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August 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20857

SUBJECT: Docket 99D-1454
DRAFT Draft Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing and Controls Documentation

Dear Sir or Madam

We refer to the June 2,. f999 Federal Register notice (64 FR 29657) requesting comments on the draft guideline "Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products." This correspondence provides comments, on behalf of the Janssen Research Foundation (a division of Johnson & Johnson).

Janssen supports the FDA initiative to provide guidance on the requirements for metered dose nasal spray and inhalation drug products, However, we are concerned that the level and scope of the proposed requirements will place an unreasonable burden on the developers of these dosage forms, without providing any additional controls on the safety, identity, strength and purity of the drug product. We respectfully urge the division to consider the attached specific comments in preparing the final Guidance-Document.

We thank the Agency for the opportunity to provide comments on this draft guidance and look forward to a continuing dialog as the Agency finalizes its guidance on this topic. Please do not hesitate to contact me at (609) 730-3081 or Jim Medley, Ph.D. at (609) 730-3049, if you have any questions regarding our comments.

Sincerely,

Sheila Alexander
Asst. Director, Technical Regulatory Affairs

99D-1454

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1. Introduction

The draft guidance document is a comprehensive list of recommendations for the chemistry, Manufacturing and Control of metered dose spray drug products, excluding pressurized aerosol inhalers and sprays. As such, it covers both nasal spray solution and suspension systems and inhalations delivered via a mechanical pump action.

The guidance document provides very stringent recommendations for these dosage forms. Based upon our background and experience in the manufacture of metered dose nasal spray mechanical pump systems, we have specific comments on these recommendations.

2. Comments

Section III C. 1. Specifications for the Formulation Components.

Lines 170-179
Microscopic examination of the drug substance particles in a suspension formulation is a subjective test which may not yield any additional information than that obtained by a more objective test such as particle size distribution analysis. In addition, surface area analysis of the particles is a very difficult test and may not have relevance to this particular dosage form. Surface area analysis is not a requirement for any other dosage form.

Lines 181-189
The crystalline form of the drug substance particles in a suspension formulation should be characterized as part of the development activities. Unless there is a demonstrated potential for a crystalline phase change, this test need not be part of the routine release testing for drug product. Assay for the non-crystallrne or amorphous content of the drug product formulation is a difficult and non-routine analytical procedure. The solid phase components of the suspension should be fully characterized during the development process.

Line 197
The limits for identification and qualification of impurities in the drug product should be in compliance with the ICH Q3b, "Guideline on Impurities in New Drug Products," and should be based on the maximum daily dose. A limit of 0.1% for identification and qualification is only required for a maximum daily dose of 2 g or more of the drug substance.

Section III C.2 Exciplents

Lines 245-249
21 CFR 211.84(d)(2) lists the specific requirements for acceptance of vendor Certificates of Analysis for all components of a drug product, including excipients. The specifics of this regulation should not be repeated in guidance.

Section III E. Method(S) Of Manufacture And Packaging

Line 292-293
This statement is ambiguous and could be interpreted to state that all spray drug products including nasalspray must be manufactured as sterile products. The statement should be clarified to specifically exclude nasal spray products.

Section. III F. 1 Specifications For The Drug Product; Nasal Sprays

Lines 393-395
As described above, the limits for identification and qualification of degradants in the drug product should be in compliance with the ICH Q3b Guideline. In accordance with ICH Q3b, related compounds arising from the synthesis of the drug substance are controlled in the drug substance specifications and degradation products are controlled in the drug product specifications. The limits for identification and qualification of new impurities should be based on the maximum daily dose.

Lines 404-413
There is no description of the number of samples to be tested for pump delivery, while under the description of Spray Content Uniformity, the number of samples is described. Both of these tests will assess the metering capability of the pump system. A requirement for both tests is redundant, and places unreasonable demands on the testing laboratory. It is our opinion that spray content uniformity is the more informative test.

Lines 417-447
The specification for spray content uniformity is more stringent than the USP compendial requirements for dose uniformity for metered dose topical aerosols or metered dose inhalation systems. This requirement in the guidance places an undue restriction on the innovator of a metered dose product to comply with a more stringent specification than a subsequent manufacturer. The requirement for spray content uniformity should be consistent with the official compendia1 requirements for this dosage system.

-Lines 476-502
Characterization of plume geometry and spray pattern is a legitimate activity in development. However, for a nasal spray product where the mean diameter of the nasal cavity is significantly less than the plume diameter, this test is irrelevant to the finished product. A more appropriate control is the droplet size and dose uniformity of the finished product, which will assure a consistent and uniform delivery of the drug product to the site of action.

Lines 538-544
This section describes potential issues related to foreign particulates but offers no guidance or recommendations for controlling or monitoring foreign particulates. Shedding of particulates from the pump system should be assessed as part of the development activities. Any changes to components or composition of the pump system may require additional assessing of particulate shedding. However, this test should not be part of the routine product release testing.

Section III G. Contalner Closure System.

Line 810
The requirement to prevent partial metering of the formulation is not technically feasible using current commercially available mechanic&nasal spray pump systems.

Lines 904-922
By only testing extraction in standard solvent systems, the test may not be relevant E^L---- assessing the toxicity of compounds from plastic components extracted into the formulation itself. A more appropriate assessment would be to focus on the identification and toxicological assessment of the leachables. Identification and toxicological assessment of leachables should be performed as a development exercise to qualify the individual

components. Once components are qualified, the assessment of leachables should only be performed to qualify changes in container-closure components or plastic resins.

Lines 926-942
Routine extraction testing of container-closure components is unnecessary since the level of extractable and/or leachable components is controlled by the manufacturing formula and process for the plastic parts. An appropriate toxicological assessment of leachables from the plastic resin formulafion, in combination with assurance that any change to the manufacturing process or resin formulation will be evaluated for impact on the level of leachable components, should be adequate. Such information could be provided in the NDA or by reference to the Type III Drug Master File provided by the pump supplier.

Line 947
Specifications for the label, ink and adhesives should not be required for HDPE bottle systems, since the leaching of fhese components through HDPE is not relevant. Such specifications may be relevant to more permeable bottle types, i.e. inhalation systems or ophthalmlcs using LDPE containers.

Section III. H. Drug Product Stability

Line 991
Inclusion of manufacturers for drug product excipients need not be included in the stability report, if these manufacturers are specified elsewhere in the application. Manufacturers of compendia1 excipients need not be provided in the application. For critical formulation components, it may be necessary to include additional qualification tests beyond the compendial requirements.

Line 1024
The requirement for four time points (0, 1, 3, 6 months) for accelerated conditions is not in accordance with the latest discussions of the ICH Q1A meeting in Brussels in 1999. Also in those discussions, the consensus was that statistical evaluation of accelerated stability data is not appropriate.

Line 1037
The optimal storage position for stability should be determined prior to formal registration stability studies. Placing three registration batches in multiple orientations in the stability protocol places an undue burden on the testing laboratory.

Lines 1057-1062
The semi-permeable packaging conditions are still under discussion in the ICH Q1A Working Group. The Working Group is considering the potential for testing water loss at the 25°C/40%RH storage condition. The standard ICH storage conditions should be specified in this guidance. These conditions are: 25°C/40%RH, 30°C/60%RH, and 40°C/less than 25%RH.

Section IV. Drug Product Characterization Studies

This section contains recommendations for characterization tests that are specific to Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products, and characterization tests which are general to any liquid solution and suspension formulations. Characterization tests such as Temperature Cycling (lines 1 195-1 2 10), Effect of Storage on Particle Size Distribution (lines 1272-1276), Preservative Effectiveness and Sterility Maintenance (lines 1289-1299), Photostability (lines 1307-1313), and Stability of Primary Package (lines 1315-

1323) are general to liquid formulations. These requirements should be incorporated as part of the stability guidance document and are not appropriate in this guidance.

Section V. Labeling

Lines 1342-I 343
Inclusion of the phrase *For Oral Inhalation Only* or *For Nasal* Use *Only* following the established name is redundant and not necessary, since the route of administration is clearly designated in the product name. Specification of the delivery route in this fashion is not required for other dosage forms.

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