Guidance

Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs

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

April 2012
Current Good Manufacturing Practices (CGMP)

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Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0003
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
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I. INTRODUCTION

This guidance is intended to help manufacturers of positron emission tomography (PET) drugs meet the requirements for the Agency's current good manufacturing practice (CGMP) regulations for PET drugs (21 CFR part 212). Most PET drugs are designed for parenteral administration and are produced by aseptic processing. The goal of aseptic processing is to make a product that is free of microorganisms and toxic microbial byproducts, such as bacterial endotoxins. A media fill is the performance of an aseptic manufacturing procedure using a sterile microbiological growth medium, in place of the drug solution, to test whether the aseptic procedures are adequate to prevent contamination during actual drug production. Media fill procedures recommended in this guidance apply only to sterile PET drugs manufactured by aseptic processes under 21 CFR part 212.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In 1997, Congress passed the Food and Drug Administration Modernization Act (Public Law 105-115) (the Modernization Act). Section 121 of the Modernization Act directed FDA to establish appropriate approval procedures and Current Good Manufacturing Practices (CGMP) for PET drugs. The procedures were finalized and an implementation timeline was instituted on December 10, 2009, when FDA published regulations that described the minimum CGMP standards that each PET drug manufacturer is to follow during the production of a PET drug.[2]

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[1] This guidance has been prepared by the PET Drugs Working Group in the Center for Drug Evaluation and Research (CDER) at FDA.

[2] The regulations, CGMP guidance, and supportive information, including historical documents, are available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm.

Under the requirements of section 121, within 2 years following that publication date, a new drug application (NDA) or abbreviated new drug application (ANDA) must be submitted for any PET drug marketed for clinical use in the United States. Accordingly, PET drug application submissions should have been received by the Agency on or before December 12, 2011. In early December 2011, FDA decided that it would exercise enforcement discretion with regard to the submission of applications until June 12, 2012. Until June 12, 2012, FDA does not intend to take enforcement action against a PET facility currently producing PET drugs for clinical use for a failure to submit a new drug application by December 12, 2011, provided that the facility complies with all other FDA requirements, including current good manufacturing practices (CGMPs). FDA will not exercise enforcement discretion after June 12, 2012. Therefore, if a facility wishes to continue to produce PET drugs for clinical use after June 12, 2012, they must have submitted a new drug application (NDA) or an abbreviated new drug application (ANDA) by that date, or be producing the drugs under an investigational new drug application (IND). PET producers who are unable to submit an NDA or ANDA by June 12, 2012 or operate under an IND must find a new supplier who has submitted an NDA or ANDA. All PET producers must be operating under an approved NDA or ANDA, or effective IND, by December 12, 2015.

Recognizing that many PET drug producers are unfamiliar with the drug approval process, FDA issued the guidance *PET Drug Applications – Content and Format for NDAs and ANDAs,*[3] and held a public meeting in March 2011 to assist applicants in preparing NDAs and ANDAs for the three most commonly used PET drugs. In comments to the guidance and in questions raised at the public meeting, stakeholders requested that FDA provide guidance on media fills for validation of aseptic preparation for PET drugs. This guidance is being issued in response to these requests and is designed to help manufacturers of PET drugs comply with FDA regulations.

III. QUESTIONS AND ANSWERS

A. What is a media fill?

A "media fill" (sometimes known as a "process simulation") is the performance of an aseptic manufacturing procedure using a sterile microbiological growth medium in place of the drug solution. Microbiological growth medium is used in place of the drug solution during media fills to test whether the aseptic procedures are adequate to prevent contamination during actual drug production. A media fill is one part of the validation of an aseptic manufacturing process.

B. What is the media fill designed to evaluate?

The media fill should evaluate the aseptic assembly and operation of the critical (sterile) equipment, qualify the operators and assess their technique, and demonstrate that the environmental controls are adequate to meet the basic requirements necessary to produce a sterile drug by aseptic processing. The media fill does not validate the ability of the filter to sterilize growth media.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

C. What are the steps involved in a media fill?

1. Design

A media fill should be carefully designed to ensure that the simulation is representative of all the aseptic manipulations performed during production. These include preparation and assembly of the product containers, transfer of the product containers to the fill area, and all process steps downstream from the "sterilizing filter" up to product release, including packaging into finished product containers. Finished product containers with medium should then be incubated to permit the growth of microbial contamination in any containers. Microbiologically contaminated containers are expected to exhibit observable evidence of microbiological contamination after suitable incubation. The same type and source of containers should be used for media fills as are used in routine production. Media fills should be conducted in the same locations where the production occurs and employ the broadest scope of possible manipulations that could occur during production. Every aseptic manipulation during production up to the point of finished product release should be included in the media fill. Because each PET finished product container is to be sampled aseptically prior to release, sample withdrawal and any adjustments should be simulated as well.

The media fill is an experiment and therefore should include controls. These controls are independent of the quality audit of the growth medium (i.e., growth promotion testing). A positive control for a media fill is a sealed product container of medium that is inoculated with a small number (i.e., less than 10^2) of microorganisms. Inoculation of the positive control container should be done in an area separate from the critical manufacturing area. Consult *United States Pharmacopeia* (USP) Chapter 71>, Sterility Tests, for appropriate organism selection (one species is enough). To ensure the absence of false positive results, a negative control should be included to demonstrate that the medium was sterile to begin with. A negative control may be prepared by preincubating the medium, or by aseptically transferring medium into a separate suitable sterile container and incubating the control simultaneously with the media fill test containers. The controls should be incubated under the same conditions as the media fill containers. These controls may not need to be repeated when multiple media fills are being done within a week and use the same lot of growth medium.

All steps intended for aseptic manufacturing should be reproduced in the media fill, including sampling and dilution of the final product. All personnel involved in the aseptic manufacture of the drug product should participate in at least one media fill per year. All processing steps that the operator normally performs during aseptic manufacturing should be simulated.

The simulation process should duplicate the actual production process where the aseptic steps are conducted, from the set-up of the vial assemblies to the transfer of the bulk drug from the sterilizing filter into the final containers that are ready for release. A connection to the container of sterile medium may be substituted in place of the filter. Alternatively,

a filter may be included during media fills, but the filter should not be used to sterilize the growth medium. If the process is expected to include the addition of sterile diluent to adjust the strength following radionuclidic assay, sterile medium should be added in the same manner during the media fill. The temperature of the medium should be the same temperature as the drug solution would be during manufacture (e.g., ambient). If multiple vials are assembled, stored, and used over a period of days, the simulation should use vials that have been assembled in advance and stored as they would be during actual production.

After the final product container is filled and ready for release, it should be incubated in a temperature-controlled incubator. Although USP <71> recommends incubation at 20°–25°C for the aerobic growth medium, as a practical matter any controlled temperature between 20° and 35°C would work for media fills. However, the "controlled temperature" should be specified in your procedures and be maintained within a range that does not exceed ±2.5°C. The incubation period of a media fill should be no less than 14 days and the containers should be examined every 2 or 3 days.

All steps in a media fill should be done in the same locations as the drug production steps. If the product container is filled within the hot cell, then the media fill should also be performed in the hot cell. If it is not filled in the hot cell, then the media fill does not need to be performed there either.

The synthesis box is generally located upstream from the sterilizing filter and is not considered a sterile component or part of the aseptic operations. In such cases, do not include the synthesis unit in the simulations.

2. Preparation for the Test

Once the media fill procedures are established, all of the components necessary for the simulation should be assembled, including all of the equipment used in the aseptic part of the process. Media to be used in the simulation may be obtained commercially or prepared on site, and should be sterile.

When media are prepared on site, sterilization should be conducted using a validated process such as steam autoclave. Filtration is not recommended to sterilize the growth medium.

D. How do I choose the growth medium?

The most commonly used growth medium is soybean casein digest medium (SCDM), which is commercially available under various names such as Trypticase Soy Broth. A recipe for this medium is found in USP <71>. Recipes for SCDM in other pharmacopeia may have slight variations from the USP, but are acceptable. Other general growth media are available, but their use may not be as practical and may require justification.

Medium from a qualified commercial vendor may be used by multiple PET facilities for media fills. Shipping, storage, preparation, and handling procedures should be carefully designed, documented, and followed to ensure media integrity and stability. Commercially prepared media should be used within the label's shelf life and stored according to the label's recommendations.

E. How often should a media fill be performed?

To initially qualify an aseptic process at a specific facility, three media fills should be conducted on three separate days at that facility using the specific production process that is being qualified. Additionally, media fills should be conducted whenever significant changes are made to the aseptic process (e.g., changes in personnel, components, or equipment) and whenever there is evidence of a failure to maintain product sterility. Media fills performed to validate an aseptic process at a specific facility should be done by an operator who previously has been trained and qualified in aseptic techniques (e.g., proper gowning, disinfection practices, handling sterile materials).

Media fills are an important element of operator qualification. To become a qualified operator for PET drug product production, an operator should perform three media fills on three separate days. A qualified operator should perform a media fill at least annually.

F. A media vendor is typically qualified by testing three batches of medium. How do I do that?

Three commercially available batches/lots of medium from a single supplier should be subject to quality control tests. These tests should include visible inspection, pH, sterility, and growth promotion. Results of this testing should conform to the results reported in the certificate of analysis (CoA). You can refer to USP <71> for conduct of growth promotion tests.

Many vendors will have samples of different batches available for purchase and testing. If three different batches are not available initially, then it may be necessary to test each of the first three incoming batches for conformance to the CoA.

According to USP <71>, SCDM should be sterile (confirmed by incubating samples for 7 days at a defined controlled temperature), pH 7.3 (±0.2), and able to permit growth of selected aerobic species (e.g., *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*). For media fills, use of only one species of bacteria is necessary once a media vendor is qualified. Media qualification programs should periodically verify the full CoA and growth promotion capability to ensure continuing vendor reliability.

G. What is growth promotion testing? How is it used in PET production?

A growth promotion test ensures that the medium used in the media fill will support the growth of contaminating microorganisms. This is an essential control for media fills because the desired test result is "no growth" and only by demonstrating the medium's ability to support microbial growth can the negative result be relied upon. Growth promotion testing should be performed on the growth medium used in media fills. This may be performed by inoculating a portion of the

batch with a small number ($\leq 10^2$) of microorganisms to confirm that the medium supports growth.

When the medium is prepared "in-house" (at the site of the PET drug manufacture), a growth promotion test should be performed for each batch of medium prepared. Medium should be prepared using autoclave sterilization processing and not by sterilizing filtration.

A "ready to use" liquid medium supplied from a commercial vendor should be confirmed as suitable by growth promotion and other testing to confirm that it meets specifications and conforms to its CoA. Once a supplier has been demonstrated to provide consistently suitable medium, the CoA and positive control will suffice to establish the medium's suitability for use in media fills (the positive control will be used in lieu of demonstrating growth promotion potential).

H. What is the difference between a growth promotion test and a positive control?

Growth promotion testing confirms the medium's ability to support growth. Growth promotion testing is commonly done before using the medium in an experiment. A positive control tests the ability of the test method to result in a positive outcome and is commonly done concurrently with an experiment.

Media fill positive control shows that the medium in the drug product container will support growth after exposure to the filling process. The positive control should be a container filled as part of a media fill. The positive control test may serve as the growth promotion test for the medium, as long as a qualified vendor is being used.

I. When do I use a positive control?

A positive control is needed for each media fill that is performed using a single batch of medium. As stated previously, a positive control in the media fill may also serve as the growth promotion test of the medium (from qualified vendor) employed for the media fill. When performing a media fill, the positive control test may be done simultaneously with the media fill by inoculating a vial of medium from the same batch used for the media fill. It is also permissible to perform a positive control at the end (after incubation) of a media fill by inoculating an uncontaminated media fill test container and returning it for additional incubation. Inoculation of the positive control container should be done in an area separate from the critical manufacturing area.