



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-N-1040]

Antiseptic Patient Preoperative Skin Preparation Products; Public Hearing; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public hearing; request for comments.

Summary: The Food and Drug Administration (FDA or the Agency) is announcing a public hearing to obtain input on how to address microbial contamination of patient preoperative skin preparation drug products. Currently, patient preoperative skin preparations are not required to be sterile. Bacteria can contaminate these products at the time of manufacture or during product use. Contaminated patient preoperative skin preparations have been associated with clinical infections and adverse outcomes. At this public hearing, FDA is interested in obtaining public comment about certain scientific and product use issues related to patient preoperative skin preparations.

Date and Time: The public hearing will be held on December 12 and 13, 2012, from 9 a.m. to 4 p.m. The meeting may be extended or may end early, depending on the level of public participation.

Location: The public hearing will be held at the DoubleTree by Hilton Hotel Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Rd., Silver Spring, MD 20910.

Contact Person: Lee Lemley, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20903, 301-796-3441, FAX: 301- 847-8753, email: AntisepticPreOpPublicMeeting@fda.hhs.gov.

Registration: The public hearing is free, and seating will be on a first-come, first-served basis. Attendees who do not wish to make an oral presentation do not need to register. If you need special accommodations due to disability, please contact Lee Lemley (see Contact Person) at least 7 days in advance.

Requests for Oral Presentations: If you wish to make an oral presentation during the hearing, you must register by submitting a written or electronic request by close of business on November 27, 2012, to Lee Lemley (see Contact Person). Provide your name, title, business affiliation (if applicable), address, telephone and fax numbers, email address, and type of organization you represent (e.g., pharmaceutical company or consumer organization). You also should submit a brief summary of the presentation, including the discussion topic(s) that will be addressed and the approximate time requested for your presentation. We encourage individuals and organizations with common interests to consolidate or coordinate their presentations to allow adequate time for each request for presentation. Persons registered to make an oral presentation should check in before the hearing.

Participants should submit a copy of each presentation to Lee Lemley (see Contact Person) no later than December 7, 2012. We will file the hearing schedule, indicating the order of presentation and the time allotted to each person, with the Division of Dockets Management (see Comments). We will mail, email, or telephone the schedule to each participant before the hearing. In anticipation of the hearing presentations moving ahead of schedule, participants are

encouraged to arrive early to ensure their designated order of presentation. Participants who are not present when called risk forfeiting their scheduled time.

Comments: Interested persons may submit either written comments regarding this document to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 or electronic comments to <http://www.regulations.gov>. Comments will be accepted after the hearing until February 12, 2013. Persons who wish to provide additional materials for consideration should file these materials with the Division of Dockets Management. You should annotate and organize your comments to identify the specific questions identified by the topic to which they refer. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Transcripts: Please be advised that as soon as a transcript is available, it will be accessible at <http://www.regulations.gov>. It may be viewed at the Division of Dockets Management (see Comments). A transcript will also be available in either hard copy or on CD-ROM, after submission of a Freedom of Information request. Written requests are to be sent to the Division of Freedom of Information (ELEM-1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857.

SUPPLEMENTARY INFORMATION: FDA is announcing a public hearing to obtain input on how to address microbial contamination of patient preoperative skin preparation drug products. To provide the public with additional background, FDA is making information available that is pertinent to this safety issue. This information is available electronically in the docket for this

Federal Register notice on the Internet at <http://www.regulations.gov> and on FDA's Web site at <http://www.fda.gov/Drugs/NewsEvents/ucm319621.htm>. This information is also available at the Division of Dockets Management and by mail (see Comments).

I. Background

Patient preoperative skin preparations are over-the-counter (OTC) topical antiseptic drug products used to reduce the number of bacteria on the skin prior to medical procedures or injections. Although they are marketed predominantly to healthcare facilities, the use of these products extends beyond the healthcare facility setting. For example, consumers with medical conditions requiring regular injections (e.g., of insulin or heparin) may use these products at home.

Patient preoperative skin preparations are marketed through one of three regulatory pathways: an OTC drug monograph, an approved new drug application (NDA), or an approved abbreviated new drug application (ANDA). Many patient preoperative skin preparations contain antiseptic active ingredients subject to an OTC drug monograph, such as povidone-iodine or alcohol. Products that are marketed under approved NDAs or ANDAs include those that contain chlorhexidine gluconate (either alone or in combination with an alcohol).

Patient preoperative skin preparations are marketed as solutions, swabs, pads saturated with a solution, and applicators containing a solution. Some patient preoperative skin preparation products are intended for one-time use only (single-use); others are intended for repeated use from the same container (multiple-use). Multiple-use containers of patient preoperative skin preparations may also be labeled for other indications, such as surgical hand scrub, healthcare personnel handwash, or skin wound and general skin cleanser.

Despite their inherent antimicrobial activity, patient preoperative skin preparations may become contaminated with bacteria. A number of product recalls have been prompted by the identification of bacterial contamination (see FDA's Archive for Recalls, Market Withdrawals, and Safety Alerts at <http://www.fda.gov/Safety/Recalls/ArchiveRecalls/default.htm>).

Furthermore, infections related to bacterial contamination of patient preoperative skin preparations have been described in the literature (Ref. 1). Some of these infections have remained localized at the site of an injection, but others have resulted in sepsis and death.

Contamination of patient preoperative skin preparations occurs by two known mechanisms. Intrinsic contamination occurs when microorganisms gain entry to the product during the manufacturing process and remain viable. Bacterial contaminants have been isolated from pharmaceutical water supplies and nonsterile antiseptic manufacturing environments. By contrast, extrinsic contamination occurs when microorganisms are introduced into a finished product by the end user. Extrinsic contamination can arise from a variety of causes, including dilution of the product with contaminated water, failure to use appropriate aseptic techniques during handling, and repeated use of nonsterile containers for product storage.

Our current good manufacturing practice (CGMP) regulations require manufacturers to have appropriate procedures in place to prevent the presence of objectionable organisms in drug products that are not sterile (21 CFR 211.113). However, the microbial limits test (United States Pharmacopeia Chapter 1111 (Ref. 2)) currently in use by many manufacturers may not detect very low levels of microbial contamination and does not screen for the types of intrinsically antiseptic-resistant organisms frequently identified as contaminants in patient preoperative skin preparations, such as Burkholderia cepacia and Bacillus cereus. Therefore, a product that passes

the premarket microbial limits test may still support the growth of contaminating microorganisms and become the source of clinical infection.

The subject of contaminated patient preoperative skin preparations was discussed at an Advisory Committee meeting held on August 5, 2009 (Ref. 3). FDA asked the Committee whether we should require patient preoperative skin preparations to be manufactured as sterile products. The Committee did not vote on FDA's question, but rather emphasized adherence to CGMP.

Reports of contaminated patient preoperative skin preparations, which have led to product recalls and clinical infections, raise a public health concern. Consequently, FDA has decided to hold a public hearing to hear from interested parties, including healthcare facilities, healthcare professionals, manufacturers, consumers, and others, about ways that these issues might be addressed.

II. Scope of the Public Hearing

FDA is holding this public hearing to seek input from interested members of the public on how to address microbial contamination of patient preoperative skin preparation antiseptic drug products. This hearing may be of interest to a wide range of audiences, including product manufacturers, those representing healthcare facilities, healthcare professionals, and consumers who use these products. FDA is interested in obtaining information and public comment on the following issues:

A. Intrinsic Contamination

1. Are healthcare providers and consumers aware that patient preoperative skin preparations generally are not sterile? What measures can be taken to increase awareness of this fact?

2. In light of the adverse events associated with contamination of patient preoperative skin preparations, should all such products be manufactured sterile?
3. Are manufacturers currently producing, or planning to produce, sterile patient preoperative skin preparations? If so, what method(s) are or will be used (e.g., terminal sterilization or validated aseptic manufacturing)?
4. What technical challenges, if any, are there in producing sterile patient preoperative skin preparation products? For a given manufacturer, approximately how long would a manufacturing switch take to allow for production of a sterile preoperative skin prep product?
5. How would the market change if all patient preoperative skin preparations were required to be manufactured sterile?
6. What can FDA do to help manufacturers overcome challenges in this area?

B. Extrinsic Contamination

1. Products manufactured sterile can be contaminated as soon as they are opened for the first time. What steps can be taken to reduce the risk of extrinsic contamination of patient preoperative skin preparations?
2. Excluding the use of these products before surgical procedures or injections, are these products used for other purposes in healthcare or home settings (e.g., wound care or maintenance care for indwelling catheters)? If so, what is the extent of these uses in healthcare or home settings? What settings or uses comprise the majority of utilization for single-use products? What settings or uses comprise the majority of utilization for multiple-use products?

3. To what extent are multiple-use containers of patient preoperative skin preparations further processed (e.g., diluted, mixed, or repackaged for subsequent redistribution) in healthcare or home settings? If these products are diluted, mixed, or repackaged, are they handled aseptically? Why are these products diluted?
4. Should patient preoperative skin preparations be marketed only in single-use containers? If single and multiple-use containers are permitted, in which ways could single-use containers be clearly distinguished from multiple-use containers (e.g., by labeling, size, volume, presence/absence of applicator)? What technical and practical challenges would manufacturers and users face should there be regulatory requirements that limit package sizes for multiple-use patient preoperative skin preparations?
5. Can product labeling, for example, instructions to “discard X days after opening,” be used to reduce the risk of adverse events associated with extrinsic contamination of patient preoperative skin preparations? How could a “discard by” date be established for individual products and how meaningful would such a date be in the context of current practices?
6. Are healthcare facilities or other entities providing information or training on safe use of multiple-use patient preoperative skin preparations, or taking other steps to reduce the risk of extrinsic contamination of these multiple-use products? If so, please describe these efforts and any available information on their effectiveness.

III. Notice of Hearing Under 21 CFR Part 15

The Commissioner of Food and Drugs is announcing that the public hearing will be held in accordance with part 15 (21 CFR part 15). The hearing will be conducted by a presiding

officer, who will be accompanied by management and technical personnel from the Center for Drug Evaluation and Research.

Under § 15.30(f), the hearing is informal, and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members may question any person during or at the conclusion of each presentation (§ 15.30(e)). Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (part 10 (21 CFR part 10), subpart C and § 10.203(a)). Under § 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. The hearing will be transcribed as stipulated in § 15.30(b) (see Transcripts for more details). To the extent that the conditions for the hearing as described in this notice conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

IV. References

The following references have been placed on display in the Division of Dockets Management (see Comments) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Weber, D.J., W.A. Rutala, and E.E. Sickbert-Bennett, "Outbreaks Associated with Contaminated Antiseptics and Disinfectants," Antimicrobial Agents and Chemotherapy, 51:4217-4224, 2007.

2. The United States Pharmacopeia 35-National Formulary 30. The United States Pharmacopeial Convention, Inc., MD, "Microbiological Examination of Nonsterile Products:

Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use,”
Chapter 1111:691, 2012.

3. Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting
transcript, available at:

<http://www.fda.gov/downloads/AdvisoryCommittee/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM179891.pdf>, 2009.

Dated: November 16, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

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