v)
Each bottle contains 26 mL.

Single application provides fast-acting, broad-spectrum, persistent antimicrobial activity.

Sterile
For Single External Use Only



Contents
One (1) 26 mL Applicator (contains sponge)
Contents in unopened, unexpired package are sterile

Drug Facts	
Active Ingredient	Purpose
Chlorhexidine gluconate 2% (w/v)	Antiseptic
Isopropyl alcohol 70% (w/v)	Antiseptic
Use - For preparation of the patient's skin prior to surgery	
Warnings	
Do not use if tampered. Keep away from fire or flame. Do not drop or use applicator until dry. Do not use on open wounds. Do not use on face. Do not use on mucous membranes. Do not use on eyes. Do not use on ears. Do not use on nose. Do not use on mouth. Do not use on genital area. Do not use on skin that is irritated or broken. Do not use on skin that is allergic to chlorhexidine or isopropyl alcohol. Do not use on skin that is allergic to any of the ingredients. Do not use on skin that is allergic to any of the preservatives. Do not use on skin that is allergic to any of the dyes. Do not use on skin that is allergic to any of the other ingredients. Do not use on skin that is allergic to any of the other ingredients.	
Directions	
To use: Wash hands thoroughly. Remove applicator from package. Hold bottle and apply to the applicator cap. Use applicator to apply to skin. Rub applicator over skin until skin is completely dry. Do not use on face. Do not use on eyes. Do not use on ears. Do not use on nose. Do not use on mouth. Do not use on genital area. Do not use on skin that is irritated or broken. Do not use on skin that is allergic to chlorhexidine or isopropyl alcohol. Do not use on skin that is allergic to any of the ingredients. Do not use on skin that is allergic to any of the preservatives. Do not use on skin that is allergic to any of the dyes. Do not use on skin that is allergic to any of the other ingredients. Do not use on skin that is allergic to any of the other ingredients.	
Other information	
Store at controlled room temperature 20°-25°C (68°-77°F). Excursions permitted to 15°-30°C (59°-86°F). Do not use after expiration date.	
Contains 26 mL (0.9 FL OZ) of solution.	

Cardinal Health
McGaw Park, IL 60085 USA
30-XXXX



(011) 0 0880420 17878 0



NR000411
Medivo-Prep-Thermal S.U.
McGaw Park, IL
M. Kraemer
9/30/04
30-XXXX

Proofed by: _____	Date: _____
Dimensions checked: _____	Copy checked: _____

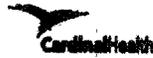
Cat 4VAIL-CHG2 N63517-015-28

Prevaid CHG
One Step Topical
Preoperative Prep
Solution and Applicator

Contains Chlorhexidine Gluconate
2% (w/v) and Isopropyl Alcohol
70% (v/v)

For Single External Use Only
Warning: Solution is flammable
until dry.

Contains 25 mL
Cardinal Health
McGaw Park, IL 60085 USA
37-XXXXX



MK090413
Medvac-Prep-Thermal B.U.
McGaw Park, IL
M. Kraemer
9/30/04
37-XXXXX

Proofed by: _____ Date: _____

Dimensions checked: _____ Copy checked: _____

Cat. **4VAIL-CHG2** NDC 63517-015-26 Qty. **20**

Prevail-CHGTM
One Step Topical Preoperative Prep
Solution and Applicator

Contains Chlorhexidine Gluconate 2% (w/v) and Isopropyl Alcohol 70% (v/v)

Sterile

Lot No.

Exp.



Warning: Solution is flammable until dry. 

Store at 20-25°C (68-77°F). Avoid freezing and excessive heat above 40°C (above 104°F).

Each Bottle Contains 28 mL

U.S. components assembled in Mexico

Cardinal Health
McGaw Park, IL 60086 USA

37-XXXXX



(01) 5 0360470 17978 5



MK098412
Medivac-Prep-Thermal B.U.
McGaw Park, IL
M. Kraemer
9/30/04
37-XXXXX

Proofed by: _____	Date: _____
Dimensions checked: _____	Copy checked: _____



Cat. No. 260700 NDC #054365-400-04 DIN#02160757

ChloroPrep® One-Step

Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% v/v
Patient Preoperative Skin Preparation • 10.5mL Applicator

**WARNING: FLAMMABLE. KEEP AWAY FROM FIRE OR FLAME.
DO NOT USE WITH ELECTROCAUTERY PROCEDURES.**

Drug Facts	
Active Ingredients	Purpose
Chlorhexidine gluconate 2% w/v	Antiseptic
Isopropyl alcohol 70% v/v	Antiseptic
Use for the preparation of the patient's skin prior to surgery	
Warnings	
For external use only	
Flammable. Keep away from fire or flame. Do not use with electrocautery procedures.	
Do not use	
<ul style="list-style-type: none"> ■ in children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption ■ on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol ■ for genital purposes or in contact with the urethra ■ on open skin wounds or as a general skin cleanser 	
When using this product, keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with cold water for 15 minutes and contact a physician. Stop use and ask a doctor if irritation, sensitization, or allergic reaction occurs. There may be signs of a serious condition.	
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.	
Directions	
<ul style="list-style-type: none"> ■ pinch the wings on the applicator to break the ampule and release the antiseptic. Do not touch the sponge. Wet the sponge by repeatedly pressing and releasing the sponge against the treatment area until liquid is visible on the skin. ■ dry surgical sites (such as abdomen or arm): Use repeated back-and-forth strokes of the sponge for approximately 30 seconds. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately 30 seconds. Do not blot or wipe away. ■ moist surgical sites (such as the inguinal fold): Use repeated back-and-forth strokes of the sponge for approximately 2 minutes. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately one (1) minute. Do not blot or wipe away. ■ maximal treatment area for one applicator is approximately 457 cm² (approximately 8.4 x 8.4 inches). Discard the applicator after a single use. 	
Other Information	
<ul style="list-style-type: none"> ■ store between 20-25°C (68-77°F) ■ avoid freezing and excessive heat above 40°C (104°F) 	
Inactive Ingredients • USP purified water	
Questions? Call 1-800-329-0000 (9 a.m.-4 p.m. CST)	

Single Use
Applicator is sterile if package is intact

Lot No:

Exp. Date:



ChlorPrep® 10.5-ml Applicator
2% (w/v) Chlorhexidine Gluconate
and 70% (v/v) Isopropyl Alcohol
Lot No. 403000 Exp. Date 04/06
Medi-Plex, Inc. Leewood, KS 66211

Part No: 6-824248
Rev. Date: 2/17/03



ChloroPrep® One-Step
10.5-mL Applicators • 25 qty.

Store at room temperature 20-25 °C (68-77 °F)
Avoid freezing and excessive heat above 30 °C (104 °F)

Cat. No. 260700

Chloro

Chlorhexidine Gluconate
Antiseptic Patient Prep

ChloroPrep® One-Step
persistent antiseptic
number of microorganisms

10.5-mL Applicator
Single Use

Applicator is **sterile**
Contents: 1 Each Sp
Quantity: 1 Box, 25 E

Store at room temperature
Avoid freezing and excessive heat

Part No: 6-824248

Rev. Date: 2/17/03

MEDI-FLEX

Chloraprep® One-Step
Applicators • 25 qty.

temperature 20-25 °C (68-77 °F)
and excessive heat above 40 °C (104 °F)

Cat. No. 260700 NDC #054365-400-

Chloraprep

**Chlorhexidine Gluconate 2% (w/
Antiseptic Patient Preoperative**

**Chloraprep® One-Step is a
persistent antiseptic that
number of microorganisms**

10.5-mL Applicator

Single Use

Applicator is **sterile** if package is intact

Contents: 1 Each Sponge, Latex Free
Quantity: 1 Box, 25 Each/Box

Store at room temperature 20-25 °C (68-77 °F)
Avoid freezing and excessive heat above

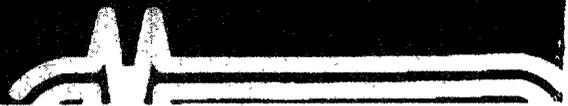
00-04 DIN#02160757

ep[®] One-Step

w/v) and Isopropyl Alcohol 70% (v/v)
ive Skin Preparation

a fast-acting, broad spectrum,
at significantly reduces the
ms on intact skin.

ntact
e





03
1 7
2 8
9
10
11
12
11



ChloroPrep® One-Step
10.5-mL Applicators • 25 qty.

Store at room temperature 20-25°C (68-77°F)
Avoid freezing and excessive heat above 40°C (104°F)



H98526070028

Lot No: **405060** Exp. Date: **04-05**

the
spectrum,

(A/A) %OL

dep

Chloro
Chlorhexid
Patient Pre

Drug Facts

Active ingredient
Chlorhexidine gluconate 2%
isopropyl alcohol 70% w/v

Use
• for the preparation of the

Warnings
For external use only
Flammable: Keep away

Do not use:
• in children less than 2 yr
• on patients with known a
• for lacerations or in
• on open skin wounds or
When using this product:
• keep out of eyes, ears, &
Stop use and seek a doc
• irritation, sensitization, or
Keep out of reach of c

Directions
• pinch the wings on the a
Wet the sponge by repeat
• dry surgical sites (e.
Completely wet the treat
• moist surgical sites
Completely wet the treat
• maximal treatment area. f

Other information
• store between 20-25°C

Inactive ingredie
Questions? Call 1-8



at significantly reduces the
 a fast-acting, broad spectrum,
 ve Skin Preparation
 W/V) and Isopropyl Alcohol 70% (V/V)

ap one-step®

00-04 DIN#02160757

ChloraPrep® One

Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% v/v
 Patient Preoperative Skin Preparation • 10.5

DI-FLEX

One-Step
 ctors • 25 qty.

re 20-25 °C (68-77 °F)
 heat above 40 °C (104 °F)



70028*

04 05

Date:

Drug Facts

Active ingredients
 Chlorhexidine gluconate 2% w/v
 Isopropyl alcohol 70% v/v

Use
 • for the preparation of the patient's skin prior to surgery

Warnings
 For external use only
 Flammable: Keep away from fire or flames. Do not use with electrocautery procedures

Do not use
 • in children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption
 • on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol
 • for lacerations or in contact with the meninges
 • on open skin wounds or as a general skin cleanser

When using this product
 • keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact
 with eyes, use cool water to flush. If contact with eyes, use cool water to flush. If contact with eyes, use cool water to flush.
 • irritation, sensitization, or allergic reaction occurs. These may be signs of a serious condition.
 Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions
 • pinch the wings on the applicator to break the ampule and release the antiseptic. Do not touch the sponge.
 • Wet the sponge by repeatedly pressing and releasing the sponge against the treatment area until liquid is visible on the
 • dry surgical sites (such as abdomen or arm). Use repeated back-and-forth strokes of the sponge for approximately
 • wet the treatment area with antiseptic. Allow the area to air dry for approximately 30 seconds. Do not blot.
 • wet surgical sites (such as the inguinal fold). Use repeated back-and-forth strokes of the sponge for approximat
 • wet the treatment area with antiseptic. Allow the area to air dry for approximately one (1) minute. Do not blot.
 • maximal treatment area for one applicator is approximately 467 cm² (approximately 8 4 x 8 4 inches). Discard the applicator.

Other information
 • store between 20-25 °C (68-77 °F). Avoid freezing and excessive heat above 40 °C (104 °F).

Inactive ingredients • USP purified water

Chloraprep One-Step is a fast-acting antiseptic that significantly reduces the number of microorganisms on the skin. Chloraprep Antiseptic Patient Preoperative Skin Preparation is a 2% (w/v) Chlorhexidine Gluconate and 70% (v/v) Isopropyl Alcohol solution.

Chloraprep

Cat. No. 260700 MDC #054365-400-04

One-Step

2% Chlorhexidine Gluconate and 70% Isopropyl Alcohol
 10.5-mL Applicator

Purpose
 Antiseptic
 Anesthetic

Increased drug absorption

After use, if contact occurs, rinse with cold water right away and contact a physician.

Use: Apply to skin.

Apply to the sponge until liquid is visible on the skin. Rub the sponge for approximately 30 seconds. Do not blot or wipe away the sponge for approximately 30 seconds. Rub the sponge for approximately 1 minute. Do not blot or wipe away the sponge. Discard the applicator after a single use.



ATTACHMENT 2



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

305

Food and Drug Administration
Rockville MD 20857

NOV 30 2004

2004-0386-CP1-RC1

Donald O. Beers
Arnold & Porter LLP
555 Twelfth Street, N.W.
Washington, D.C. 20004-1206

William F. Cavanaugh, Jr.
Patterson, Belknap, Webb & Tyler LLP
1133 Avenue of the Americas
New York, NY 10036-6710

Re: Docket No. 2004P-0386/CP1 & RC1

Dear Mr. Beers and Mr. Cavanaugh:

This letter responds to your citizen petition dated August 31, 2004 (Petition). The Food and Drug Administration (FDA) has also considered the comment to the petition filed by Reliant Pharmaceuticals Inc. (Reliant) dated September 24, 2004, as well as the reply to Reliant's comment you submitted dated November 1, 2004. Your petition requests, on behalf of Abbott Laboratories and Laboratoires Fournier SA (collectively Abbott), that FDA refuse to approve Reliant's new drug application (NDA) 21-695 for fenofibrate capsules until Reliant "fulfills its statutory obligations by certifying to all patents properly listed for NDAs 21-203 and 19-304" (Petition at 1). You suggest that section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(b)(2)) requires Reliant to certify not only to the patents for the listed drug that Reliant's 505(b)(2) application references and on which it relies for approval, but also to all patents on all other later-approved Abbott products that were approved based, in part, on some or all of the same underlying investigations. You contend that certification to patents on all these later-approved products is required regardless of the similarity or dissimilarity of the later-approved products to the product described in Reliant's 505(b)(2) NDA (Petition at 3). For the reasons described in detail below, your petition is denied.

I. Background

Abbott obtained approval for NDA 19-304 for a 100-milligram (mg) nonmicronized fenofibrate capsule on December 31, 1993 (*the first NDA*). This NDA contained all of the clinical and preclinical investigations required of a full NDA under section 505(b)(1) of the Act. As part of its application, Abbott submitted patent 4,895,726 (*the '726 patent*) for NDA 19-304. FDA listed that patent in *Approved Drug Products With Therapeutic Equivalence Evaluations* (*the Orange Book*). This patent is due to expire on January 19, 2009. Abbott has never marketed the 100-mg nonmicronized capsules approved in NDA 19-304.

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On February 9, 1998, FDA approved a supplement to NDA 19-304 for 67-mg micronized fenofibrate capsules. One year later, FDA approved an additional supplement to NDA 19-304 for 134- and 200-mg micronized capsules. These two supplements were approved based on studies in healthy volunteers that compared the bioavailability of the proposed drug products with that of the previously approved -- but never marketed -- 100-mg nonmicronized capsule. The supplements did not include additional clinical or preclinical studies to establish safety or effectiveness. No additional patents were submitted by Abbott in conjunction with these two supplements.

On September 4, 2001, Abbott obtained approval for NDA 21-203 for 54- and 160-mg fenofibrate tablets (*the second NDA*). This NDA contained no new safety or effectiveness studies. It was also supported by the clinical and preclinical studies previously submitted by Abbott in the first NDA, as well as by a newly conducted study in healthy volunteers comparing the bioavailability of the proposed Abbott tablets with that of the previously approved -- but never marketed -- Abbott 100-mg capsules from the first NDA (NDA 19-304). Abbott submitted, and FDA listed, the '726 patent as claiming the tablets approved in NDA 21-203. Abbott subsequently submitted, and FDA listed, patent numbers 6,277,405 (the '405 patent), 6,074,670 (the '670 patent), 6,589,552 (the '552 patent), and 6,653,881 (the '881 patent) for the tablets approved in NDA 21-203.¹ The '405, '670, '552 and '881 patents are all due to expire on January 9, 2018.

On September 3, 2002, Teva Pharmaceuticals (Teva) obtained approval for an abbreviated new drug application (ANDA) for 67-, 134-, and 200-mg micronized fenofibrate capsules. Teva cited the first NDA (NDA 19-304) as the reference listed drug. In early 2003, Abbott discontinued marketing all strengths under the first NDA. FDA subsequently determined that the fenofibrate capsules approved in the first NDA were not discontinued from marketing for reasons of safety or effectiveness (68 FR 56636; October 1, 2003).

On February 18, 2004, Reliant notified Abbott that it had submitted a 505(b)(2) NDA for micronized fenofibrate capsules in 43-, 87-, and 130-mg strengths. Reliant's NDA also cited as its listed drug Abbott's first NDA (NDA 19-304) for fenofibrate capsules. Reliant included in its application a paragraph IV certification for the '726 patent listed for that NDA and provided Abbott notice of the certification (21 U.S.C. 355(b)(2)(A)(iv)). Abbott did not sue Reliant within 45 days of receipt of notice of Reliant's paragraph IV certification. Instead, Abbott informed Reliant that Reliant was also required to certify to the '405, '670, '552, and '881 patents that claim the fenofibrate tablets approved in the second NDA. Reliant refused to certify to the patents listed for NDA 21-203. Abbott filed this petition seeking an FDA determination that Reliant is required to do so.

¹ Abbott has never submitted the '405, '670, '552, or '881 patents to the first NDA (NDA 19-304). Because submission by the NDA holder of patents that claim the approved drug substance (active ingredient), drug product (formulation or composition), or method of use is mandatory, not permissive, FDA assumes that Abbott does not contend that these patents claim the drug substance, drug product, or method of use approved in the first NDA.

II. Positions of the Parties

Abbott and Reliant disagree about the proper scope of patent certification obligations under section 505(b)(2) of the Act. Abbott argues that a section 505(b)(2) applicant such as Reliant must certify not only to patents that claim the listed drug product or products it references, and on whose finding of safety and effectiveness it relies, but also to patents on any other drug product that was approved on the basis of the same underlying investigations as the drug product referenced in the 505(b)(2) NDA. Abbott contends that the word *drug* in section 505(b)(2) of the Act "is not limited to a particular drug product (*i.e.*, a finished dosage form)." Rather, Abbott claims that the word *drug* in this context "also includes a drug substance, which is a component of a drug product" (Petition at 5). Abbott further contends that the "plain meaning" of the phrase "drug for which such investigations were conducted" in section 505(b)(2) compels Reliant to certify to patents on formulations and compositions of the drug on which the underlying investigations establishing safety and effectiveness were conducted *as well as* to patents on "future formulations whose approval the investigations may support" (Petition at 5).

According to Abbott, if Congress had intended to limit patent certification obligations to exclude patents on future formulations, it would have required section 505(b)(2) applicants to certify to patents for the drugs *on which not for which* the investigations were conducted (*Id.*). Abbott asserts that because Congress used the word *for* instead of the word *on*, if Reliant seeks to rely on the investigations submitted in the first NDA (NDA 19-304), Reliant must certify to the patents on the first NDA, *as well as* to the patents on any future NDA, including but not limited to the second NDA (NDA 21-203), that also relies on the same underlying investigations.

Reliant, by contrast, argues that the patent certification obligations described in section 505(b)(2) require applicants to certify "whether the proposed products may infringe the patents on the listed drugs they reference in their applications" (Comments Opposing Citizen Petition Filed on Behalf of Abbott Laboratories and Laboratories Fournier SA (Opp.) at 5 (quoting consolidated FDA response to citizen petitions in Docket Nos. 2001P-0323, 2002P-0447, and 2003P-0408 (October 14, 2003) (505(b)(2) Petition Response) at 5). Reliant argues that once the appropriate listed drug or drugs (*i.e.*, the approved drug product or products on which investigations relied upon for approval were conducted)² are identified, the scope of the certification requirement becomes clear. Reliant suggests that because the Orange Book lists the drug substance (active ingredient), drug product (formulation and composition), and method of use patents that claim the listed drug identified, "a 505(b)(2) applicant need only consult the Orange Book patent

² In contrast to an ANDA (which generally relies on a showing of bioequivalence to a single listed drug to support its own safety and effectiveness), a 505(b)(2) application may rely on approvals for several listed drugs to support its approval. Where no single FDA finding of safety or effectiveness is sufficient to supplement the data submitted in the 505(b)(2) application and findings of safety and effectiveness for different listed drugs support different aspects of the 505(b)(2) approval, the 505(b)(2) applicant should certify to multiple sets of patents. For example, if a proposed 505(b)(2) application relies on the finding of safety and effectiveness for one NDA to support one aspect of its approval (*e.g.*, dosage form) and the finding of safety and effectiveness for another NDA to support another aspect of the approval (*e.g.*, indication), the 505(b)(2) applicant should certify to all patents listed for both drugs. This type of dual certification was not requested here because, as explained later in this response, the finding of safety and effectiveness for the first NDA (NDA 19-304) was sufficient to provide all the information needed for approval of Reliant's application.

listings for the listed drug upon which it relies to identify those patents that claim the drug *for which and on which* investigations that are relied upon by the applicant for approval of its application were conducted" (Opp. at 7 (emphasis added)). Reliant notes that Abbott's reading of the statute would allow NDA holders to protect their monopolies on drug products long after patent protection on those products has expired and would result in "perpetual evergreening" that is "contrary to both the spirit and the letter of the Hatch-Waxman Amendments and FDA's regulations" (Opp. at 2).

III. Legal Framework

A. Requirements for Patent Submission and Listing

Abbott is concerned about the scope of patent certification obligations because, in determining their scope, FDA is also determining the scope of protection that the statute gives Abbott, the NDA holder. The patent certification requirements for ANDA and section 505(b)(2) applicants are determined by reference to the patents submitted by the NDA holder and published by FDA. Thus, to determine the proper scope of the patent certification requirements under section 505(b)(2) of the Act, FDA must also consider the scope of the patent submission and listing requirements. Section 505(b)(1) of the Act describes the patents that must be submitted for listing as follows:

The applicant shall file with the application the patent number and the expiration date of *any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture use, or sale of the drug. If [sic] application is filed under this subsection for a drug and *a patent which claims such drug or [a] method of using such drug* is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences.

21 U.S.C. 355(b)(1) (emphasis added).³

Although FDA acknowledges that the word *drug* can have different meanings in different contexts,⁴ in this context the statutory language establishes that patents are submitted as part of the new drug application process, that is, the process by which *drug products* are approved for marketing. Because applications are submitted and approved for drug products, not active ingredients or active moieties, FDA interprets the phrases "patent which claims the

³ Section 505(c) of the Act further requires that if "the holder of an approved application could not file patent information under [505(b)(1)] because no patent had been issued when an application [had been] approved, the holder shall file such information under this subsection not later than [30] days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it." (21 U.S.C. 355(c)(2)).

⁴ See 21 U.S.C. 321(g).

drug for which the applicant submitted the application" and "a patent which claims such *drug*" as meaning patents claiming the *drug product* described in the NDA.

Accordingly, FDA regulations adopt this reading of the text and make explicit that, under this provision, NDA applicants must submit with their applications patents that claim the *drug product* for which the applicant is seeking or has obtained approval (see 21 CFR 314.50(h) (requiring applications to contain patent information described in 21 CFR 314.53); 54 FR 28872 at 28877 (July 10, 1989) ("For purposes of this proposed rule, FDA interprets the term 'drug' to mean 'drug product' unless otherwise specified")). These include patents on the approved active ingredient, formulation and composition, and methods of use for the drug product described in the NDA. See 21 CFR 314.53(b) ("For patents that claim the drug substance, the applicant shall submit information only on those patents that claim the drug substance that is the subject of the pending or approved application ... For patents that claim a drug product, the applicant shall submit information only on those patents that claim a drug product, as it is defined in § 314.3, that is described in the pending or approved application. For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use that are described in the pending or approved application"). NDA applicants may not submit, and FDA will not publish, patent information under this provision for patents on active ingredients⁵ or formulations they have chosen not to pursue, or methods of use for which they are not seeking or have not obtained approval (*Id.*).

B. Requirements for Patent Certification

Section 505(b)(2) of the Act describes when a section 505(b)(2) applicant must certify to the patents listed and published for a previously approved drug product as follows:

An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) . . . and relied upon 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 shall also include--

(A) a certification . . . with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c)--

21 U.S.C. 355(b)(2) (emphasis added).

⁵ FDA regulations permit NDA holders to submit patents on polymorphic forms of the active ingredient that have not been approved in the NDA if the alternative polymorphic form is "the same" as the approved active ingredient, and the NDA holder has test data establishing that the alternative polymorphic form will have the same performance characteristics as the approved polymorphic form of the active ingredient (see 21 CFR 314.53(b)). That exception is not at issue here.

With respect to each patent as to which the section 505(b)(2) applicant must certify, the certification must state:

- (i) that such patent information has not been filed,
- (ii) that such patent has expired,
- (iii) the date on which such patent will expire, or
- (iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.

21 U.S.C. 355(b)(2)(A).

If a section 505(b)(2) applicant does not challenge the listed patents by filing a paragraph IV certification, the application will not be approved until all the listed patents claiming the listed drug have expired. If an applicant wishes to challenge the validity of the listed patent, or to claim that the listed patent would not be infringed by the product proposed in the section 505(b)(2) application, the applicant must submit a paragraph IV certification to FDA. The applicant must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed (21 U.S.C. 355(b)(2)(B)). Once the NDA holder and patent owner have received notice, they have 45 days within which to sue the applicant for patent infringement and thus trigger a 30-month stay on FDA approval of the proposed drug (21 U.S.C. 355(c)(3)(C)). FDA will approve the proposed drug before the 30-month period expires only if a court finds the patent invalid or not infringed or the court shortens the period because the parties fail to cooperate in expediting the litigation (21 U.S.C. 355(c)(3)(C)).

The query, then, is what listed drug or drugs must a 505(b)(2) application cite and, as a result, for what patents will certification be required. The relevant statutory provision is section 505(b)(2) quoted above. Abbott argues that *drug* in section 505(b)(2) of the Act is not limited to *drug product*. Abbott also makes much of the use of the word *for* instead of *on* in the statutory language. Specifically, it contends that because *drug* means *active ingredient* as well as *drug product*, by specifying "the drug for which such investigations were conducted" instead of "the drug on which such investigations were conducted" in section 505(b)(2)(A) of the Act, Congress required certification to all patents for every drug containing the same active ingredient that relied in part on the same underlying investigations on which the section 505(b)(2) applicant seeks to rely.

This language does not bear the weight Abbott ascribes to it. The phrase "the drug for which such investigations were conducted" neither implicitly nor explicitly requires certification to patents on "future formulations whose approval the investigations may support." At most, this language may be ambiguous in describing which drugs' patents must be certified to. Moreover, FDA's interpretation of this provision looks not at these eight words in isolation but at the entire patent certification provision in context and at the Hatch-Waxman statutory scheme as a whole. The language of section 505(b)(2) of the Act explicitly links the *drug* relied on for approval to the *drug* for which patent certifications must be made. Consistent with its interpretation of section 505(b)(1) discussed above, FDA interprets *drug* in section 505(b)(2) to refer to *drug*

product, not active ingredient. Applications are submitted for drug products, not drug substances or active ingredients. Accordingly, the phrase "application . . . for a drug for which the investigations . . . relied upon by the applicant for approval . . . were not conducted by or for the applicant" in section 505(b)(2) refers to an application for a *drug product* relying for approval on investigations the applicant did not conduct. Moreover, section 505(b)(2)(A) of the Act states that the 505(b)(2) applicant must certify to "each patent which claims the drug for which such investigations were conducted . . . and for which information is required to be filed under [505(b)(1)]." As noted above, section 505(b)(1) requires that patent information be filed for drug products, not active ingredients. Therefore, the requirement that a 505(b)(2) applicant certify to "each patent which claims the drug for which such investigations were conducted . . . and for which information is required to be filed under [505(b)(1)]" requires certifications to patents listed for the drug product relied on for approval, but not to patents for all other drug products that contain the same drug substance and rely on the same underlying investigations.⁶

FDA's implementing regulations reinforce this relationship between reliance and certification. They establish that an applicant seeking approval for a modification of a previously approved drug product may submit a 505(b)(2) application that contains only the information necessary to support the modification (21 CFR 314.54(a)). However, if a 505(b)(2) applicant relies on a previously approved drug product in this fashion, that applicant must certify to the patents listed under section 505(b)(1) of the Act for that drug product. FDA's regulations require that a 505(b)(2) applicant that seeks to rely in any way on a previously approved drug product must identify "the listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product" (21 CFR 314.54(a)(1)(iii)). The regulations require 505(b)(2) applicants to submit "[a]ny patent certification or statement required under section 505(b)(2) of the [A]ct with respect to any relevant patents that claim the listed drug or that claim any other drugs on which investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug"⁷ (21 CFR 314.54(a)(1)(vi); see also 21 CFR 314.50(i)(1)(i)). A listed drug is defined as "a new drug product that has an effective approval" (21 CFR 314.3).

Together, these provisions establish that a section 505(b)(2) applicant is permitted to rely in whole or in part on the Agency's previous findings of safety and effectiveness for one or more previously approved drug products (listed drugs). As a condition of doing so, however, the section 505(b)(2) applicant must identify in its application the drug product or products on which it relies and certify to any relevant patents for those drug products. Patent certification obligations thus are linked to identification of the listed drug or drugs on which the application

⁶ See also Drug Price Competition and Patent Term Restoration Act, House Report 98-417, Part 1 at 32 (When an NDA "is submitted for a listed drug under 505(j)(6) [now section 505(b)(2) of the Act], it must 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 which the applicant is seeking approval...the applicant must certify....") (emphasis added).

⁷ The phrase "or that claim any other drugs on which investigations relied on by the applicant for approval of the application" refers to the situation where a 505(b)(2) applicant references one listed drug to support one aspect of its proposed drug product (e.g., active ingredient or indication) and another listed drug to support another aspect of its proposed drug product (e.g., extended release dosage form). In such a case, more than one listed drug will be referenced and more than one set of patent certifications will be required.

relies and are limited to the patents submitted and published for the listed drug or drugs identified.⁸

FDA's longstanding interpretation of the statute does not permit 505(b)(2) applicants to rely on particular investigations in previously approved NDAs that are not reflected in the NDA approvals. Rather, they can only rely on previous findings of safety and effectiveness for a listed drug or drugs. Therefore, if a sponsor has submitted a study to an NDA, the results of which are not reflected in the NDA's approval (e.g., a study for an indication that FDA has rejected), a 505(b)(2) applicant cannot rely on that study to support its own approval (see 505(b)(2) Petition Response at 10, footnote 14 (distinguishing reliance on the finding of safety and effectiveness from reliance on the underlying data)).

This interpretation also treats ANDAs and 505(b)(2) applications comparably. As discussed in detail in the 505(b)(2) Petition Response, such treatment is a guiding principle for Hatch-Waxman interpretation that reflects the parallel structure and logic of the patent certification provisions in sections 505(b)(2) and 505(j) of the Act.⁹ Just as ANDAs need only certify to patents on the listed drugs they reference and on which they rely for approval (and not to patents on other products in the product lines that reference the same underlying investigations that supported the approval of the listed drug referenced), so too, are the 505(b)(2) applicant's patent certification obligations correlated to patents on the listed drug or drugs relied on for approval.¹⁰

C. Choosing the Listed Drug

In contrast to Abbott's sweeping approach to identifying listed drugs for patent certifications, FDA's approach is tailored more narrowly to reflect the logic and language of the statute. Given

⁸ FDA notes that this approach is appropriate because if two listed drugs from the same sponsor were to rely on the same investigations to support approval, any patents that claim the results of those investigations must be listed for both products. If two NDAs from the same sponsor have different patents listed, it can be assumed that patents listed for product B and not for product A claim some aspect of product B (e.g., formulation, indication) that is not present in product A. An applicant that seeks to duplicate the aspect of product B that is not present in product A (and to rely on product B's approval to support this feature) will cite product B as its listed drug and must certify to the patents for product B. An applicant that does not seek to duplicate this aspect of product B should be permitted to cite product A as its listed drug and certify only to the patents on product A.

⁹ See 54 FR 28872 at 28875 ("[T]he new statutory provisions impose on a 505(b)(2) applicant additional requirements with respect to patent certification . . . that are generally the same as those that apply to ANDA's"); 54 FR at 28891 ("[B]ecause the patent certification and exclusivity provisions apply equally to applications described under section 505(b)(2) or 505(j) of the act, an applicant will not be disadvantaged by the review of its application under section 505(j) of the act rather than section 505(b)(2) of the act."); 54 FR at 28892 ("An applicant submitting a section 505(b)(2) application must make the same certifications with respect to patents as an applicant submitting an ANDA"). See also 505(b)(2) Petition Response at 9 (Hatch-Waxman amendments ensured that "the patent and exclusivity bars to approval that apply to ANDAs apply as well to the approval of 505(b)(2) applications").

¹⁰ FDA has consistently made clear that, in approving a 505(b)(2) application, FDA will rely on a previous NDA approval only to the extent it would be permitted to do so in an ANDA submitted under 505(j). See Draft Guidance at 2 to 3 ("[The 505(b)(2) mechanism] 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."); see also 54 FR 28872 at 28892 ("Like similar supplements to approved ANDAs, [505(b)(2) applicants seeking to make a change to a listed drug] will rely on the approval of the listed drug together with the data needed to support the change. The applicant will thus be relying on the approval of the listed drug only to the extent that such reliance would be allowed under 505(j) of the act: to establish the safety and effectiveness of the underlying drug."); 505(b)(2) Petition Response at 3, 9, 10, and 14.

that a 505(b)(2) applicant must certify only to patents on the listed drug relied on for approval, each proposed 505(b)(2) application must identify the listed drug or drugs on which it seeks to rely. Once a listed drug has been identified, the 505(b)(2) applicant need only provide sufficient information to support any change from the listed drug proposed (21 CFR 314.54(a)). FDA's Draft Guidance for Industry, *Applications Covered by Section 505(b)(2)* (Draft Guidance), makes clear, however, that "[i]f there is a listed drug that is the pharmaceutical equivalent"¹¹ [of] the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug"¹² (Draft Guidance at 8). It further provides that, "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" (Draft Guidance at 8). These provisions ensure that the 505(b)(2) applicant does not use the 505(b)(2) process to end-run patent protections that would have applied had an ANDA been permitted.¹³ They further ensure that the 505(b)(2) applicant (and FDA) can rely, to the maximum extent possible, on what is already known about a drug without having to re-prove (or re-review) what has already been demonstrated. See 505(b)(2) Petition Response at 3 ("FDA's longstanding interpretation of section 505(b)(2) is intended to permit the pharmaceutical industry to rely to the greatest extent possible under the law on what is already known about a drug").

When there is no listed drug that is a pharmaceutical equivalent to the drug product proposed in the 505(b)(2) application, neither the statute, the regulations, nor the Draft Guidance directly addresses how to identify the listed drug or drugs on which a 505(b)(2) applicant is to rely. However, because, under 21 CFR 314.54(a), a 505(b)(2) applicant seeking approval for a change to a listed drug need only supply information sufficient to support the change proposed, it follows that the more similar a proposed drug is to the listed drug cited, the smaller the quantity of data that will be needed to support the proposed change. Accordingly, to avoid unnecessary duplication of research and review, when a section 505(b)(2) application has been submitted and no pharmaceutically equivalent drug product has previously been approved, the 505(b)(2) applicant should choose the listed drug or drugs that are most similar to the drug for which approval is sought.

¹¹ FDA's regulations at 21 CFR 320.1(c) define pharmaceutical equivalents as:

drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as pre-filled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and 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.

¹² A 505(b)(2) application may be submitted for a pharmaceutical equivalent to a previously approved drug product when, for example, the 505(b)(2) contains a novel excipient that requires a safety study and therefore cannot be approved in an ANDA. FDA regulations establish, however, that FDA may refuse to file a 505(b)(2) application eligible for approval under section 305(j) (21 CFR 314.101(d)(9)).

¹³ Similarly, if a tablet and a capsule are approved for the same moiety with patents listed for the tablet and none listed for the capsule, an ANDA applicant seeking approval for a tablet should cite the approved tablet as the reference listed drug. It should not circumvent the patents on the tablet by citing the capsule as the reference listed drug and filing a suitability petition under section 505(j)(2)(C) of the Act and 21 CFR 314.93 seeking to change to a tablet dosage form.

Similarly, if all the information relied on by FDA for approval (excluding information submitted in the 505(b)(2) application itself) is contained in a single previously approved application and that application is a pharmaceutical equivalent or the most similar alternative to the product for which approval is sought, the 505(b)(2) applicant should certify only to the patents for that application. This is the case even when another application also contains some or all of the same information. This approach ensures that patent certification obligations for 505(b)(2) applications and for ANDAs are parallel. Each application will certify only to patents listed for drugs on whose finding of safety and effectiveness FDA relies for approval (including patents for pharmaceutical equivalents or, if there is no pharmaceutical equivalent, for the most similar alternative), not to patents submitted for applications on which FDA could have relied but did not.

IV. Application of Legal Framework to Reliant's NDA

Abbott does not question whether Reliant's decision to certify to the patents on the first NDA was appropriate; it merely asserts that additional patent certifications were also required. It is worth noting, however, that once FDA rejects Abbott's statutory interpretation requiring certification to all future formulations relying on the same underlying investigations, Reliant's choice of listed drug was clearly proper. Reliant's section 505(b)(2) application for fenofibrate capsules did not seek approval for a pharmaceutical equivalent to an approved drug product. Accordingly, Reliant certified to all patents for the listed drug on which it relied for approval. In approving Reliant's NDA, FDA has relied only on studies Reliant conducted, as well as on the finding of safety and effectiveness for fenofibrate capsules approved in the first NDA (NDA 19-304). The fenofibrate capsules approved in the first NDA are the approved products that are most similar to the fenofibrate capsules described in Reliant's NDA. Reliant's product differs from the Abbott product approved in the first NDA only in strength. In contrast, Reliant's product differs from the Abbott product approved in the second NDA (NDA 21-203) in both strength and dosage form. In addition, Reliant used the 200-mg capsules approved in the first NDA as its comparator drug for its bioavailability study, and the first NDA did not, itself, rely on studies in any previously approved NDA or on a previous Agency finding of safety and effectiveness.¹⁴ Nor did Reliant need to reference any other finding of safety and effectiveness to support its own approval or labeling. For all of these reasons, it was appropriate for Reliant to rely on the finding of safety and effectiveness for the first NDA. There were no gaps in Reliant's NDA that the previous finding of safety and effectiveness for the first NDA could not fill. Therefore, no additional patent certifications by Reliant were required.¹⁵

¹⁴ Where a 505(b)(2) application seeks to rely on the finding of safety or effectiveness for a listed drug that is a 505(b)(2) NDA which, itself, relied on a previous finding of safety and effectiveness, the 505(b)(2) applicant should certify to the patents of the 505(b)(2) NDA relied on, as well as to the patents of any underlying NDA on which that approved 505(b)(2) NDA relied for approval. This is analogous to the requirement that an ANDA applicant referencing an approved suitability petition (or another ANDA approved pursuant to a suitability petition) certify to the patents for the approved NDA upon which the suitability petition or ANDA approval was based.

¹⁵ The New Jersey district court's unpublished opinion in *Marion Merrell Dow, Inc. v. Hoechst-Roussel Pharms., Inc.*, Civ. No. 93-5074, 1994 WL 424207 (D.N.J. May 5, 1994) does not dictate a contrary result. First, that opinion is factually distinguishable from the case here. In the *Marion Merrell Dow* case, Hoechst-Roussel was seeking approval for a drug product with an approved pharmaceutical equivalent. To circumvent patent protection on the approved pharmaceutical equivalent, Hoechst-Roussel failed to certify to patents on that pharmaceutical equivalent. Instead, Hoechst-Roussel compared its drug product to a pharmaceutically inequivalent product with more limited patent protection. In this case, by contrast, Reliant has certified to the patents on the product that is

V. Conclusion

FDA rejects Abbott's argument that the statute requires Reliant to certify not only to patents for NDA 19-304, but also to patents on any additional NDA that has relied on the studies contained in NDA 19-304 for approval. Under the language and logic of the statute and relevant regulations, Reliant is under no obligation to certify to patents submitted for an NDA (such as NDA 21-203) that was not a pharmaceutical equivalent or the most similar approved alternative to Reliant's drug product and on which Reliant did not rely. If the same patent protections apply to both NDA 19-304 and NDA 21-203, those patents must be listed for both NDAs, thus protecting Abbott's patent rights. If the patent protections differ, Reliant need certify only to the patents protecting the drug product relied on to support its approval. To divorce patent certification obligations from reliance and require Reliant to certify to patents on additional drug products on which FDA did not rely for approval would upset the delicate balance struck by the Hatch-Waxman Amendments. Such an approach would permit Abbott to obtain new patents on future products and potentially use them to protect its fenofibrate capsules long after the patent and exclusivity protection on that product has expired. For all of these reasons, your petition is denied.

Sincerely,



Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

most similar to its own. Therefore, there can be no argument here (as there was in that case) that Reliant used the 505(b)(2) process to circumvent patent certification obligations that would have applied had the application been submitted under section 505(j) of the Act. Moreover, the *Marion Merrell Dow* opinion, which includes only cursory analysis of the statutory language, was issued before FDA's regulations regarding patent certification obligations for 505(b)(2) applicants were finalized (see 59 FR 50338 (October 3, 1994)). Thus, the decision makes no attempt to interpret the relevant regulations, which make clear that a 505(b)(2) applicant can rely on a finding of safety or effectiveness for a previously approved drug product if it certifies to the patents listed for that drug product. In addition, the *Marion Merrell Dow* opinion erroneously interprets the word *drug* in section 505(b)(2)(A) to mean drug substance, not drug product. As explained above, when section 505(b)(2)(A) is read in the context of the entire statutory scheme, it becomes clear that *drug* in that context means drug product, not drug substance. Thus, 505(b)(2) applicants are obligated to certify to patents listed for any drug product they reference (including patents claiming the drug substance, drug product, or methods of use approved in the NDA for that drug product). However, 505(b)(2) applicants are not obligated to certify to patents for other drug products on whose findings of safety and effectiveness they do not seek to rely. This interpretation adequately protects an NDA holder or patent owner's rights, because any patent that claims the underlying drug substance approved in an NDA is, as previously explained, required to be listed for that NDA and must be certified to by a 505(b)(2) applicant seeking to rely on that previous approval. In this case, if there are any patents that claim the drug substance, fenofibrate, on which the underlying investigations establishing the safety and effectiveness of both the first and second NDAs were conducted, those patents are required to be listed not only for the second NDA, but also for the first NDA, which contains that drug substance. As we stated in footnote 1, because the patents at issue were not listed for the first NDA, it can be assumed that Abbott does not believe these patents claim the drug product approved in that NDA.

ATTACHMENT 3

CONFIDENTIAL DISCLOSURE AGREEMENT

BY THIS CONFIDENTIAL DISCLOSURE AGREEMENT (hereinafter "the Agreement") Medi-Flex, Inc., having a place of business at 11400 Tomahawk Creek Parkway, Leawood, Kansas 66211 (hereinafter "Recipient"), and Cardinal Health, Inc., having a place of business at 7000 Cardinal Place, Dublin, Ohio 43017 (hereinafter "Provider") agree as follows:

1. Provider agrees to provide Recipient with certain proprietary and confidential information related to Provider's Abbreviated New Drug Application ("ANDA") 77-271 and the generic chlorhexidine gluconate 2% and isopropyl alcohol 70% product(s) covered therein (hereinafter "Confidential Information").

2. All Confidential Information shall be clearly identified as "confidential" when disclosed. If the initial disclosure of information is not in written or other tangible form, the Provider must reduce it to written or tangible form within thirty (30) days from the time of disclosure and clearly mark the written form as "confidential."

3. Recipient shall use the Confidential Information solely for purposes of evaluating possible patent infringement and determining whether a patent infringement action should be brought.

4. Recipient agrees to accept the Confidential Information and employ all reasonable efforts to maintain the Confidential Information secret and confidential, such efforts to be no less than the degree of care employed by the Recipient to preserve and safeguard its own confidential information. The Confidential Information shall not be disclosed, revealed, or given to anyone by the Recipient except employees, outside counsel, and independent consultants and experts who have a need for the Confidential Information in connection with the evaluation of whether to bring a patent infringement action. Such employees, outside counsel, and independent consultants and experts shall be advised by the Recipient of the confidential nature of the Confidential Information and that the Confidential Information shall be treated accordingly.

5. The obligations of the Recipient specified in Paragraph 4 above shall not apply, and the Recipient shall have no further obligations with respect to any Confidential Information to the extent that such information;

- (a) at the time of disclosure is generally available to the public, or thereafter becomes generally available to the public through no breach of the Agreement by Recipient; or
- (b) was in the Recipient's possession prior to the time of disclosure by the Provider; or
- (c) is independently developed by the Recipient without the use of Provider's Confidential Information; or
- (d) is provided to the Recipient by a third party that is not under an obligation of confidentiality to the Provider; or
- (e) is required to be disclosed by law or court order.

6. The Recipient agrees to return all written or tangible items containing Confidential Information to the Provider or destroy such items when its use of the Confidential Information under Paragraph 3 is complete. One copy of the items containing Confidential Information may be retained by the Recipient, however, for archival purposes.

7. The Confidential Information shall remain the property of the Provider and nothing herein shall be construed to grant Recipient a license or intellectual property rights in the Confidential Information.

8. This Agreement may only be modified or waived in writing by an authorized representative of the Recipient and Provider. If any provision of the Agreement is found to be unenforceable, such provision will be limited or deleted to the minimum extent necessary so that the remaining terms remain in full force and effect.

Acknowledged and agreed to by:

For the Recipient:

Signature

Name and Title (please print)

Date

For the Provider:

Signature

Name and Title (please print)

Date