COMMENTS

on a draft Guidance for Industry
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products
Chemistry, Manufacturing, and Controls Documentation
(Docket No. 99D-1454)

Submitted by
The International Pharmaceutical Aerosol Consortium

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I. INTRODUCTION

The International Pharmaceutical Aerosol Consortium (IPAC) is an association of companies that develop and manufacture oral inhalation and intranasal products for local and systemic treatment of chronic obstructive pulmonary disease (COPD), rhinitis, and migraine. These comments are being submitted on behalf of the following members of IPAC's Working Group on FDA Guidance: Aradigm, AstraZeneca, Boehringer Ingelheim, Dura Pharmaceuticals, Eli Lilly, GlaxoWellcome, Inhale Therapeutic Systems, Inc., Medeva Americas, Norton Healthcare, Pfizer, Rhône-Poulenc Rorer, Schering-Plough Corporation and 3M Pharmaceuticals. The members of the IPAC Working Group on FDA Guidance are committed to the highest standards of safety, efficacy and quality in the development and manufacture of drug products for oral inhalation and intranasal delivery.

Patients rely on nasal spray medications and inhalation solutions and suspensions for the safe and effective treatment of diseases. The pharmaceutical industry and the Food and Drug Administration (FDA) share a common goal, that is, to respond to the needs of patients for these medications by expediting the availability of new products to the market while maintaining appropriate standards of safety, efficacy and quality.

The member companies of the IPAC Working Group on FDA Guidance commend the Inhalation Drug Products Working Group of the Chemistry, Manufacturing, and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) on their efforts to develop this Draft Guidance for Industry. We recognize the value of having this guidance as an aid to facilitate the development and approval of new nasal and oral inhalation medications. The IPAC Working Group also appreciates the opportunity to provide the following comments to the Agency. We hope that through our comments we may assist the Agency in developing a final Guidance that will clarify for industry the aspects of pharmaceutical performance and quality that the Agency considers important to control and, consequently, assist developers in understanding more clearly the Agency's expectations. Such a Guidance will enable industry to avoid unnecessary drug development delays and will better serve patients by facilitating the prompt approval of safe and effective new nasal and oral inhalation drug therapies.

We wish to refer to the comments submitted by the International Pharmaceutical Aerosol Consortium on February 17, 1999 (Docket No. 98D-0997) on the related draft *Guidance for Industry Metered Dose Inhaler (MDI) and Dry Power Inhaler (DPI) Drug Products; Chemistry, Manufacturing and Controls Documentation*. The Draft Guidance for Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products and the

draft CMC Guidance for MDIs and DPIs are closely related in content and format. Therefore, many of the comments herein are similar or closely related to those submitted by IPAC on the draft CMC Guidance for MDIs and DPIs.

We also reference the Statement presented by the International Pharmaceutical Aerosol Consortium at the *AAPS/FDA/USP Workshop on Regulatory Issues Related to Drug Products for Oral Inhalation and Nasal Delivery*, held on 3-4 June 1999 in Washington, D.C. The IPAC Statement offered an industry perspective on the draft CMC Guidance for MDIs and DPIs, but also proposed that a process for collaboration be undertaken by the FDA with respect to the development of the CMC Guidance for MDIs and DPIs. The IPAC request for further collaboration on CMC issues prior to the publication of a final CMC Guidance for MDIs and DPIs applies equally to the Draft Guidance for Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products, as our principal concerns with each draft CMC Guidance are substantially similar.

II. THE DRAFT GUIDANCE APPEARS TO REQUIRE MORE TESTING OF DRUG PRODUCTS THAN IS NECESSARY

The IPAC Working Group on FDA Guidance fully supports the development of a Draft Guidance for Industry for Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products. In general, we find that the Draft Guidance is comprehensive and, in certain areas, describes appropriate procedures for drug product development and quality control. As in the Draft CMC Guidance for MDIs and DPIs, however, in several places, the Draft Guidance appears to require testing of drug products for attributes that can be properly controlled at earlier stages in drug development or at the component level. For example:

- The Draft Guidance establishes spray pattern and plume geometry measurements to control finished component parameters. (Lines 476-502). We agree it is appropriate to conduct spray pattern and plume geometry studies during product development. Control of the components with appropriate sampling plans and dimensional measurements, however, is more precise than measuring the spray plume reproducibility. Spray pattern and plume geometry measurements are redundant and generally ineffective procedures to control component parameters.

- The Draft Guidance includes microscopic evaluation as a release and stability-testing requirement. (Lines 525-536). Microscopic evaluation is subjective, non-specific and relatively crude in measurement capability. The Draft Guidance should be revised to state that in most cases except foreign particulate matter, microscopy as a routine

control procedure is subjective and insensitive and should not be a release and stability-testing requirement.

- Control of leachables is more appropriate at the component or bulk material level rather than on the product level. Correlation between component levels and product levels should be evaluated during development. In addition, if levels are consistently well below the threshold of any safety concern, such testing may be eliminated altogether. The Agency should rely on cGMPs to control component composition and compliance during manufacture of components or product. (Lines 580-591)

- The Draft Guidance does not refer to ICH *Q3B Impurities in New Drug Products* and does not incorporate any of the ICH concepts regarding impurities and degradation products in drug products. Instead, the Draft Guidance does not differentiate between degradation products and synthetic impurities. Drug substance impurities are fully controlled by the specification and test methods for the drug substance. We recommend that the Draft Guidance be amended to remove drug substance impurities from the drug product controls. (Lines 389-395).

- The Draft Guidance includes pump delivery as a release and/or stability specification. We recognize that pump delivery is an important test criterion for pump components and is often useful as a development tool and in investigations of out-of-specification dosing results. However, pump delivery is a redundant control procedure and should not be used for a release or stability specification. We recommend that the Draft Guidance be revised so as not to include pump delivery as a release or stability specification. (Lines 404-413).
- The Draft Guidance includes a requirement for a complex multi-stage droplet size control for nasal sprays. (Lines 504-512). We believe that control of the pump or pump sub-components with an end-product test is redundant and an ineffective means of controlling product quality. Control of components with appropriate sampling plans and dimensional measurements is far more precise than measuring droplet size.

III. SPECIFICATIONS IN THE DRAFT GUIDANCE

As we also stated in the comments submitted by IPAC on the draft CMC Guidance for MDIs and DPIs, we agree that the Draft Guidance should allow for alternative approaches that accommodate many different products and technologies but

ensure the safety, efficacy and quality of the drug product. We believe, however, that the incorporation of very detailed specifications in a Draft Guidance runs counter to the Agency's statement that "alternative approaches may be used." Such detailed specifications may, in effect, restrict development to a common standard when that standard may not be applicable or appropriate in all cases.

Specifically, the Draft Guidance establishes a single, one-size-fits-all specification for spray content uniformity that does not provide for the consideration of relevant development or production data or the criteria set forth in *The United States Pharmacopeia and The National Formulary* (USP) standard (USP 23, Suppl. 10, General Chapters *<601> and <905>*). (*See* lines 415-474). Rather than providing a single specification for spray content uniformity, we recommend that the Agency establish a process by which a spray content uniformity specification should be determined, on a product-by-product basis, in light of currently accepted statistical and quality control procedures and relevant product-specific development and manufacturing data.

We also believe that the use of the compendial process, through the USP, is a better mechanism for establishing, publishing, and maintaining specifications. The compendial process includes the collaborative participation of the FDA and recognized technical experts outside FDA and also involves public comment. This process has established many monographs for excipients used in pharmaceutical products and has produced numerous test procedures and specifications used in the pharmaceutical industry. In fact, the Agency refers to several USP specifications in the Draft Guidance (*e.g.*, USP <61> (line 176), USP <87> and <88>, (lines 912-913)).

A further concern is that the Draft Guidance does not address the Agency's criteria for setting specifications. We recommend that the Draft Guidance be revised to incorporate the use of scientifically recognized statistical and other quality control concepts and procedures to determine specifications. In addition, we recommend that the Draft Guidance include a statement of principles that should be considered by industry when setting specifications, such as is included in the draft ICH position on specifications. The draft ICH guideline states:

> *Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development upon which specifications are based, adherence to good manufacturing practices (GMPs), and a validated manufacturing process, e.g., raw material testing, in-process testing, stability testing.*
>
> *Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should*

focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included. The justification should refer to relevant development data, pharmacopeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate. Additionally, a reasonable range of expected analytical and manufacturing variability should be considered. It is important to consider all of this information.

*(*Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, 62 Fed Reg 62890, 62891-62892*).*

IV. CONSISTENCY WITH OTHER RELEVANT STANDARDS AND PRACTICES; CLARITY

Consistency with Other Relevant Standards and Practices

There are several areas where the Draft Guidance is not consistent with other relevant standards (*e.g.*, regulations and guidances) and practices. As we also noted in our comments on the draft CMC Guidance for MDIs and DPIs, we believe it is important that FDA guidance maintain consistency with these other standards. We recommend that the Agency modify the Draft Guidance to make it more consistent with other relevant standards and practices. For example:

- The Draft Guidance applies some of the ICH guidelines while disregarding certain others. For example, the Draft Guidance contains references to ICH *Q2A Text on Validation of Analytical Procedures*, ICH *Q2B Validation of Analytical Procedures: Methodology* (*See* line 347) and ICH *Q1B Photostability Testing of New Drug Substances and Products* (*See* line 1313). The Draft Guidance, however, makes no reference to the ICH concepts related to impurities and stability which are contained in two ICH guidelines, ICH *Q3B Impurities in New Drug Products* and ICH *Q1A Stability Testing of New Drug Substances and Products*. While ICH guidelines do not address the unique technologies required for nasal and inhalation solutions and suspensions, these guidelines are widely accepted and could provide a robust framework for the manufacturing controls that are generally applicable to drug substances and drug products. We recommend that the Draft Guidance be revised to incorporate ICH

guidelines where possible and provide justification in cases where tighter or more extensive controls are required.

- The Draft Guidance makes several references to "product consistency," "batch-to-batch consistency" and "reproducibility" (*e.g.*, lines 172, 778, 930). However, no information is provided to allow a quantitative approach to defining "consistency" or to determine when "reproducibility" has been violated. In contrast, however, there is a discussion of statistical techniques (with references) included in the FDA's *Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products*. We believe similar references and discussion should be included in the Draft Guidance. There are suitable approaches that are applicable to nasal sprays and solutions and suspension inhalation products that are well accepted in the fields of process and quality control and could be adopted by FDA. We recommend that the Draft Guidance be amended to address the use of scientifically recognized statistical and other quality control concepts and procedures to determine specifications.

- The Draft Guidance should acknowledge the provision relating to spray content uniformity as established by the USP in the *Draft-in-Process Revision on Testing Aerosols <601> Pharmacopeial Forum*, Volume 24, Number 5. Without explanation, the Draft Guidance establishes an entirely different test for spray content uniformity. We believe this discrepancy should be resolved if the final version of the Guidance is to contain a spray content uniformity specification.

- The Agency's approach to container closure systems appears to be inconsistent with current quality control concepts for manufactured products. Although the Agency published a final *Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Documentation* in July 1999, that Guidance states that guidance regarding the container closure system information to support the approval of applications for inhalation drug products will be provided in the final *Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products; Chemistry, Manufacturing and Controls Documentation* and the final *Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing and Controls Documentation*. The Container Closure section of the Draft Guidance for Nasal Spray and Inhalation Solutions, however, appears to overlook the fact that quality is built into the product through careful management and testing of components and materials. Specifically,

the Draft Guidance requires retesting of the same parameters in materials, sub-components (parts), components, and the finished product. As a result, the Draft Guidance does not recognize the state-of-the-art in quality systems and GMP systems for supplier quality. The highest level of container closure control as described in the final *Guidance for Industry Container Closure Systems* has been accepted as suitable for injection products and should be adopted for inhalation products. We believe that any concerns about the supply chain of raw materials (*e.g.*, polymers, resins), parts, and components as delivered to the pharmaceutical production facilities should be addressed as a GMP supplier quality issue and not in the Draft Guidance.

- The Draft Guidance confuses the approval of nebulizers as Class II medical devices by the Center for Devices and Radiological Health, Office of Device Evaluation Division of Cardiovascular and Respiratory Devices (CDRH) with the approval of inhalation solution drug products by the Pulmonary Division. According to the 1991 Intercenter Agreement between CDER and CDRH, the device component of the combination product will be reviewed and regulated by CDRH. The current thinking of CDRH regarding performance testing including in vitro, in vivo, and clinical evaluations is presented in *Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators.* The CDRH Reviewer Guidance clearly states that nebulizers are regulated by CDRH and clarifies that the review process for 510(k) premarket notifications is intended to ensure that nebulizers and other devices are safe and effective. The Draft Guidance, therefore, should not establish requirements for nebulizers, such as the identification of specific nebulizers as part of the drug product labeling, that exceed what CDRH requires. (*See* lines 71-72, 1301-1305 and 1513-1515). We recommend that the Draft Guidance recognize the Intercenter Agreement and the role of the CDRH as the regulatory authority on devices.

Clarity

The Draft Guidance, in many places, does not clearly set forth the Agency's recommendations. One specific concern is that the Draft Guidance contains confusing and inconsistent terminology. We recommend that the Draft Guidance be revised to use consistent and well-defined terminology, such as has been defined by the ICH in its guidelines. We also recommend that the Draft Guidance offer clarification that will assist industry in understanding the Agency's expectations for the registration of future inhalation and nasal spray products. For example:

- The Draft Guidance contains a reference to maintaining product performance "through its lifetime under patient-use conditions." As all drug products are required to maintain performance during shelf-life and as labeled, this reference is confusing. We interpret this to mean that studies must be undertaken to demonstrate product performance under labeled patient-use conditions. (*See* lines 105-112).

- The Draft Guidance states that excipients used in oral inhalation products should be "completely" characterized. The meaning of the term "completely" is unclear. We interpret "completely" in the same way as it is used when applied to excipients used in other dosage forms. In addition, the reference to additional "strict quality controls" is unclear. We believe "strict quality controls" is the same as quality controls pursuant to good manufacturing practices (GMPs). (*See* lines 211-220).

- The Draft Guidance, in lines 292-293, states that "all inhalation solutions, suspensions and spray drug products should be manufactured as sterile products." This wording is in conflict with the *Federal Register* Notice 96N-0048, Vol. 62, No. 184, p. 49638, which applies only to the inhalation solutions dosage form. This *Federal Register* notice specifically states that "inhalation solutions for nebulization, as the term is used in this document, refers to inhalation solutions administered as a fine aqueous mist created by an atomizer or nebulizer." Nasal sprays are not included. Suspensions and spray drug products may be more like MDIs and DPIs, which are not required to be sterile. For instance, spray drug products compounded in ethanol as a vehicle are bactericidal. The Agency should clarify the sterility requirements by developing a decision criteria for the suspension and spray drug products based upon the route of administration and the ability of the formulation to support microbial growth.

- As discussed above, the reference to two CDRH guidances does not provide sufficient information regarding how the electronic components of a drug product would be handled within the review process. We request that the Draft Guidance clearly state that compliance with the CDRH guidance documents will provide sufficient information for review and approval of electronic components. (*See* lines 818-820).

V. ACCEPTANCE OF ALTERNATIVE APPROACHES

We strongly agree with the Agency's position, as stated in the Introduction to the Draft Guidance, that the Guidance "does not impose mandatory requirements" and that "alternative approaches may be used" (lines 18- 20). We also strongly support the statement that "applicants are encouraged to discuss significant departures from the approaches outlined in this guidance with the appropriate Agency division before implementation" (lines 20-22). We believe, however, that the Agency should clarify what it considers a "significant departure" from the approaches set forth in the Draft Guidance. In addition, the utility of the Draft Guidance would be strengthened if the provision regarding alternate approaches were emphasized further throughout the document. The diversity of products and technologies requires that the Draft Guidance not be unnecessarily restrictive. The Draft Guidance should focus on inhalation product standards that apply to the diversity of products and technologies that are currently approved and to the new innovative technologies of the future. The specifics of how the standards are achieved should be developed and justified by the innovator company on a product-by-product basis. All approaches that ensure the safety, efficacy and quality of the drug product should be considered if supported by reliable scientific data.

VI. CONCLUSION

The Agency took an important step toward addressing CMC issues for MDI and DPI delivery systems at the *AAPS/FDA/USP Workshop on Regulatory Issues Related to Drug Products for Oral Inhalation and Nasal Delivery*, held on 3-4 June 1999 in Washington, D.C. Since the *Draft Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products* was posted on 2 June 1999, however, the June Workshop did not provide the opportunity for meaningful review and discussion of the CMC issues specific to the nasal and solution and suspension dosage forms. The IPAC proposal, which was presented at the *AAPS/FDA/USP Workshop* on 3 June 1999, specifically requested further collaboration on CMC issues for MDIs and DPIs. Our proposal for collaboration, however, should apply equally to the Draft Guidance for Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products.

We strongly recommend that the Agency utilize an appropriate technical process to assemble the best available medical, pharmaceutical and academic expertise, from within and outside the FDA, to make recommendations for a revised draft of the *Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products*; *Chemistry, Manufacturing and Controls Documentation* and a revised draft of the *Guidance for Industry Metered Dose Inhaler (MDI) and Dry Power Inhaler (DPI) Drug Products; Chemistry, Manufacturing and Controls Documentation*. We believe that a consensus-building process that addresses, among other things, scientific, technological,

and quality control issues for MDI, DPI, nasal solution and suspension products is critical to the future development of these products.

We strongly support the development of guidance for nasal spray and inhalation drug products and appreciate the Agency's efforts in developing the current Draft Guidance. We hope our comments will be of value to the Agency and we look forward to the ultimate publication of a final Guidance that will effectively serve the current and future needs of the inhalation drug product industry.

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