

STATEMENT TO ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

***On the Work of ITFG/IPAC-RS Collaboration
Regarding Chemistry, Manufacturing, and Controls and
In Vitro and In Vivo Bioavailability/Bioequivalence Issues in
Draft Guidance Documents for Orally Inhaled and Nasal Drug Products***

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INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM ON REGULATION AND SCIENCE

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I. EXECUTIVE SUMMARY

- Between October 1998 and June 1999, the FDA issued three draft Guidances for Industry.¹ The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) and the Inhalation Technology Focus Group (ITFG) of the AAPS recognize the value of guidance documents in facilitating the development and approval of new nasal and orally inhaled medications. However, the ITFG and IPAC-RS strongly believe that certain sections of the draft Guidance documents need to be modified to be consistent with today's drug development technologies and capabilities.
- In addition to providing the Agency with our written comments on the draft Guidance documents, the ITFG and IPAC-RS have undertaken an extensive collaboration to combine the scientific expertise, industrial experience and regulatory knowledge of both organizations to address a number of important issues in the draft Guidances. Specifically, the ITFG/IPAC-RS Collaboration has collected and analyzed relevant data in order to propose scientifically justified modifications to the draft Guidance documents. We believe it is important that the conclusions of our data analyses be given full consideration before the draft Guidances are finalized.
- We recognize and appreciate that the Agency has taken several initial steps toward addressing CMC and BA/BE issues in the draft Guidance documents, including the June 1999 *Workshop on Regulatory Issues Related to Drug Products for Oral Inhalation and Nasal Delivery*, the first meeting of the Orally Inhaled and Nasal Drug Products (OINDP) Subcommittee of the Advisory Committee for Pharmaceutical Science, held on 26 April 2000, and a planned meeting to discuss the ITFG/IPAC-RS Collaboration's extensive database on dose content uniformity. We believe, however, that additional interactive, science-based dialogues need to occur to provide full opportunity to discuss each of the important issues in depth in order to achieve meaningful and necessary changes in the draft Guidances.
- We respectfully request that the Advisory Committee for Pharmaceutical Science support the importance and value of continuing scientific dialogue on the important CMC and BA/BE issues for orally inhaled and nasal drug products. Specifically, we ask that the Advisory Committee for Pharmaceutical Science endorse our request that opportunities be identified for a continued dialogue between FDA and the ITFG/IPAC-RS Collaboration regarding the Collaboration's data-based conclusions.

¹ 1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls (CMC) Documentation*; 2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation*; and 3) *Bioavailability and Bioequivalence (BA/BE) Studies for Nasal Aerosols and Nasal Sprays for Local Action*.

II. BACKGROUND

- At the June 1999 *Workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery*, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) proposed the creation of a post-Workshop consensus building process to address several issues in the draft Guidances for orally inhaled and nasal drug products (OINDP). The FDA agreed to consider opportunities for more dialogue on these issues.
- In October 1999, the FDA created the OINDP Expert Panel to facilitate information sharing on scientific, technical, compendial and research issues relevant to the draft OINDP Guidances. In January 2000, the FDA announced plans to re-evaluate the Expert Panel process, and consequently, in March 2000, the OINDP Expert Panel was converted into the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science.
- The Inhalation Technology Focus Group (ITFG) supported IPAC-RS's proposal at the June Workshop and agreed to undertake a data-driven collaborative effort with IPAC-RS to combine scientific expertise and regulatory knowledge and address key issues on CMC and BA/BE in the draft Guidance documents. The ITFG/IPAC-RS Collaboration was initiated prior to the deliberations of the OINDP Subcommittee in order to provide the Agency and the Subcommittee with timely technical reports and recommendations for consideration during the Subcommittee's deliberations.
- Over 100 individuals from more than 25 companies and institutions are participating in the ITFG/IPAC-RS Collaboration. The Collaboration involves five Technical Teams: 1) BA/BE In Vitro and In Vivo Tests Technical Team; 2) CMC Specifications Technical Team; 3) CMC Tests and Methods Technical Team; 4) CMC Leachables and Extractables Technical Team; and 5) CMC Supplier Quality Control Technical Team. The ITFG/IPAC-RS Technical Teams have developed hypotheses or position statements on key issues in the draft Guidance documents and have obtained data and scientific information to investigate these issues.
- Since the first OINDP Subcommittee meeting in April 2000, the Collaboration has submitted the following four reports to the FDA and to the OINDP Subcommittee:
 - 1) Initial Assessment of the ITFG/IPAC Dose Content Uniformity (DCU) Database;**
 - 2) Initial Assessment of the ITFG/IPAC Aerodynamic Particle Size Distribution Database;**
 - 3) Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at 26 April OINDP Advisory Subcommittee Meeting;** and
 - 4) Review of In Vivo and In Vitro Tests in FDA's Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and Anticipated Forthcoming Guidance for Orally Inhaled Drugs.**

In the near future, several additional data-based technical reports will be submitted to the Agency and the OINDP Subcommittee.

- This Statement provides an overview of the approach taken by each ITFG/IPAC-RS Technical Team, describes the conclusions reached to date, and outlines remaining commitments to contribute constructively to the deliberations of the OINDP Subcommittee and Advisory Committee for Pharmaceutical Science and the Agency's development of the OINDP Guidance documents.

III. STRUCTURE OF ITFG/IPAC-RS COLLABORATION

ITFG/IPAC-RS COLLABORATION ON CMC AND BA/BE ISSUES

The Inhalation Technology Focus Group (ITFG) is a technical focus group of the American Association of Pharmaceutical Scientists (AAPS) comprised of technical experts who seek to foster and advance the art and science of pharmaceutical aerosol products, aerosol technology and related processes. The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) is an association of companies that develop and manufacture orally inhaled and nasal products for local and systemic treatment of asthma, chronic obstructive pulmonary disease (COPD), and rhinitis, as well as products for non-respiratory disease indications such as migraine and diabetes. The ITFG and IPAC-RS share common views on CMC and BA/BE issues in the draft Guidances for orally inhaled and nasal drug products (OINDP). ITFG and IPAC-RS also share the Agency's goals of developing scientifically justified guidance for OINDP and making these drug products available to patients in an expeditious manner, while maintaining appropriate standards of safety, efficacy and quality.

In the months following the June 1999 Workshop, while awaiting the Agency's proposal on the appropriate forum for further consideration of OINDP regulatory issues, representatives of the ITFG and IPAC-RS established and initiated the ITFG/IPAC-RS Collaboration, a joint, data-driven scientific effort. Over 100 individuals from more than 25 companies and institutions are participating in the ITFG/IPAC-RS Collaboration. The objective of the ITFG/IPAC-RS Collaboration is to combine the scientific expertise, industrial experience and regulatory knowledge of both organizations to address specific CMC and BA/BE issues in a manner that most effectively contributes to the deliberations of the OINDP Subcommittee and the Agency's development and finalization of the OINDP Guidance documents.

The ITFG/IPAC-RS Collaboration is overseen by the ITFG/IPAC-RS Steering Committee. The Collaboration includes the following five Technical Teams:

- BA/BE In Vivo and In Vitro Tests Technical Team
- CMC Specifications Technical Team
- CMC Tests and Methods Technical Team
- CMC Leachables and Extractables Technical Team
- CMC Supplier Quality Control Technical Team

The Technical Teams are responsible for addressing specific BA/BE and CMC issues in the draft Guidance documents. The Teams have collected data and scientific information from the Collaboration's participants to investigate selected BA/BE and CMC issues in the draft Guidances. The Steering Committee provides guidance to the Technical Teams and reviews the findings of each Team.

The following is a list of the companies or institutions with which the scientists participating in the ITFG/IPAC-RS Collaboration are affiliated:

Aradigm	Lovelace Respiratory Institute
AstraZeneca	Magellan Laboratories
Aventis	Microdrug Development
Bespak	Pfeiffer
BI Roxane	Pfizer
Boehringer Ingelheim	Presspart
Dura Pharmaceuticals	Primedica
Eli Lilly	Schering-Plough
Glaxo Wellcome	Sciarra Laboratories
Inhale Therapeutics Systems	3M Pharmaceuticals
Inspire Pharmaceuticals	Trudell Medical
IVAX	University of Rhode Island
Kos Pharmaceuticals	Valois

IV. FINDINGS TO DATE AND COMMITMENTS TO UNDERTAKE FURTHER WORK

The ITFG/IPAC-RS Technical Teams have identified for comment a number of key CMC and BA/BE issues in the draft Guidance documents for OINDP. In addition, the Teams have developed hypotheses or position statements on these key issues and have collected and assessed available information and, where appropriate, data as provided by the participants in the Collaboration.

The following summary provides an overview of the five Technical Teams and describes the contributions made, or soon to be made, by these Teams to the deliberations of the OINDP Subcommittee and the Agency's development of the OINDP Guidance documents. The summary below: 1) describes each Team's approach to addressing questions or issues in the draft Guidance documents; 2) describes the work completed, or to be completed, by each Team; and 3) outlines each Team's data-based proposals for improving the draft Guidance documents, or plans to offer such proposals in the near future.

IV.1. BA/BE TECHNICAL TEAM

1. BA/BE TEAM'S APPROACH

Since January 2000, the BA/BE Technical Team of the ITFG/IPAC-RS Collaboration has focused on the in vitro and in vivo tests in the Agency's draft *Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*. The Team, composed of branded and generic companies, agreed on several working assumptions and identified two main position statements, one for in vitro tests and the other for in vivo tests in the draft BA/BE Guidance.

The Team's main position statements are:

- *In Vitro Tests*: In vitro testing is essential for pharmaceutical product equivalence and should be included as part of BA/BE Guidance for all nasal and oral inhalation products, but is not currently sufficient for determining BE without also establishing in vivo BE; and
- *In Vivo Tests*: For BE determinations, BA/BE Guidance documents for nasal and oral inhalation drug products for local action should require use of validated human models for in vivo testing for local and systemic exposure, efficacy and safety.

The Team's working assumptions, upon which its conclusions are based, are as follows:

- Specific BA/BE recommendations apply to locally acting drugs per the current draft BA/BE Guidance for nasal aerosols and sprays, and should apply, as appropriate, to orally inhaled drug products in the anticipated forthcoming BA/BE Guidance for orally inhaled drugs;
- The Team's conclusions apply to both orally inhaled and nasal drug products, but these dosage forms should be treated in separate Guidances;
- Scientific and clinical bases for developing BA/BE Guidance are evolving; and
- The Team's BA/BE position statements reflect only the current state of knowledge.

During the past several months, Team members submitted and evaluated data and scientific articles related to the Team's position statements. In July 2000, the Team submitted to the Agency and the OINDP Subcommittee a technical paper on these position statements, entitled *Review of In Vivo and In Vitro Tests in FDA's Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and Anticipated*

Forthcoming Guidance for Orally Inhaled Drugs. This paper sets forth a broad perspective on BA/BE questions. The Team prepared this paper on in vitro and in vivo tests in the draft BA/BE Guidance in order to:

- highlight areas where there are not enough data at present to draw conclusions; and
- review available technical documentation related to BA/BE issues addressed by the Team and offer the Team's conclusions based on that documentation.

The Team also considered the BA/BE questions presented by the Agency at the 26 April OINDP Subcommittee meeting. The Team's responses to these questions are contained in the Team's *Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at 26 April 2000 OINDP Advisory Subcommittee Meeting*, also submitted to the Agency in July 2000.

Each of the BA/BE Team's papers should be publicly available on the FDA's website at http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_reports.htm.

2. BA/BE TEAM'S FINDINGS TO DATE

(i) Summary of Team's Paper Entitled *Review of In Vivo and In Vitro Tests in FDA's Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and Anticipated Forthcoming Guidance for Orally Inhaled Drugs*

Based on the currently available information and the Team's assumptions listed above, Team members reached the following conclusions:

1. Conclusions on In Vitro Tests

- In vitro tests described in the draft BA/BE Guidance are not necessarily more relevant or discriminating than clinical studies for BE assessment;
- The assumption that in vitro studies alone are sufficient for determinations of BE for solutions is unfounded. The draft BA/BE Guidance should not distinguish between nasal suspensions and solutions for in vivo BE; and
- Based on the available literature, current in vitro tests may predict lung deposition, but the utility of those tests to demonstrate clinical equivalence of inhaled drug products has not been shown.

2. Conclusions on In Vivo Tests

- Systemic PK/PD estimates systemic exposure (i.e., safety) but does not estimate local delivery (i.e., efficacy and local tolerance);
- Efficacy assessments alone cannot establish in vivo BE since they will not assure comparable safety (systemic exposure);

- Lung deposition studies are a promising new technique, but currently cannot replace the local delivery requirement;
- In vitro data, regional deposition data, PK/PD studies, and clinical efficacy studies are needed to establish relationships and to characterize the formulation when a new inhaled drug is developed; and
- Reduction of testing requirements for a new formulation of an approved drug should be negotiated between the sponsor and the Agency depending on available data for each particular drug.

(ii) **Summary of Team's Paper Entitled *Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at 26 April 2000 OINDP Advisory Subcommittee Meeting***

1. **In Vitro BA/BE Testing**

A. Profile Analysis

Question:

1. ***Should all stages, including the inlet (throat) of the cascade impactor (CI) be considered in a comparison of test and reference products?***

Summary of Answer:

1. Yes, in general, all stages, including the throat of the CI should be considered in a comparison of Test and Reference products having polydisperse particle size distributions in order to achieve a discriminating test.

Question:

2. ***Should a statistical approach rather than a qualitative comparison be used for profile comparisons? If yes, does the chi-square comparative profile approach seem appropriate?***

Summary of Answer:

2. Yes, a statistical approach should be used for particle size profile comparisons. The chi-square (multivariate) comparative approach may be appropriate for particle size comparisons; however, further assessment is needed to determine the discriminatory capabilities of the test. Further, the Guidance should define "equivalence limits" (*i.e.*, the extent to which two profiles can differ and still be considered equivalent).

B. In Vitro Tests for DPIs: ComparabilityQuestion:

1. ***Prior to doing in vivo studies to establish equivalence of a test DPI product, a firm would need to design its product to have the best likelihood of being found equivalent in these in vivo studies.***
 - 1a. ***What design features of the device and formulation and what parameters should be considered in determining pharmaceutical equivalence?***

Summary of Answer:

- 1a. In vitro testing of the following characteristics of a Test Product would be an appropriate prerequisite for further characterization by in vivo studies:
 - the formulation;
 - the device elements; and
 - the chemical, physical and in-vitro characteristics that demonstrate the performance of the assembled system.

The factors that could influence the qualities of the delivered dose are complex, and not all are well understood at present. Accordingly, no sufficiently predictive or convincing in vitro/in vivo relationship has yet been demonstrated for products intended for local action.

Question:

- 1b. ***What comparative in vitro tests should be conducted to help support bioequivalence?***

Summary of Answer:

- 1b. The following comparative tests should be conducted to help support bioequivalence:
 - delivered dose amount;
 - delivered dose uniformity;
 - aerodynamic particle size distribution of the delivered dose, dispersing the formulated powder to the desired particle size distribution across a physiologically relevant range of airflows and environmentally realistic range of temperatures and humidities;
 - aerodynamic particle size distribution of the carrier or excipient materials;
 - microbiological burden in the powder formulation;

- chemical, physical and microbiological stability of the contained formulation;
- chemical and physical composition of the device, including extractive materials; and
- reliability of the device throughout the defined use period.

The draft BA/BE Guidance should specify those aspects of any of these tests that are considered to be critical for proper execution and interpretation. For example, it may not be sufficient to show equivalent performance under one test condition, but over a range reflecting clinical usage. Comparative in vitro tests should be conducted to demonstrate equivalence in performance features that affect the efficacy of the pharmaceutical agent and the safety profile of the delivery system.

2. In Vivo BA/BE Testing

A. Clinical Studies for Local Delivery of Nasal Aerosols and Sprays

Question:

1. ***Three study designs have been proposed in the draft guidance for drugs intended to have local action; traditional treatment study; day(s) in the park study, and environmental exposure unit study. These study designs are based on seasonal allergic rhinitis (SAR).***

Is it feasible to demonstrate a dose-response for locally acting nasal drugs? If not, what other approaches can be relied upon to establish equivalent local delivery?

Summary of Answer:

1. At present, the studies proposed in the draft BA/BE Guidance for nasal aerosols and nasal sprays describe studies that are useful for determining the comparability of products. However, their value for establishing clinical equivalence and substitutability is unproven. The traditional treatment study offers the most appropriate study design for assessing nasal drug products intended for local delivery. However, given the utility of this study design, it is not adequate to confidently establish dose-response relationships for locally acting nasal drugs nor is there an alternative method that can be relied upon to establish equivalent local delivery. Also, there is a need for the draft Guidance to further develop the statistical requirements for this study if it is to be used for equivalence testing.

Question:

- 2. Can bioequivalence established based on SAR assure bioequivalence for other indications such as recurrence of nasal polyps, or other non-SAR conditions?**

Summary of Answer:

2. A pre-existing indication for PAR, PNAR or nasal polyps at the same dose should be transferable from the Reference product to the Test product if the Q1, Q2 and container-closure standards are met and bioequivalent performance in terms of efficacy, onset of effect, duration of action, systemic and local safety have been clearly demonstrated in SAR. In order to transfer a pre-existing indication for use in children from Reference to Test product, care should be taken to ensure that the studies conducted to assess systemic safety are predictive of all potential patient subgroups.

B. Clinical Studies for Local Delivery of Orally Inhaled Corticosteroids (ICS)Questions:

- 1. A number of approaches have been proposed to assess bioequivalence of ICS (e.g., clinical trials, bronchoprovocation tests, steroid reduction model, trials with surrogate measures such as exhaled nitric oxide (eNO), etc.

Are any of these study designs proven to offer better discrimination in terms of dose-response sensitivity?**
- 2. What other in vivo approaches (e.g., surrogate markers) might be sufficiently sensitive and validated to establish in vivo BA and BE for inhaled corticosteroids?**

Summary of Answer:

- 1., 2. To assess the local delivery bioequivalence of two oral inhalation corticosteroid products, the comparative dose-response trial with pulmonary function measurements as the primary analysis parameters remains the method of choice.

However, variability is large, and metrics sensitive enough for establishing local delivery bioequivalence with trial designs that are practical from both a subject number and length of study perspective are not yet available. Further, although desirable, no alternative design has been sufficiently validated that will meet this need. One exciting possibility that may offer both a more sensitive method and a simpler clinical study for inhaled corticosteroids is the cross-over design

suggested by Dr. Ahrens at the 26 April 2000 OINDP Subcommittee meeting. We recognize that this concept must be appropriately tested in the clinic and hope that sufficient funds can be found to permit this analysis in the near future.

C. PK or PD Studies for Systemic Exposure of Locally Acting Drugs

Question:

- 1. *Are there situations where in vitro data plus systemic PK and systemic PD data can be relied on to assure local drug delivery for either nasal or inhaled drugs?***

Summary of Answer:

1. Yes, there could be situations where in vitro data plus systemic PK and systemic PD data may be relied upon to assure BE of two products of the same formulation for nasal and/or inhaled drugs. If a predictive in vitro/in vivo correlation can be documented from the literature or from experimental clinical data, the sponsor should have the opportunity to discuss the possibility of waiving clinical studies with the Agency. At present this is not the case for intranasal or inhaled corticosteroids. Post-approval changes to manufacture of approved Reference or approved Test products may not require extensive testing, but such changes are outside the scope of this draft Guidance.

The Team encourages the Agency to solicit further scientific discussion on BA/BE studies before issuing further guidance.

3. *BA/BE TEAM'S COMMITMENT TO UNDERTAKE FURTHER WORK*

The BA/BE Technical Team would like to discuss with the Agency or the OINDP Subcommittee the conclusions contained in the technical papers. The BA/BE Team is willing to conduct further assessments of its data to address more completely any of the BA/BE questions raised by the Agency at the 26 April OINDP Subcommittee meeting or to address any subsequent BA/BE questions the Agency may have.

IV.2. CMC SPECIFICATIONS TECHNICAL TEAM

DOSE CONTENT UNIFORMITY (DCU) WORKING GROUP

1. DCU WORKING GROUP'S APPROACH

At the public hearing of the 26 April meeting of the OINDP Advisory Subcommittee, the Specifications Technical Team committed to investigate the following hypothesis:

The current state of OINDP technology may not allow general compliance with the dose content uniformity specifications in the draft FDA CMC Guidances.

In addition, at the same meeting, the FDA asked the OINDP Subcommittee the following questions:

Should there be a single content uniformity standard for all orally inhaled and nasal drug products?

Should the FDA continue development of the proposed statistical approach to evaluating content uniformity?

To investigate the Team's hypothesis and to provide guidance on the FDA's questions, the DCU Working Group of the Specifications Team collected a worldwide blinded database containing delivered dose content uniformity (DCU) data for OINDP.

2. DCU WORKING GROUP'S FINDINGS TO DATE

The DCU Working Group collected a database containing data for 77 products from 10 companies (with a total of 46,016 individual DCU observations), analyzed the collected data and prepared and submitted the *Initial Assessment of the DCU Database*² to FDA on 31 July 2000.

The initial assessment of the database focused on the draft CMC Guidances requirement that none of the DCU determinations be outside the "outer limits" of 75-125% LC (label claim). For the purposes of the main analysis, the Working Group identified 60 products that met certain criteria outlined in the *Initial Assessment*. Main analysis showed that while the overall mean delivered dose was 100% LC, the requirement on the outer limits was violated for 68% of the products (Figure 1). The occurrence of DCU values outside the specified limits is a consequence of the inherent variability in DCU observations (the relative standard deviation of measured dose content varied between products from 3.5% to 18.1%).

² The full text of the *Initial Assessment of the DCU Database* is publicly available on the FDA's website at http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_reports.htm.

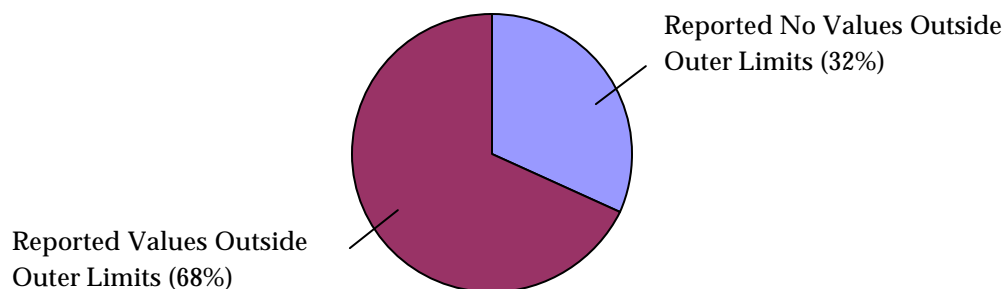


Figure 1. Percentage of products that reported DCU values outside 75-125% LC (“outer limits”) in violation of the draft Guidance recommendation that no such values may be observed.

The median proportion of determinations outside 75-125% LC was 1.1% (range: 0-14%), and varied depending on the product type from pre-metered DPIs (range 0-1.9%, median 0.0%) to CFC suspension pMDIs (range 0-1.4%, median 0.7%) to HFA suspension pMDIs (range 0-7.8%, median 1.3%) to device-metered DPIs (range 0-14%, median 3.3 %). The diversity of the analyzed products is illustrated in Figure 2.

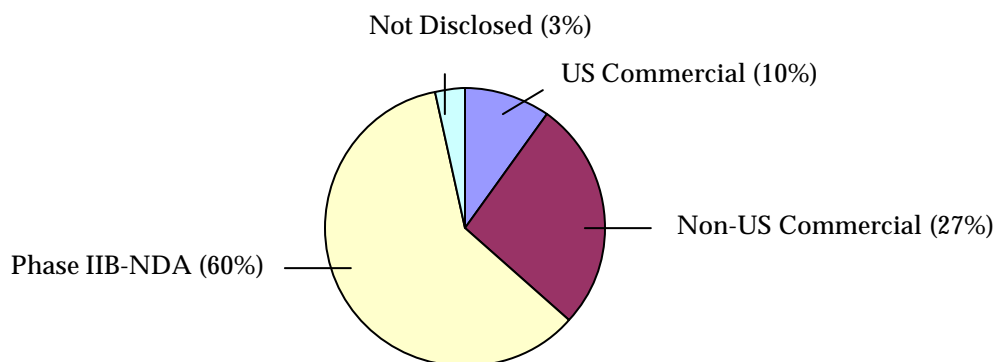


Figure 2. Status of products included in the main analysis.

The initial assessment of the database supports the hypothesis that orally inhaled products do not in general comply with the DCU specification in the FDA’s draft Guidances. The relatively large differences between products and between product types suggest that a single content uniformity specification for all inhaled and intranasal drug products is not suitable.

3. DCU WORKING GROUP'S COMMITMENT TO UNDERTAKE FURTHER WORK

The DCU Working Group prepared and submitted for the Agency's consideration a *Proposed Plan for Stage 2 Analysis of DCU Database* that outlines the following steps for further analysis of the collected data:

- Develop and Validate Simulation Approach;
- Assess Compliance of DCU Database with Complex Criteria Proposed in Draft Guidances (DCU Between Containers and DCU Through Life);
- Investigate ICH Approach;
- Investigate Dr. Hauck's Approach and its Variations; and
- Make Plans for Developing Recommendations Based on Results of Stage 2 Analysis.

The results of the Stage 2 Analysis will indicate the degree to which drug products meet the requirements of different approaches to DCU testing and will set the stage for investigation of such important questions as:

- What statistical approach is suitable for DCU specifications?
- Given an approach, what limits are appropriate?

The Group believes that the results of this work will be of value to the Agency in the establishment of a long-term solution to the assessment of DCU for orally inhaled and nasal drug products.

Representatives of the DCU Working Group will be meeting with the Agency on 20 November to discuss the *Initial Assessment of the DCU Database* and *Proposed Plan for Stage 2 Analysis of DCU Database*.

PARTICLE SIZE DISTRIBUTION (PSD) WORKING GROUP

1. PSD WORKING GROUP'S APPROACH

At the 26 April meeting of the OINDP Subcommittee, the Specifications Team made a commitment to collect a world-wide database of PSD data for orally inhaled and nasal drug products in order to investigate actual PSD capabilities of OINDP and appropriate statistical approaches to PSD testing. As a first step, the Team committed to explore the following question:

Can the current state of OINDP technology generally comply with the mass balance criterion in the draft FDA CMC Guidances?

Upon completion of the initial assessment of the PSD database, the PSD Working Group will explore different statistical approaches, various metrics and specific sets of criteria that would be appropriate for characterizing PSD of OINDP.

2. PSD WORKING GROUP'S FINDINGS TO DATE

The PSD Working Group collected a world-wide PSD database containing data from 7 companies on 35 orally inhaled and intranasal drug products - currently on the market or under development - with results for individual stages, for a total of 3,606 particle size determinations.

The Working Group analysed the collected data and prepared and submitted the *Initial Assessment of the PSD Database* to FDA on 29 August 2000. The draft Guidances require that the total amount of drug collected on all stages and accessories of a cascade impactor ("the mass balance") be within 85-115% of the label claim for drug content. The results of the initial assessment of the PSD database indicate that this mass balance requirement is not generally suitable for OINDP. Only 4 out of 35 examined products had all mass balance determinations within the prescribed limits.

In addition, the Team believes that it is not appropriate to use the mass balance as a means to control total emitted dose. Particle size testing should be used only for characterizing particle size distribution of the batch. The total emitted dose is adequately controlled by appropriate DCU tests. The PSD Working Group's analysis shows that the mass balance requirement proposed in the draft Guidances is not suitable as a drug product specification but could be appropriate as a system suitability test defined on a case-by-case basis.

The full text of the *Initial Assessment of the PSD Database* should be publicly available on the FDA's website at http://www.fda.gov/ohrms/dockets/ac/00/techpro/3609_reports.htm.

3. PSD WORKING GROUP'S COMMITMENT TO UNDERTAKE FURTHER WORK

The PSD Working Group is currently developing a plan for further analysis of the PSD database and would welcome an opportunity to meet with the Agency to discuss such a plan as well as results of the *Initial Assessment of the PSD Database*.

This more detailed analysis will address such issues as:

- further investigation of the relevance of the mass balance criterion as a specification versus system suitability criterion;
- investigation of the question whether fewer than 3-4 stage groupings can provide adequate control of PSD; and
- other general studies to compare different metrics and sets of criteria for characterizing the PSD of OINDP.

The PSD Working Group is open to the suggestions from the Agency on how to maximize the benefits of the collected database, which is unique in its scope and size.

SPECIFICATIONS TEAM'S COMMITMENT TO UNDERTAKE FURTHER WORK

The CMC Specifications Team recognizes the importance of meaningful specifications for the routine control of product quality. The initial data-based analyses conducted by the Team indicate that the DCU and PSD specifications in the draft CMC Guidances are not generally suitable for OINDP. The databases collected by the Collaboration are unprecedented in their scope and size and provide a unique opportunity to further address differing views concerning CMC specifications in an open discussion of all interested parties. The Team urges the Agency to employ all available avenues for a data-based scientific discussion on the best approach to setting specifications in OINDP.

IV.3. CMC TESTS AND METHODS TECHNICAL TEAM

1. TESTS AND METHODS TEAM'S APPROACH

The Team committed to collecting and analyzing data from commercial products and products under development in order to evaluate objectively the requirements for a number of tests in the draft CMC Guidances. The Team identified the following general issues in regard to tests and methods in the draft CMC Guidance documents:

- Although there are core tests which apply to all drug products, the need for certain tests should be driven by a critical evaluation of data generated during the development phase of each product.
- Currently, the two draft CMC Guidances attempt to address all the testing required for four distinct dosage forms for orally inhaled and nasal drug products (*i.e.*, MDIs, DPIs, nasal sprays and inhalation solution, suspension and spray drug products). The Team believes that in order to more clearly define the testing requirements for each product class, the draft CMC Guidances should be edited or a separate Guidance should be developed for each dosage form.
- In many instances, the language in the draft CMC Guidances is ambiguous.

In light of these issues, the Team examined the testing requirements in the draft CMC Guidances for all orally inhaled and nasal drug products, and found specific areas of concern. The Team is addressing MDIs first, and has identified the requirements for the following MDI tests to be of most concern:

- Water (Moisture) Content
- Spray Pattern
- Shot Weight
- Plume Geometry
- Impurities and Degradants
- Pressure Testing
- Particle Size Distribution
- Dose Content Uniformity

At the 26 April OINDP Subcommittee meeting, the Team presented position statements regarding these MDI tests, and committed to performing data-based investigations of some of them.

2. TESTS AND METHODS TEAM'S PRELIMINARY DATA-BASED CONCLUSIONS

In evaluating the identified MDI tests, the Team has collected data for water content, spray pattern, shot weight, plume geometry, and particle size distribution. The Team has also compiled relevant data from the literature for particle size distribution and pressure tests. Team members have analyzed the data and are preparing technical reports and recommendations for submission to the Agency in December 2000.

The Team's position statements and preliminary data-based conclusions are listed below:

(i) Water Content

Position Statement: The Team believes that water or moisture content should only be controlled and analyzed if it has been demonstrated during development studies to affect product performance.

Preliminary Conclusions: Development and stability data for 12 different HFA and CFC suspension and solution products reveal that for some products there is no correlation between increase in water content and either delivered dose or fine particle fraction.

(ii) Spray Pattern

Position Statement: The Team believes that Spray Pattern testing for finished MDI drug products is redundant to the dimensional analysis conducted during component release testing. Spray pattern is not a meaningful test for routine analysis of MDI product quality.

Preliminary Conclusions: Data collected for 8 different HFA and CFC suspension products demonstrate that there is no correlation between spray pattern and parameters specified in the draft Guidance as effecting product quality: size and shape of the actuator orifice, size of metering chamber, size of valve stem orifice, vapor pressure in the container, and nature of formulation.

(iii) Shot Weight

Position Statement: Shot weight testing is a device or component acceptance test used to control the quality of incoming materials. Although shot weight testing is a good diagnostic tool, it is not appropriate to set specifications for this test since it is redundant to the dose delivery test.

Preliminary Conclusions: An initial assessment of 13 different products show that (i) there is no clear correlation between shot weight and delivered dose, and (ii) shot weight values likely show no change on stability.

(iv) Plume Geometry

Position Statement: The plume geometry test does not provide assurance of product quality nor does it offer meaningful functional performance characterization.

Preliminary Conclusions: The Team is investigating current industry practices regarding this test.

(v) Particle Size DistributionPosition Statements:

The requirements of particle size method capabilities should be described in general. The specific approach should not be prescribed, i.e., Cascade Impaction. The draft CMC Guidance should also allow for suitable and validated alternate approaches to the determination of particle size distribution, which may assure control of the product, and manufacturing process.

Relative humidity and temperature may not need to be controlled for the testing of all MDI products. The requirement to control these parameters may be evaluated in the validation of the method and based on the development data for the product.

Preliminary Conclusions: There is a wide body of literature that supports the Team's position statement regarding alternate methods. Collected data and literature data are being analyzed by Team members to determine the validity of their position regarding the effects of relative humidity and temperature.

(vi) Pressure Testing

Position Statement: The Team believes that pressure testing of MDIs should not be required for single propellant/co-solvent systems.

Preliminary Conclusions: In the case of single propellant plus alcohol co-solvent metered dose inhalers, data from the literature suggest that pressure testing during development is not a reliable means of measuring propellant/co-solvent ratio. The integrity of the propellant-alcohol mixture is better controlled by alcohol content analysis.

The Team is also preparing for submission to the Agency papers addressing the following tests:

(vii) Impurities and Degradants

The Team believes that synthetic impurities that are not degradants should be controlled in the drug substance and not in the drug products. The testing of the drug product for synthetic impurities that are not degradants is redundant and as such unnecessary. The ICH approach to impurities and degradants should apply to inhalation drug products.

(viii) Dose Content Uniformity³

Clarification should be provided for the term "stability indicating method" in the draft CMC Guidance for MDIs and DPIs (Line 528). Since the chemical stability of the formulation is assessed elsewhere in product testing, i.e., during degradation products assay, it is suggested that the phrase, "a validated, specific, and unbiased method" be considered as a potential replacement for "stability indicating."

In early 2001, the Team will undertake similar analyses for non-MDI dosage forms. The Team is committed to developing position statements on any identified issues and to collecting and assessing relevant data.

³ The Tests and Methods Team and the Specifications Team are addressing different aspects of PSD and DCU. The Tests and Methods Team, unlike the Specifications Team, is not addressing specifications for mass balance and delivered dose.

3. TEST AND METHODS TEAM'S COMMITMENT TO UNDERTAKE FURTHER WORK

The Team is evaluating the collected data on key MDI tests and is preparing technical papers and recommendations to be submitted to the Agency in December 2000. In early 2001, the Team will undertake data collection and analysis for non-MDI dosage forms.

The Team believes that its reports will assist the Agency in eliminating redundant or unnecessary testing recommended by the draft CMC Guidance documents. Further, the Team hopes that its suggestions of alternate language for the draft Guidances will help clarify testing criteria and make such criteria specific to particular dosage forms.

IV.4. CMC LEACHABLES AND EXTRACTABLES TECHNICAL TEAM

1. LEACHABLES AND EXTRACTABLES TEAM'S APPROACH

The Team has examined in detail the sections of the draft CMC Guidances which address the areas of extractables and leachables. The Team agrees with the Agency that control of extractables and leachables is important for ensuring the safety and quality of inhalation drug products. The Team has focused on the four general topics as listed in the following sections, and has collected and examined data with regard to these topics. Based on the data, the Team is drafting a technical paper that proposes alternate language for those areas of the Guidances that could be enhanced by clarification or require reassessment. The Team will also request the opportunity to discuss with the Agency our proposal for a leachables strategy.

2. LEACHABLES AND EXTRACTABLES TEAM'S PRELIMINARY CONCLUSIONS

The four general topics on which the Team has focused are: (i) analytical characterization of extractables (controlled extraction studies), (ii) analytical characterization of leachables, (iii) safety qualification of leachables, and (iv) routine extractables testing.

(i) Analytical Characterization of Extractables (Control Extraction Studies)

The Team suggests alternate language for the draft CMC Guidance documents that clarifies the specific requirements for analytical characterization studies of extractables for each of the relevant dosage forms.

(ii) Analytical Characterization of Leachables

The Team proposes that a leachables study should be a one-time study, and may also be conducted on drug product intended for pivotal toxicological studies and clinical trials.

Furthermore, the Team has collected data from both suppliers and pharmaceutical companies for over 30 different products and components in order to determine how a correlation might be established between leachables and extractables. Based on the data, the Team has concluded that a correlation is established when each leachable in the drug product can be assigned qualitatively, directly or indirectly, to an extractable. The Team recommends that provided a correlation between leachables and extractables can be demonstrated, a specification for leachable compounds in the drug product should not be required.

The Team recommends that the draft Guidances be amended to include reporting and qualification thresholds for leachables. The Team is currently discussing proposals for these thresholds and requests the opportunity to discuss this topic in detail with the Agency.

(iii) Safety Qualification of Leachables

The Team's Toxicology Working Group has reviewed current industry practices regarding the safety evaluation of leachables and extractables. Based on this review, the Toxicology Working Group has found areas of agreement and disagreement with the draft Guidances. Specifically the Working Group concludes that (i) a separate section should be added to each Guidance to describe the toxicology evaluation process, including a flowchart, (ii) toxicological qualification should be performed only on leachables, (iii) guidelines for toxicological evaluation should distinguish between genotoxic and non-genotoxic leachables; (iv) toxicological qualification should be conducted only on those leachables that occur above a data-supported threshold, and (v) for component suppliers, USP <87> and <88> may have utility for extractable testing. However for a pulmonary drug product, USP <87> and <88> are not necessary when a more comprehensive in-vivo toxicological evaluation is available.

(iv) Routine Extractables Testing

The Team reviewed existing extractables data from suppliers and assessed the suitability of routine extractables testing to ensure component composition, function and safety. The Team has concluded that routine extractables testing is appropriate for those critical components which contact either the formulation, patient's mouth or nasal mucosa in order to ensure a consistent lot to lot extractables profile for a given component. However, after a careful examination of the available data, the Team has also concluded that routine extractables testing is not appropriate for control of component composition or function. Supplier qualification, in-process controls and functional testing are more effective for control of component composition and quality.

3. LEACHABLES AND EXTRACTABLES TEAM'S COMMITMENT TO UNDERTAKE FURTHER WORK

The Team will offer its data-based technical report and recommendations to the Agency and the OINDP Subcommittee for consideration in late 2000 – early 2001. The Team seeks to initiate a discussion with FDA, PhRMA, ICH and other interested parties in order to develop recommendations regarding reporting and toxicological qualification thresholds for non-genotoxic leachables. Furthermore, if the Agency considers it valuable, the Leachables and Extractables Team, in collaboration with the Supplier Quality Control Technical Team, will propose a control strategy (including appropriate testing criteria) for ensuring the relevant performance and safety characteristics of critical components.

IV.5. CMC SUPPLIER QUALITY CONTROL TECHNICAL TEAM

1. SUPPLIER QUALITY CONTROL TEAM'S APPROACH

The Team believes that the draft CMC Guidance documents should more clearly distinguish between development and product characterization data, and data routinely generated for quality control purposes. 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. The Team's thesis is:

The qualification and control of critical components (in the areas of performance related physical testing, extractables and leachables) and excipients should be achieved by a combination of appropriate scientific practices, cGMP controls and supplier qualification systems.

2. SUPPLIER QUALITY CONTROL TEAM'S DATA-BASED PROPOSALS FOR MODIFYING THE DRAFT CMC GUIDANCE DOCUMENTS AND PRELIMINARY DATA-BASED CONCLUSIONS

The Team conducted a survey of suppliers of finished components, sub-components, excipients, raw materials and active drug substances used in the manufacture of inhaled drug products. The purpose of the survey was to evaluate the quality and compliance of the different levels of suppliers to the pharmaceutical industry. The information was collected by collating the responses to a detailed questionnaire that required supplier companies to assess their performance with respect to specific cGMP program elements. The questionnaire was circulated to the pharmaceutical manufacturers and delivery system manufacturers participating on the Team.

The outcome of the survey can be summarized as follows:

- Information was obtained on 53 supplier companies.
- A high level of cGMP compliance is evident with Active Pharmaceutical Ingredient (API) suppliers.
- The level of cGMP awareness and compliance in the components and raw materials supply chain is increasing, but there continues to be room for improvement.

- There are specific cGMP program elements which remain to be generally accepted and implemented, especially at the beginning of the supply chain (*i.e.*, sub-component suppliers).
- There are currently no generally accepted cGMP guidelines for the component and sub-component supply chain.

As a result of the Team's findings, the Team proposes that a cGMP guideline for all component suppliers be developed. The Team endorses the International Pharmaceutical Excipients Council (IPEC) Guideline for the control and cGMP compliance of excipients as a means of controlling excipient supply. The Team supports the development of similar guidelines for critical components and raw bulk materials in order to raise the compliance level of suppliers. The Team believes that implementation of cGMP guidelines for component suppliers will improve quality and compliance at all levels of the supply chain, and in turn offer increased assurance of quality in the finished product.

3. SUPPLIER QUALITY CONTROL TEAM'S COMMITMENT TO UNDERTAKE FURTHER WORK

The Team proposes that an industry-wide initiative be established to undertake the development of a cGMP guideline for all component suppliers and seeks the FDA's support of such a process. The Team requests that the Agency be receptive to reviewing and commenting on draft cGMP guidelines when available. The Team also urges the FDA to consider inserting into the draft CMC Guidance documents a statement that recognizes the value of a cGMP guideline for component suppliers, and acknowledges that if sufficient supplier control mechanisms are in place, appropriate reductions in testing will be considered. Pending FDA support for the process, the Team will take a leadership role in establishing the initiative to develop a cGMP guideline for components.

V. CONCLUSION

IPAC-RS and ITFG strongly support the Agency's development of draft Guidance documents for orally inhaled and intranasal drug products. We recognize the value of having guidance documents to facilitate the development and approval of new types of such products. However, much debate and differing views surround a number of important CMC and BA/BE issues for nasal and orally inhaled medications.

After substantial consideration of CMC and BA/BE issues in the draft Guidance documents, including extensive analysis of relevant data, the more than 100 scientists participating in the ITFG/IPAC-RS Collaboration representing more than 25 companies and institutions, have concluded that certain aspects of the draft Guidances should be revised. We believe that in-depth, interactive scientific dialogues on these outstanding issues should take place to facilitate necessary changes in the draft Guidances. We believe it is important that the Collaboration's data-based conclusions and proposals for modifying the draft Guidance documents be given full consideration before the Guidances are finalized.

The members of the ITFG/IPAC-RS Collaboration strongly recommend that the Agency continue to work towards resolving these important issues by utilizing existing avenues for interactive, scientific dialogues, including, as appropriate, the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science, the Product Quality Research Institute (PQRI), another FDA/USP/AAPS workshop on OINDP regulatory issues, or meetings with representatives of the ITFG/IPAC-RS Technical Teams. Such dialogues will ensure that the OINDP Guidances bring maximum value to regulators and industry, and most of all, to patients and physicians.

We respectfully request that the Advisory Committee for Pharmaceutical Science support the need for continuing scientific dialogue on important CMC and BA/BE issues for orally inhaled and nasal drug products before the draft Guidance documents are finalized. Further, we ask that the Advisory Committee for Pharmaceutical Science endorse our request that opportunities be identified for a continued dialogue between FDA and the ITFG/IPAC-RS Collaboration regarding the Collaboration's data-based conclusions.

We appreciate the opportunity to submit this statement to the Agency and the members of the Advisory Committee for Pharmaceutical Science. We hope that this statement and our past and future submissions and interactions will assist the Agency, the Advisory Committee for Pharmaceutical Science and the OINDP Subcommittee in their work to finalize these important Guidance documents based on all currently available scientific evidence.