COMMENTS

on a draft Guidance for Industry
Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products
Chemistry, Manufacturing, and Controls Documentation
(Docket No. 98D-0997)

Submitted by
The International Pharmaceutical Aerosol Consortium

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I. INTRODUCTION

The International Pharmaceutical Aerosol Consortium is an association of leading manufacturers of metered dose inhalers (MDIs) and dry powder inhalers (DPIs). Its members include: Astra A.B., Boehringer Ingelheim, Glaxo Wellcome, Medeva Americas, Norton Healthcare, Rhône-Poulenc Rorer and 3M Pharmaceuticals. These comments are also being submitted on behalf of Kos Pharmaceuticals, Inc.

These companies are committed to the highest standards of safety, efficacy and quality in the development and manufacture of metered dose inhalers and dry powder inhalers. During the past 40 years, these companies have developed, implemented and continuously improved quality testing to ensure that these high standards are met. These products have become the mainstay of therapy for asthma and chronic obstructive pulmonary disease in the United States and are relied upon by over 15 million Americans for the treatment of respiratory disease.

The IPAC member companies greatly appreciate the Food and Drug Administration's (FDA) efforts to develop a Guidance for Industry for MDI and DPI Drug Products. Given the variety and complexity of formulations and devices in the MDI and DPI areas, IPAC recognizes the difficulties and challenges present in the development of a single guidance document that adequately covers this range of diverse products. IPAC also recognizes the value to industry of a guidance of this type. We believe it is important that this guidance be written in a way that recognizes and incorporates the diversity of MDI and DPI products.

We are pleased to have the opportunity to comment on the Draft Guidance and hope the following comments are helpful to the Agency.

II. THE SCOPE OF THE DRAFT GUIDANCE

As mentioned above, IPAC supports the development of a Guidance for Industry for MDI and DPI Drug Products. Such a Guidance will clarify for industry what aspects of pharmaceutical performance and quality the Agency considers important to control. In addition, a Guidance will help industry understand the reasoning behind the Agency's views. With this information, developers will understand more clearly the Agency's expectations. Further, when product attributes and technical issues dictate alternate approaches, developers can easily focus their interactions with the Agency on those specific issues. We fully agree with the Agency's position, as stated in the Introduction to the Draft Guidance, that "alternative

approaches may be used" (line 14). We believe adherence to this concept is essential if this, or any guidance, is to be useful and stand the test of time.

We believe that the Draft Guidance would be strengthened if the provision regarding alternate approaches were emphasized further in the document. The diversity of products and devices and the prospect of new technologies will be best served with a Guidance that is not unnecessarily restrictive.

Our comments on specific elements of the Draft Guidance are presented below.

III. SPECIFICATIONS IN THE GUIDANCE

As mentioned above, we agree that the Draft Guidance should allow for alternative approaches that accommodate many different MDI and DPI technologies (*e.g.*, different formulations, device characteristics, processing conditions). The Agency's provision for allowing alternative approaches is very important. We believe, however, that the incorporation of very detailed specifications for excipients and active ingredients in the Draft Guidance runs counter to this important principle. The inclusion of detailed specifications in the Draft Guidance may limit the utility of the document by apparently restricting development to a common standard when, in fact, that standard may not be applicable or appropriate in all cases.

In regard to excipients, for example, the Draft Guidance contains specifications for CFC 11, CFC 12, CFC 114 and HFA 134a propellants (lines 349 – 403). While the list of impurities and their levels cited in the Draft Guidance may be accurate for today's suppliers of these propellants, they may not be the right variables or levels to apply to a new supplier's production or may not be consistent with process modifications that will occur in the future. With respect to specifications for HFA 134a, we also support the comments of the 134a Consortium, submitted separately to the Agency.

In regard to active ingredients, for example, we refer to the specifications for content uniformity. In this instance, the Agency has established a single, one-size-fits-all specification for dose 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 on dose content uniformity testing of aerosols (*Draft-in-Process Revision on Testing Aerosols <601> Pharmacopeial Forum,* Volume 24, Number 5). (*See* lines 521 – 578 for MDIs and lines 758 – 773 for DPIs). Rather than providing a single specification for dose content uniformity, we recommend that the Agency establish a process by which a dose content uniformity specification should be determined, on a product-by-product basis, in light of relevant product-specific development and manufacturing data.

The Agency's Draft Guidance will best serve the industry and the Agency if it focuses on describing the type of testing and evaluation that should be taken into account in MDI and DPI development and manufacturing without specifying in detail the results that must be achieved or the methodology that must be used.

We recommend that the Draft Guidance include a statement of principles that should be taken into account when setting specifications, as such a statement is valuable to industry. We recommend that the Agency consider adopting the draft ICH position on specifications, presented below for the Agency's convenience:

> *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*).*

IPAC's belief that detailed specifications (and methodologies) should not be part of the Guidance for Industry does not mean that we consider these to be unimportant. On the contrary, we fully agree that common specifications and methodologies should be established, wherever possible. However, we believe that the use of the compendial process, through the USP, is a better mechanism for establishing, publishing, and maintaining specifications. The compendial process, which involves participation by both FDA and recognized technical experts outside FDA, and which also involves

public comment, has been used successfully to establish many test procedures and specifications used in the pharmaceutical industry as well as to establish many monographs for drug substances and excipients used in pharmaceutical products. In fact, the Agency refers to several USP specifications in the Draft Guidance (*e.g.*, USP <87> and <88>, (lines 889, 897, 996, 1080, and 1177 - 1178)).

IV. 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. We believe it is important to maintain consistency with these other standards. Further, the Draft Guidance provides a level of detail not found in other guidance documents. While we agree that MDI and DPI products are different from other dosage forms, we do not necessarily agree that existing guidance documents and other standards are not directly applicable. 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 makes several references to "product consistency", "future batch-to-batch consistency" and "reproducibility" (*e.g.*, lines 299, 425, 1010 and 1086). However, no information is provided to allow a quantitative or numerical 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 MDIs and DPIs 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 in detail the use of scientifically recognized statistical and other quality control concepts and procedures to determine specifications.

- IPAC has already expressed its view that the Draft Guidance should not contain detailed specifications but rather rely on the USP compendial process to establish relevant specifications, where appropriate. Regardless of the final method adopted by the Agency to deal with certain specifications, in the case of content uniformity, the Draft Guidance should acknowledge the provision relating to 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 content uniformity. We believe this discrepancy should be resolved if the final version of the Guidance is to contain a content uniformity specification.

- 21 CFR 314.50 (d)(ii)(b) does not require submission of completed batch records for representative clinical batches, rather, it requires completed batch records only for bioavailability or bioequivalance and primary stability studies. (*See* line 426). We recommend the Draft Guidance be modified to be consistent with the regulation.

- The 25 °C/75 %RH stability requirement is not consistent with ICH Q1A *Stability Testing of New Drugs and Products* or the Agency's *Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products*. (*See* line 1283).

- Equipment qualification (lines 605 – 606 for cascade impactor) is typically covered by cGMP inspections and not included in an application.

- The suggestion that drug product characterization studies should be performed on three batches of commercial product deviates from established practices. Generally, it is normal for developers of other dosage forms to conduct drug product characterization studies on drug product that is representative of the commercial product. (*See* lines 1363 - 1364).

- The Draft Guidance includes monitoring drug substance impurities in drug product controls. (Lines 517-520 and 756-757). The requirement to monitor synthetic impurities in drug products is not consistent with ICH Q3B *Impurities in New Drug Products.*

- The Draft Guidance is not consistent with ICH Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.*

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

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. Following are a few examples:

- The Draft Guidance includes microscopic evaluation as a release and stability-testing requirement. (Lines 639-653 and 796-802). While microscopy may be used in the early stages of product design and development to confirm other product characterization findings, finished product attributes such as particle size, morphology and agglomeration are better controlled by other test methods.

- The Draft Guidance establishes spray pattern and plume geometry measurements to control finished component parameters (*e.g.*, critical dimensions, metering chamber capacity, functional parameters). (Lines 655-678). We agree it is appropriate to conduct spray pattern and plume geometry studies during product development. However, such measurements are redundant and generally ineffective as controls of component parameters.

- Control of leachables is more appropriate at the component or bulk material level rather than on the product. 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 resist the temptation to use leachables as a confirmation of composition or process compliance during manufacture of components or product, which falls more appropriately in the realm of cGMP. (*See* Lines 716-725)

VI. THE DRAFT GUIDANCE REQUIRES TESTING THAT IS NOT NECESSARY FOR EITHER CONTROL OF QUALITY OR SAFETY/EFFICACY

The draft Guidance for Industry includes a method and specification for color. (Lines 467-474 and 730-737). There is no value in terms of product quality, safety or efficacy provided by the inclusion of a method and specification for color. Analyses for impurities methods and finished product specifications provide adequate control of any parameter of concern.

VII. THE DRAFT GUIDANCE ATTEMPTS TO SET GENERAL SPECIFICATIONS FOR ALL MDI/DPI PRODUCTS RATHER THAN PROVIDE A PROCESS TO DEVELOP SPECIFICATIONS FROM PRODUCT-SPECIFIC DEVELOPMENT AND MANUFACTURING TEST RESULTS

- The Draft Guidance establishes a single specification for dose content uniformity. (*See* lines 537-548, 563-578, 759-761 and 771-773). We again refer the Agency to our comments above which address our concerns regarding the inclusion of a detailed specification in the Draft Guidance and the omission of any reference to USP <601> or discussion of its relevance. Those comments notwithstanding, the Guidance should be revised so as to provide a process for setting a dose content uniformity specification that applies currently accepted statistical and quality control procedures. Product uniformity specifications for new products should be determined by development and manufactured product test data as developed for the specific product.

- The Draft Guidance indicates that the total mass collected in the particle size determination should be +/- 15% on a per actuation basis. (*See* line 625). This requirement is not scientifically based or reasonable. The mass balance criterion should be a system suitability requirement for Andersen particle size distribution testing, not a specification. The mass balance criterion should be determined during method development and should be based on the content uniformity specification proposed for the product as well as the analytical variability associated with the particle size distribution method. It should be noted that the proposed mass balance requirement of +/- 15% is not consistent with the Agency's proposed specification for content uniformity which allows broader limits of 75–125% for individual actuations. Likewise, this requirement is inconsistent with the recommendation of the pharmacopeias (*i.e.*, Ph. Eur. 3rd Ed., Supplement 1999, Monograph 671 and USP <601>).

VIII CONCLUSION

We strongly support the development of Guidance for Industry on MDIs and DPIs and appreciate the Agency's efforts in developing the current Draft Guidance and the opportunity to comment. We look forward to the upcoming Workshop sponsored by the Agency to discuss the Draft Guidance. We intend to continue our review of this

thorough and complex Draft Guidance and will bring any additional comments to the Workshop meeting for consideration by the Agency.

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 MDI and DPI industry.

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