CDRH Final Guidance Cover Sheet

REVIEWER GUIDANCE FOR NEBULIZERS, METERED DOSE INHALERS, SPACERS AND ACTUATORS

Office of Device Evaluation
Division of Cardiovascular and Respiratory Devices
Anesthesiology and Defibrillator Devices Branch

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Comments and suggestions may be submitted at any time for Agency consideration to**, Emil Wang, Center for Devices and Radiological Health, 9200 Corporate Boulevard, HFZ- 450, Rockville, MD 20850.** Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance **Emil Wang at (301) 443-8609.**

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INTRODUCTION

This guidance document is designed to replace "Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers, and Actuators" dated November 9, 1990. All previously released draft versions of this document are considered obsolete. This new document provides supplemental guidance to Food and Drug Administration (FDA) staff in the office of Device Evaluation (ODE) who review 510(k) premarket notification applications for aerosol delivery devices. This guidance does not replace the requirements of the Food and Drug Cosmetic Act, applicable regulations, ODE policies, or the Draft Reviewers Guidance for Respiratory Devices.

This guidance document presents an outline of the information that should be submitted in support of a 510 (k) premarket notification for an aerosol delivery device. Devices often require more than descriptive information for ODE staff to determine whether the device is substantially equivalent to a legally marketed device. Testing information is required to demonstrate that the performance of the device in the intended environment is as safe and effective as that of a legally marketed device and that the device performs in accordance with the claims made in its labeling. Performance testing information may include in vitro, in vivo,, and clinical evaluations.

The purpose of this document is to suggest the important in vitro testing information which should be present in 510(k) premarket notifications to justify the substantial equivalency of aerosol delivery devices for their intended uses. The suggestions and recommendations written in this document reflect methodologies which the Center for Devices and Radiological Health (CDRH) has determined to be acceptable and which, if followed, would help to produce scientifically valid data to support equivalency. In this context, several points concerning guidance documents should be remembered:

I. GUIDANCE DOCUMENTS

This guidance document suggests important evaluation criteria and test procedures. If the same objective, the demonstration of the safety and effectiveness of the device in the intended environment, can be achieved by other means, the manufacturer may do so; however, the burden is on the manufacturer to demonstrate that the alternate methods are comparable to those specified in this guidance document and adequately simulate the intended environment of use.

If the manufacturer has reason to think that a certain . recommendation of this reviewer guidance is not applicable to the device, the manufacturer may omit this recommendation; however, the manufacturer should provide sufficient justification for the omission of that recommendation.

The guidance document should be viewed as a "living" document. As the body of scientific knowledge expands and scientific techniques are improved, CDRH will periodically revise the criteria in this guidance document. When changes are made, the revised document will be made available through the Division of Small Manufacturers Assistance (1-800-638-2041 or 301-443-6597). We will attempt to inform the manufacturers, associations, and interested persons of the availability of the revised guidance document. Nonetheless, it should be remembered that the basic objectives remain the same.

The words "may", "should",, "shall", and "must" have been used frequently in this document to emphasize the importance of a specific aspect of a test or protocol.

This guidance is directed towards those devices that do not feature new technological characteristics that raise new types of safety and effectiveness issues (refer to the 510(k) decision-making chart in the ODE Blue Book). If a device does feature such new technological characteristics, only parts of this guidance document may be applicable. To complete an evaluation of a device which utilizes new technological characteristics, additional information may be required.

II. SCOPE

The Center for Devices and Radiological Health has been asked questions on a number of important issues related to the preparation of a 510(k) premarket notification for nebulizers, metered dose inhalers, and other related components such as actuators and spacers. This document is intended to respond to many of these questions and to provide a general awareness of the present perspectives held by the FDA on issues related to these devices. FDA regards all nebulizers and MDI's as prescription devices. The device manufacturer must have a cleared 510(k) premarket notification before marketing the device.

This reviewer guidance document suggests the importance of environmental testing, performance evaluations, and labeling information for aerosol delivery devices. It is expected that the device is a complete system suitable for its intended use as described in the 510(k) premarket notification. Within the scope of a device application, the applicant should also consult the Intercenter Agreements of October 31, 1991, referenced below for examples of the status of regulated products as devices or drugs. Also note the Intercenter Agreements define that an aerosol delivery device will be considered a drug product and regulated by the Center for Drug Evaluation and Research (CDER), when the primary purpose of the device is delivering or aiding in the delivery of a drug and the device is distributed with the drug. Therefore, if a device is intended to deliver a specific drug or if the labeling references a specific drug product, the device will be considered a drug product and regulated by CDER. It is important to note that Metered Dose Inhalers and Actuators are reviewed in the Center for Drug Evaluation and Research (CDER), where Nebulizers and Spacers as well as Metered Dose Inhalers intended for a ventilator circuit are reviewed in the Center for Devices and Radiological Health (CDRH). Since there are a variety of medical products in the category of nebulizers and MDIS, it is not possible to develop an exhaustive guidance document which will cover all modalities in most applications. However, the general principles regarding the information to be contained in a 510(k) should be valid for all cases.

III. FDA DOCUMENTS

The following documents feature the requirements applicable to 510(K) premarket notification submissions. All of these documents are available from the Division of Small Manufacturers Assistance (DSMA) at 800-638-2041 or 301-443-6597.

(1) Federal Food, Drug, and Cosmetic Act, as Amended, and Related Laws.

(2) Code of Federal Regulations, 21 CFR Parts 50, 56, 8071, 812, and 868.

(3) Premarket Notification: 510 (k) - Regulatory Requirements for Medical Devices (August 1990) (FDA 90-4158).

(4) Investigational Device Exemptions Manual, (June 1992) (FDA 92-4159).

(5) Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 29, 1998)

(6) Reviewer Guidance For Premarket Notification Submissions, DCRND/ARDB (November 1993).

(7) ISO 10993-1.

(8) Division of Bioequivalence Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers).

(9) Intercenter agreement between The Center for Drug Evaluation and Research and The Center for Devices and Radiological Health, October 31, 1991.

IV. APPLICABLE ENVIRONMENTAL DOCUMENTS

The following documents are referenced and form a part of this reviewer guidance document to the extent that some aerosol delivery devices are electronically controlled, and therefore,, would 6e subject to the requirements in the following documents.

(1) IEC 601-1 Second Edition (1988): Medical electrical equipment, Part 1: General Requirements for Safety, second edition. Available from the American National Standards Institute, 11 West 42nd Street, New York, NY 10036.

(2) IEC 529 (1989): Classification of Degrees of Protection Provided by Enclosures. Available as above.

(3) IEC 801-1 (1984): Electromagnetic Compatibility for Industrial Process Control Equipment. Available as above.

(4) IEC 801-2 (1991): Electrostatic Discharge Requirements, Available as above.

(5) IEC 801-3 (1984): Radiated Electromagnetic Field Requirements. Available as above.

(6) IEC 801-4 (1988): Electrical Fast Transient/Burst Requirements. Available as above.

(7) CISPR 11 (1990): Limits and Methods of Measurement of Radio-Interference Characteristics of Industrial, scientific, and Medical (ISM) Equipment. Available as above.

(8) CISPR 16 (1987): CISPR Specification for Radio Interference Measuring Apparatus and Measurement Methods. Available as above.

(9) ANSI C95.5 - 1981: Recommended Practice for the Measurement of Hazardous Electromagnetic Fields, 300 kHz to 300 GHz. Available as above.

(10) IEC 68 (1988): Environmental Testing. Available as above.

(11) MIL-STD-461C (August 4, 1986): Electromagnetic Emissions and Susceptibility Requirements for the Control of Electromagnetic Interference. Available from Naval Publishing and Printing Service Office, 700 Robbins Avenue, Philadelphia, PA 19111-5094.

(12) MIL-STD-462 (July 31, 1967): Standard for the Measurement of Electromagnetic Interference Characteristics. Available as above.

(13) MIL-STD-810E (July 14, 1989): Environmental Test Methods. Available as above.

V. PREMARKET NOTIFICATION SUBMISSIONS.

The following basic information should be included in a premarket notification submission. This information is necessary in the evaluation of the safety and efficacy, and the substantial equivalence of aerosol delivery device. Depending on the intended use and the technological characteristics of the device, additional information may be required to complete an evaluation.

A. EXECUTIVE SUMMARY

The premarket notification should include an executive summary which serves as a general description of the device and its indications for use. The summary should indicate if the device is a modified or enhanced version of a legally marketed device, whether it be modifications in hardware, software, features, accessories, components, or intended use. The summary should also identify all configurations, components, sizes, and accessories of the device.

B. INTENDED USE

The 510(k) premarket notification submission should identify the intended use of the device under review. The intended use statement should identify the purpose and function of the device, the target patient population, the intended environment of use, and all claims for the device. The submission should also identify a legally marketed predicate device(s) with the same intended use statement. If the intended use of the device under review differs in any way from that of the legally marketed device(s), it must be shown that the differences do not adversely affect safety and effectiveness.

1. Pursuant to 21 CPR 807.87(e), each premarket notification shall contain proposed labeling including advertisements sufficient to describe the device, its intended use, and the directions for its use. This information must be provided with any specific claims that are to be made regarding the drugs to be used with the nebulizer or the MDI. The labeling must also include any claims for the prevention of the spread of viruses or other disease processes. The labeling must state if the device is intended for single patient use and if the device is disposable.

2. In accordance with 21 CFR 801.109 (b) (1) , the nebulizer, MDI, or accessory should bear the prescription labeling statement: "Caution: Federal law restricts this device to sale by or on the order of a physician."

3. Adequate instructions for use must also accompany the device. The instructions should include, but not be limited to, the governing principle behind the nebulization process (i.e., jet, ultrasonic, Venturi, etc.). This should include instructions for the application of the device principles, any special instructions needed to personalize the device for a particular drug, and an-explanation of the actuator mechanism of the device if necessary. Depending on the nature of the device, it may be necessary to include instructions for both the physician and the patient. The instructions should include necessary cautionary statements for the nebulizer/MDI and particular drugs which may be used. The labeling should include a statement against reuse and resterilization of the device if filters are used in the device configuration.

C. DEVICE DESCRIPTION

The 510(k) premarket notification submission should include a precise description of the device. This information should include detailed discussions of the device features, functions, detection capabilities, method of operation, materials, alarm capabilities, software, specifications and operating ranges, power source, parameter detection ranges, etc. This description should contain engineering drawings, pictures, and all device labeling, such as instructions for use and promotional materials.

The device description should also address the following questions:

1. Is the device life-supporting or life-sustaining?
2. Is the device an implant (short-term or long-term)?
3. Is the device sterile?
   If the device sterile, then sterility information should be provided in accordance with the .510 (k) Sterility Review Guidance.

4. Is the device for single use?
   If no, validation data demonstrating that the device may be resterilized (if required) and reused should be provided. If appropriate, the labeling should address how often the device can be reused or identify a performance test(s) or inspection(s) that the device must meet after each sterilization.
5. Is the device for prescription use?
   If yes, the required caution prescription statement must be included in the labeling.
6. Is the device for home use or portable? Whether the answer is yes or no, adequate environmental testing should be conducted on the device (see 6).
7. Does the device contain a drug or biological product as a component?
   If yes, consultation from other FDA Centers may be required.
8. Is this device a kit?
   If yes, and some or all of the components are not new, the submission should include a certification that the components were either preamendment or were found substantially equivalent (provide 510(k) number(s) and proof of preamendment status).
9. Is the device Software-driven?
   If yes, the firm should provide a hazard analysis, software requirements and design information, adequate test plans/protocols with appropriate data and test reports, documentation of the software development process including quality assurance activities, configuration management plan, and verification activities and summaries, commensurate with the level of concern, as discussed in the Reviewer Guidance for Computer Controlled Medical Devices. The level of concern should be identified with the hazard analysis, and the most recent software version should be included in the file.
10. Is the device electrically operated?
    If yes, AAMI or IEC allowable leakage current requirements should be met and information should include the test protocol, data, and results. Electrical safety requirements should also be discussed including applicable standards to which conformance has been demonstrated. This may also include appropriate data (test protocol, data, and results).
11, Are there applicable standards for this device to which conformance has been demonstrated in addition to those already mentioned (e.g., IEC, ANSF, ASTM, etc.)?
    If standards applicable to the device include testing to demonstrate conformance, test data should be provided to demonstrate conformance (protocol, data, and results).

D. TABLE OF COMPARISON TO LEGALLY MARKETED DEVICE

The 510(k) premarket notification application should include a table identifying and differences between the device under review and a legally marketed predicate device. The comparison should identify similarities and differences in the intended use, specifications, materials, design, features, method of operation, accessories, etc. For the device to which equivalence is claimed, the manufacturer, product name (model number), and 510(k) number or preamendment status should be provided. For a preamendment predicate device, documentation demonstrating that the device was marketed prior to May 28, 1976 is necessary.

E. DISCUSSION OF SIMILARITIES AND DIFFERENCES

The 510(k) premarket notification application should include a discussion of the similarities and differences between the device under review and a legally marketed predicate device. This discussion should elaborate on the similarities identified in the table of comparison and should explain and justify the differences with a supporting rationale and/or data. If the differences are new technological characteristics, it must be shown that the differences do not adversely affect safety and effectiveness.

If the device is a modified or enhanced version of a legally marketed device, whether it be modifications in hardware, software, features, accessories, components, or intended use, the discussion should include this information, along with a rational for each modification. If the modifications are being implemented to correct problems, this should also be addressed. If the device comes in a variety of configurations, sizes, or accessories, or is sold with a variety of other

components, every configuration or combination should be included in the comparison and 510(k) numbers or proof of preamendment status for components or accessories should be provided.

If reference literature is used to support any differences, copies of the articles must be provided as opposed to listing the author and titles, the significant areas of the articles must be highlighted, and a summary must be provided relating the information to the issues at hand, including a discussion of the study protocol, data, statistical analyses, and a summary of the results. Reference literature may not always be acceptable to justify the differences between a new and predicate device.

Differences in technological characteristics may also require the submission of performance evaluations to assess the effects of new characteristics on safety and effectiveness. If the differences include material changes, biocompatibility testing may be required.

F. PERFORMANCE EVALUATIONS

The 510(k) premarket notification application should include testing information demonstrating safety and effectiveness of the performance characteristics of the device in the intended environment of use. The type of the device and its intended environment will determine the type of testing that is necessary.

1. Evaluations of the device performance characteristics should include adequate environmental testing demonstrating the safety and effectiveness of the device in its intended environment of use. Recommended environmental, electrical, and mechanical test procedures and protocols are in Reviewer Guidance For Premarket Notification Submissions, DCRND/ARDB (November 1993). referenced above. The submitted information should include the test procedures and protocols, an explanation as to how the test procedures simulate the intended environment of use and/or are comparable to the test procedures, test results, and an analysis of the results.

2. Evaluations of performance characteristics may include nonclinical laboratory performance testing and/or comparative in vitro testing. Reports of such testing should include the test protocol and procedures, test apparatus (if any), results including statistical and clinical considerations, comparative data from a predicate device tested under the same conditions, and a summary explaining how the testing and data demonstrate that the device performs within specifications (see In Vitro Section for specific performance requirements).

   All nonclinical laboratory performance testing utilizing a test system as defined by 21 CFR 58.3(i) should be performed in accordance with 21 CFR Part 58 - Good Laboratory Practice For Nonclinical Laboratory Studies. This part describes good laboratory practices for conducting nonclinical laboratory studies that are intended to support 510(k) premarket notification applications.

3. Evaluations of performance characteristics may include biocompatibility testing performed in accordance with ISO 10993-1. The submitted biocompatibility information should include the protocol for each test required as outlined in ISO 10993-1, the pass/fail criteria, test results, and an analysis of the results.

G. CLINICAL-PERFORMANCE EVALUATIONS DATA

Demonstration of performance characteristics, new technological characteristics, and a new intended use may require clinical performance evaluations or the collection of clinical data. The submitted information should include the test procedures and protocols, justification of the patient population, test results, and an analysis of the results.

All clinical performance evaluations and collections of clinical data should be conducted in accordance with 21 CFR Part 812 - Investigational Device Exemptions, 21 CFR Part 50 - Protection of Human Subjects, and 21 CFR Part 56 Institutional Review Boards. The determination of whether a clinical performance evaluation or the collection of clinical data involves a significant risk or a

nonsignificant risk device is normally made by an institutional review 13@oard (IRB); however, in some cases it may be made by FDA. If the FDA or IRB(S) at the institution(s) where the evaluation will be conducted considers the device to be one of significant risk, then any clinical evaluation must receive FDA and IRB approval before initiating a clinical evaluation with the device. Otherwise, if the IRB(S) at the institution(s) where the evaluation will be conducted determine that the device is a non-significant risk device, then the evaluation should be conducted under the auspices of the IRB, even though an IDE would not need to be filed with the FDA. In the case of a non-significant risk determination, the submission should include documentation from the IRB identifying the determination and documentation demonstrating that subject informed consent was obtained.

H. 510(k) SUMMARY OR STATEMENT

In accordance with the Safe Medical Devices Act of 1990 (SMDA), the 510(k) premarket notification application must include either a summary of the safety and effectiveness information in the premarket notification submission upon which an equivalence determination could be based (510 (k) summary), or a statement that safety and effectiveness information will be made available to interested persons upon request (510(k) statement).

I. CLASS III CERTIFICATION AND SUMMARY

Any person who asserts that the device under review is substantially equivalent to a class III device must (1) certify that he or she has conducted a reasonable search of all information known, or otherwise available, about the generic type of device, and (2) provide summary description of the types of safety and effectiveness problems associated with the type of device and a citation to the literature, or other sources of information, upon which they have based the description.

VI. PERFORMANCE REOUIREMENTS - IN VITRO

The in vitro performance section of the premarket notification must detail adequate protocols and bench testing procedures which demonstrates equivalency of the subject aerosol delivery system and the predicate device. The manufacturer must provide a summary of the procedures used for the performance characterization of the device. To address these areas, options available to the manufacturer include bench testing, previously published scientific literature, and development of theoretical rationales based on current knowledge. A combination of these approaches will prove to be the best choice in most situations.

The requirements for bench characterization will be influenced by the principle of operation of the aerosol delivery system. For example, if the nebulizer is pneumatically powered, the required flow rates and pressures to achieve effective nebulization will be important. In addition, the test method utilized to determine the particle size of the drug may vary depending upon toe test method, the type of drug that is tested, and the set-up of the testing procedure.

A comprehensive summary of all in vitro testing should be included in addition to specific detailed test descriptions. For each test, the manufacturer should specify the device component (s) being tested, the test procedures including equipment, protocol, measurement techniques, and test parameters. A clear summary of the results must be presented. The consequences of test results should also be discussed in terms of the potential in vivo performance of the aerosol delivery system. Consultation may be made at an early stage with DCRND to determine what in vitro tests are appropriate.

In terms of actual in vitro performance testing- requirements of an aerosol delivery device, the following items should be included by the manufacturer in developing equivalency data for incorporation in a 510(k) premarket notification:

1. As stated previously, the bench testing protocol must begin with a clearly defined objective. This should include precise, well-defined testing methods and device configurations. The

testing method should be designed to fulfill protocol requirements.

2. The specific aerosol delivery system must be completely described (including what type is it? pneumatic, ultrasonic, heated, gas, venturi, etc.). The description must include detailed drawings of all component parts of the device, and include a summary section on the principles of use. Specific components of a nebulizer system must be described. For example, does the nebulizer utilize any one-way valves, and if so, what type of valve is utilized (i.e., flutter, flapper, duckbill, etc.)? What are the operational pressures of the valve? The manufacturer should also include the testing procedures that have been done to assure that the valve(s) do not leak during a forceful exhalation.

3. Complete specifications for filter or scavenging systems including the material that is used must be included. specifications such as the effective filtering size in microns, and any other specifications from the manufacturer should be submitted.

4. Other specifications that should be included are the required flow rates and pressures optimized to achieve effective nebulization for a pneumatically driven nebulizer.

5. If the aerosol delivery device is intended t% be used for more than single usage, simulated life-time testing must be presented. This information should address disassembly, cleaning, and reassembly procedures. The life testing should demonstrate that the device will perform according to its specifications as identified by the in vitro performance results specified below throughout the usable lifetime of the device. The instructions for use of the device should also identify functional checkout procedures which provide pass/fail guidance procedures that ensure proper device performance following a cleaning/reassembly procedure.

The following tests are intended to characterize in part the in vitro performance of the aerosol delivery device under review in the premarket notification relative to that of a comparable predicate device.

VII. PARTICLE SIZE DELIVERED FROM MOUTHPIECE

For each aerosol delivery device or accessory such as an add-on spacer device, particle size distribution testing must include testing with at least one bronchodilator and one steroid. Particle size distribution testing must include at least three different drugs consisting of bronchodilators, steroids, antiallergics, mucokinetic agents, or antiviral agents.

Several particle sizing techniques are currently used to size aerosol particles. Of these, the most commonly used and the most widely recognized is the cascade impactor method. Other methods include optical microscopy, laser light scattering, laser doppler methods, and others. Particle size distributions from the mouthpiece connection should be determined using at least two different methods since apparent particle size distributions may differ depending upon the particle sizing technique. At least one of the methods utilized must be with the cascade impactor.

The cascade impactor provides an assessment of particles in the aerodynamic diameter range of 0.5 - 32 microns. The following variables shall be determined:

1. The total mass of drug released from the inhalation aerosol;

2. The quantity of drug collected at each location of the cascade impactor device;

3. The mass median aerodynamic diameter (MMAD - the diameter above and below which lies 50% of the mass of the particles (1)); and

4. The geometric standard deviation (GSD (2,3)).

The cascade impactor system should consist of a sampling chamber, the cascade impactor (with at least six stages), a vacuum pump and a flow meter. Standard dimensions and shapes of the sampling chamber have not been established, however, the volume of the chamber should not be less than 0.5 liters and the length of the unobstructed path between the mouthpiece connection and the far side of the sampling chamber should not be less than 13 cm. The distance should be sufficient that no coalescence occurs in the chamber. The airflow rate should be approximately 10 - 15 liters per minute. The specific chamber dimensions, shape and the airflow rate through the chamber should be described. Based upon the airflow rate, aerodynamic equivalent particle diameters should be tabulated for each of the six or more impactor stages and presented in graphical form for distribution results. other physical testing information for aerosols can be found in U.S. Pharmacopoeia documents (4).

Other methods for comparative particle size distribution data can be utilized provided that the technical details such as the particle size range and reproducibility are acceptable. A complete description of the instrument and experimental variables should be submitted. For nebulizers, the dose rates and particle size distributions as a function of time should also be presented.

VIII. METERED DOSE INHALER, ACTUATOR, AND SPACERS

In addition to the particle size distribution testing for all aerosol delivery devices referenced above, the following tests should be conducted to further characterize the performance of metered dose inhaler devices, actuators, and spacers. The three drugs tested for particle size distribution should be tested as follows:

1. The metered dose inhaler/actuator device must be directly compared to a predicate device. For example, particle size distribution data should be gathered for the predicate and new device so that a direct comparison utilizing the identical particle sizing method can be made. Particle size distributions should be collected at three different times during the life of the canister, i.e., when the drug canister is full, 1/2 full, and toward the end of the canister lifetime.

2. Spray pattern and plume geometry are used to characterize primarily the performance of the valve and actuator. Spray pattern and plume geometry must be collected for the MDI/actuator assembly. Spray pattern should be determined by impingement of the spray on a thin-layer chromatography (TLC) plate. Since the observed spray pattern may vary with the distance from the actuator orifice to the TLC plate, a spray pattern profile should be determined a-t-7-a distance between 2.5 and 7.5 cm from the mouthpiece for the new device and a legally marketed predicate device. Dimensional analysis of the geometry of the plume and the distribution of particles in the plume may vary depending on the configuration of the device. Plume geometry (side view of the plume) data for the new product and the reference product are optional but highly encouraged for both products.

3. A spacer device must be directly compared to a predicate spacer as well as directly compared to an MDI alone without the spacer attached. Particle size distribution data should be gathered for the predicate device and the new device utilizing the identical MDI attached to the devices. Furthermore, a particle size comparison between the new spacer device and the attached MDI alone must be presented. Each spacer must have particle size distribution data for each drug classification type for which it is intended (in this context drug classification type refers to the general types listed above, i.e., bronchodilators, steroids, anti-allergics, etc.). For example, data must be gathered with at least one bronchodilator, one anti-allergic, and one steroid if the spacer is intended for use with each specific drug classification type.

   In vitro data must be confirmed with small in vivo confirmational trials to assess the relative

safety and effectiveness of the spacer device when compared to the MDI drug product alone. The in vivo trials must consist of at least two trials per drug classification type; one trial to assess the effectiveness and one trial for safety. The trials should directly compare the relative effectiveness and safety of the spacer to the MDI. Labeling for the spacer should be consistent with the results of the in vitro and in vivo study results.

4. The potency or the average amount of drug delivered per spray must be specified. Potency tests should be performed for each specific drug in the claims of intended use.

IX. REFERENCES

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