
INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM

STATEMENT

Of The International Pharmaceutical Aerosol Consortium On The
Draft Guidance For Industry Metered Dose Inhaler (MDI) And Dry
Powder (DPI) Drug Products Chemistry, Manufacturing, And
Controls Documentation

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I. INTRODUCTION

Good Morning. My name is Joseph Ferrara. I am the Director of Government Policy at Boehringer Ingelheim Pharmaceuticals, Inc. I am addressing you this morning on behalf of the International Pharmaceutical Aerosol Consortium's Working Group on CMC Guidance in my capacity as Chairman of IPAC's Committee on U.S. Regulatory Affairs.

The International Pharmaceutical Aerosol Consortium is an association of leading manufacturers of metered dose inhalers (MDIs) and dry powder inhalers (DPIs). The members of IPAC's Working Group on CMC Guidance include: Astra A. B., Boehringer Ingelheim, Glaxo Wellcome, Inhale Therapeutic Systems, Inc., Kos Pharmaceuticals, Inc., Medeva Americas, Norton Healthcare, Rhône-Poulenc Rorer and 3M Pharmaceuticals.

Members of IPAC are committed to the highest standards of safety, efficacy and quality. For the past 40 years, these companies have developed and continuously improved product quality and testing to ensure that these high standards are met.

IPAC members provide affordable inhalation products for millions of Americans suffering from life-threatening respiratory diseases. We are now developing new, environmentally friendly, innovative inhalation drug products, including aerosols containing gases with no-ozone depleting potential, for the treatment of respiratory diseases. In addition, the inhalation drug products industry is developing new inhalation products for therapeutic indications, other than respiratory diseases.

We welcome this opportunity to share our experience, and our vision of the future, in regard to the development, testing and manufacture of metered dose inhalers and dry powder inhalers.

This Workshop is a significant first step in the development of broadly supported and scientifically sound FDA CMC guidance for MDIs and DPIs. As you know, regulatory standards related to the chemistry, manufacturing and controls documentation of MDI and DPI products have been primarily addressed in the United States on a case-by-case basis in the context of individual drug applications, and secondarily through meetings such as this. This is the first time in many years that U.S. health regulators, academicians, professional associations, standard-setting bodies, and company and industry representatives have convened to exchange their views on this critical subject.

The MDI and DPI deliver fine particles to the lungs and, therefore, unique manufacture and control procedures are required. While the fundamental basis for

CMC controls for these products will be the same, the particular controls should be product-specific. To that end, IPAC fully supports the FDA's publication of a Guidance for MDIs and DPIs. The foundation of this Guidance rests on the broad base of experience with existing inhalation delivery systems, but the Guidance must also anticipate the emergence of new inhalation drug products, including non-respiratory therapies. This will require the best thinking of everyone involved in the development, manufacturing and regulation of these products.

We commend the FDA for having the foresight and dedication to develop a comprehensive first draft of the CMC Guidance. We also appreciate this opportunity to participate in the Workshop.

In the next few moments, I will summarize IPAC's principal concerns with the draft Guidance. I will then recommend a time-limited, efficient process by which we can reach consensus on these issues.

II. SUMMARY OF CONCERNS WITH THE DRAFT GUIDANCE

We have four principal concerns with the draft Guidance. They may be summarized as follows:

CMC Guidance should provide a flexible framework that outlines clearly the regulatory expectations, but acknowledges and encourages a product-specific approach to development and the selection of control methods. The primary purpose of CMC Guidance should be to address types of tests and testing objectives. The Guidance should defer to compendia procedures, scientific literature, and supporting scientific documentation of individual product sponsors for detailed test procedures, as may be appropriate for individual drug development programs;

The draft Guidance should adopt the philosophies and guidelines developed through technical and regulatory consensus building processes, such as those sponsored by the International Conference on Harmonization, the United States and European pharmacopoeias, and the American Association of Pharmaceutical Scientists;

The draft Guidance should not include detailed quality specifications but, rather, should outline a product specific, data driven process for setting specifications; and

The draft Guidance should not require testing of finished product for aspects of quality already assured in product development and supplier control.

I will explain each of these concerns in turn.

A Guidance Framework For Adapting Control Methods To Specific Product Needs

I will first address the subject of a “Guidance Framework” under which product sponsors can adapt control methods to specific product needs.

The draft Guidance is replete with detailed and specific requirements. It leaves the impression that these requirements are appropriate for most, if not all, MDI and DPI products.

However, drug development programs differ significantly from one therapy, and one company, to another. Quality testing that works well for one product may not assure quality for another.

Product sponsors are, of course, intimately familiar with their drug development programs. As a result, they are often in the best position to determine how to assure the quality of their products. This has been recognized by the FDA. In its “Good Guidance Practices,” the FDA encourages product sponsors to propose alternative approaches for achieving safety, efficacy and quality, based on their special knowledge of the products they have developed.

Unfortunately, by its highly detailed description of test methods and, in some cases, inclusion of elaborate specifications, the draft Guidance could be interpreted as discouraging the consensus-method process of the pharmaceutical compendia and the innovation of the scientific community and product sponsors. In some cases, detailed common procedures and test criteria may be appropriate, but, as a general matter, regulators and industry should support and encourage established technical consensus building processes.

We believe that CMC Guidance should be less detailed and concentrate on the primary objectives and broader elements of a framework for quality testing. Guidance of this kind would respect the role of product sponsors, the pharmacopoeias, and other scientific bodies by providing them with support in the application of their special knowledge and experience in pursuit of product quality.

Consistency With Guidance Developed By Other Technical And Regulatory Consensus-Building Processes

Our second concern relates to consistency with guidance developed by other technical and regulatory consensus-building processes.

The United States is actively participating in the international effort to harmonize pharmaceutical standards. The goal of this effort is greater efficiency in product development and more rapid introduction of new medicines, consistent with the highest standards of safety, efficacy and quality.

Similarly, the United States Pharmacopeia establishes authoritative standards of quality for pharmaceutical products. These standards are developed through collaboration among committees of experts in medicine, pharmacy and other scientific disciplines.

We believe that CMC Guidance for MDIs and DPIs should be consistent with the guidelines and standards established through these efforts. For example, we believe that CMC Guidance should incorporate harmonized guidelines and compendial standards in regard to:

- Stability testing on new drug substances and products (ICH Q1A)
- Monitoring of degradants (and not synthetic impurities) in drug products (ICH Q3B)
- Methods which are being harmonized by the United States and European Pharmacopoeia (e.g., particle size distribution by MDIs and DPIs)
- The use of non-stability indicating methods, where appropriate (ICH Q6A)
- The USP standard on dose content uniformity testing of aerosols (*Draft-in-Process Revision on Testing Aerosols <601> Pharmacopeial Forum, Volume 24, Number 5*).

CMC Guidance which is consistent in these respects will enable product sponsors to generate one set of data that will be acceptable for registration internationally, simplify method validation testing by regulatory laboratories, and promote further harmonization efforts.

Process for Establishing Quality Specifications

Our third concern involves the way in which quality specifications are established.

The draft Guidance includes detailed quality specifications in regard to dose content uniformity and propellants. As I explained earlier, we believe that detailed specifications should not be included in a guidance document. Rather, we believe that quality specifications are more appropriately determined through the compendial process or during the review of individual product applications.

We do believe, however, that CMC Guidance should set forth an approach for establishing specifications similar to the one outlined in the ICH's Draft Guidance on Specifications (ICH Q6A). We agree with the ICH that specifications

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

We also agree with the ICH that specifications should be justified on a product-by-product basis by:

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.

Finally, we agree with the ICH that

a reasonable range of expected analytical and manufacturing variability should be considered in the establishment of specifications.

We believe that the FDA's CMC Guidance should discuss acceptable empirical and statistical methodologies for evaluating this variability in establishing quality specifications.

We believe that the CMC Guidance should adopt the ICH approach and include a discussion on establishing specifications. Such a modification would strengthen the use of the Guidance by all effected parties.

Aspects Of Quality Already Assured In Product Development And Supplier Control

Our final concern relates to testing requirements for aspects of quality that are already assured in product development and supplier control.

We believe that the draft Guidance should more clearly distinguish between development and product characterization data, on the one hand, and data routinely generated for quality control purposes, on the other. The purpose of quality testing is to generate data which assures that the finished product meets the standards

established during product approval. However, testing that simply confirms what has already been determined during development, characterization and manufacture is unnecessary for assurance of product quality.

For example, the plume geometry and spray pattern of actuators is extensively tested during development and characterization, and as a basis for component acceptance during manufacture. We believe it unnecessary to conduct these tests yet again at the finished drug product stage.

In addition, the draft Guidance includes redundant testing requirements. For example, leak rate is appropriate as a development test but not as a regulatory specification, as the test for dose content uniformity will detect significant leakage during release and stability testing. In addition, the USP Stimulus to Revision for Chapter <601> has deleted the requirement for a specification for leak rate.

III. A PROCESS FOR BUILDING CONSENSUS ON CMC GUIDANCE

I have now completed my discussion on IPAC's four principal concerns with the draft Guidance. We appreciate this opportunity to set forth our concerns. Now I will shift my discussion to IPAC's simple proposal for an efficient, time-limited, consensus-building process following this Workshop. We recognize that the industry's perspective is only one of several and that our larger task is to reach broad consensus on assuring product quality. I will now offer our thoughts on where we go from here.

We propose that following this Workshop, four small Working Groups be established under the auspices of the AAPS Inhalation Technology Focus Group. These Working Groups would be comprised of approximately two representatives of each of the FDA, AAPS, the USP and industry. During the 90-day period following today's Workshop, each Working Group would address one of the four principal concerns that I have discussed this morning. The objective of each Working Group would be to develop a consensus statement that includes recommendations for revising the initial draft CMC Guidance. In early Fall of this year, the Working Group would present these recommendations at a second and final Workshop on CMC guidance.

We offer this proposal for collaboration in the same spirit as other important and constructive consensus-building initiatives undertaken by the FDA in recent years, including the highly successful collaboration on the SUPAC guidances and the recently established Product Quality Research Institute. We believe that the time-limited and highly focused nature of our proposal is particularly well-suited for the development of this CMC Guidance. We seek the support of the FDA, AAPS and the USP in reaching broad consensus in the development of this CMC Guidance.

IV. CONCLUSION

The FDA, by publishing its initial draft Guidance, the FDA, AAPS and the USP, by sponsoring this Workshop, and Workshop participants, by their contributions here today, have taken an important step in the development of this Guidance document. There is still work to be done, however. As we move ahead, we will benefit from the models of collaboration that have worked so well for other guidance documents. The collaborative process we propose today, however, is, because of the FDA's efforts in preparing a comprehensive initial draft Guidance, time-limited, focused and efficient. We feel confident that our joint efforts will assist in the timely development of a highly useful and resilient guidance for industry.

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