

STATEMENT

Of the ITFG/IPAC Collaboration on Chemistry, Manufacturing, and Controls and In Vitro and In Vivo Bioavailability/Bioequivalence Issues in Draft Guidance Documents for Orally Inhaled and Nasal Drug Products

Submitted by:

THE INHALATION TECHNOLOGY FOCUS GROUP OF THE AAPS
THE INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM

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I. OVERVIEW

- At the June 1999 Workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery, the International Pharmaceutical Aerosol Consortium (IPAC) proposed the creation of a post-Workshop consensus building process to address several issues in the draft CMC Guidance for MDIs and DPIs. Following IPAC's proposal, the FDA agreed to consider further the opportunity 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 product quality 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's proposal at the June Workshop and agreed to undertake a data-driven collaborative effort with IPAC to combine scientific expertise and regulatory knowledge and address key CMC and BA/BE issues in the draft Guidance documents.
- The ITFG/IPAC 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.
- Approximately 85 individuals and more than 20 companies are participating in the ITFG/IPAC 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- The ITFG/IPAC Technical Teams have developed hypotheses or position statements on key issues in the draft Guidance documents and are obtaining data and scientific information to investigate these issues.
- This Statement provides an overview of the approach taken by each ITFG/IPAC Technical Team and describes the commitment to contribute constructively to the deliberations of the OINDP Subcommittee and the Agency's development of the OINDP Guidance documents.

II. BACKGROUND

Publication of Draft Guidance Documents and June Workshop

Between October 1998 and June 1999, the FDA issued the following three draft Guidances for Industry: 1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*; 2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation*; and 3) *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*. On 3-4 June 1999, the FDA/AAPS/USP sponsored a Workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery. At the Workshop, the International Pharmaceutical Aerosol Consortium (IPAC) proposed the creation of a post-Workshop consensus building process to address several issues in the draft CMC Guidance for MDIs and DPIs. The Inhalation Technology Focus Group (ITFG) of the American Association of Pharmaceutical Scientists (AAPS) supported the IPAC proposal, and agreed to consider a collaborative effort with IPAC's Working Group on FDA Guidance to address these issues.

At the June Workshop, the FDA agreed to consider the opportunity for further dialogue in regard to chemistry, manufacturing and controls (CMC) and bioavailability and bioequivalence (BA/BE) issues in the draft Guidance documents for OINDP. During the months following the June Workshop, IPAC maintained contact with the Agency and kept the Agency up to date on its plans to undertake a collaborative scientific effort with the ITFG.

In early October 1999, the Office of Pharmaceutical Science (OPS) in the Center for Drug Evaluation and Research (CDER) at FDA proposed the creation of an Orally Inhaled and Nasal Drug Products (OINDP) Expert Panel. The Agency selected several academicians to become members of the Expert Panel, and solicited from interested trade associations and professional organizations nominations for experts to serve on the OINDP Expert Panel. An initial meeting of the OINDP Expert Panel was held in November 1999. At this meeting several CMC and BA/BE issues were identified and it was agreed that the Expert Panel should be divided into two working groups, one focused on CMC issues and the other on BA/BE issues.

In January 2000, the Agency announced plans to re-evaluate the Expert Panel process. As a result of this re-evaluation, in March 2000, the Agency converted the OINDP Expert Panel into the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science.

ITFG/IPAC Collaboration on CMC and BA/BE Issues

The ITFG is comprised of pharmaceutical scientists who seek to foster and advance the art and science of pharmaceutical aerosol products, aerosol technology and related processes. IPAC 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), rhinitis, and migraine, as well as new products for non-respiratory disease indications such as diabetes. The ITFG and members of the IPAC Working Group on FDA Guidance share common views on CMC and BA/BE issues in the draft Guidances for OINDP. ITFG and IPAC 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 Workshop, while awaiting the Agency's proposal on the appropriate forum for further consideration of OINDP regulatory issues, representatives of the ITFG and IPAC's Working Group on FDA Guidance established and initiated the ITFG/IPAC Collaboration, a joint, data-driven scientific effort. Approximately eighty-five individuals from more than twenty companies are participating in the ITFG/IPAC Collaboration.

The objective of the ITFG/IPAC 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 of the OINDP Guidance documents. The ITFG and IPAC agreed that they would commence the work of the Collaboration prior to the deliberations of the OINDP Subcommittee in order to be in the best position to provide the Agency and the Subcommittee with timely technical reports and recommendations for consideration during the Subcommittee's deliberations. While the ITFG and IPAC have identified a number of key CMC and BA/BE issues, and feel strongly that CMC and BA/BE issues for OINDP should be given equal attention by the OINDP Subcommittee, the ITFG/IPAC Collaboration is also willing to provide relevant information, if available, on issues raised by the Subcommittee and the Agency but not currently being addressed by the Collaboration.

The ITFG/IPAC Collaboration is overseen by the ITFG/IPAC 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 are obtaining data and scientific information 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.

III. PROGRESS OF THE ITFG/IPAC COLLABORATION

The ITFG/IPAC 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 started the collection and assessment of 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 how the work of these Teams could contribute constructively to the deliberations of the OINDP Subcommittee and the Agency's development of the OINDP Guidance documents. The summary below: 1) lists the company or institutional affiliation of the scientists participating on each Technical Team; 2) identifies issues in the draft Guidance documents and describes the Team's approach to addressing these issues; and 3) describes the Team's commitment to deliver a work product that may assist the Subcommittee and the Agency in the deliberations on CMC and BA/BE issues for OINDP.

III.1. BA/BE TECHNICAL TEAM

1. *BA/BE Team Membership*

Scientists and other individuals from the following companies/institutions are members of the BA/BE Technical Team:

| | |
|-------------------------|--------------------------------|
| Agouron Pharmaceuticals | Inhale Therapeutics Systems |
| Astra Zeneca | Eli Lilly |
| Aradigm | Lovelace Respiratory Institute |
| Aventis | Magellan Laboratories |
| IVAX | Primedica |
| Boehringer Ingelheim | Schering-Plough |
| BI Roxane | 3M Pharmaceuticals |
| Dura Pharmaceuticals | Trudell Medical |
| Glaxo Wellcome | University of Rhode Island |

2. BA/BE Team's Approach

The BA/BE Team has considered a number of issues relating to the draft BA/BE Guidance for nasal aerosols and nasal sprays. The members of the Team have agreed on the working assumptions underlying the Team's work, and have identified two main working propositions. During the past several months, Team members have submitted and evaluated data and scientific articles related to the two main working propositions. The Team has drawn conclusions based upon the working assumptions and currently available information.

The Team has agreed on the following working assumptions:

- The Team's BA/BE recommendations apply to locally acting drugs only (per the current draft BA/BE Guidance for nasal aerosols and nasal sprays);
- The Team's comments 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 working propositions reflect only the current state of knowledge.

The Team's working propositions 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 BE approval without establishing in vivo BE.

IN VIVO TESTS:

For BE approval, 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.

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

- Based on the available literature, current in vitro tests may predict lung deposition but BE predictability has not been shown.
- In vitro tests described in the current draft BA/BE Guidance for nasal aerosols and nasal sprays are not necessarily more relevant or discriminating than clinical studies for BE assessment.
- 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 (*i.e.*, systemic exposure).
- Because all of the preceding statements apply equally to solutions and suspensions, the assumption that in vitro studies alone are sufficient for BE of solutions is unfounded. The draft BA/BE Guidance should not distinguish between nasal suspensions and solutions for in vivo BE.

3. *BA/BE Team's Commitment*

The Team is committed to prepare for submission to the OINDP Subcommittee and the Agency a technical paper on the BA/BE issues in the draft BA/BE Guidance. The Team expects that it will need no more than three months to finalize the technical paper. The purpose of the paper will be to:

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

The Team's work will be applicable to the existing draft BA/BE Guidance for nasal aerosols and sprays as well as the Agency's forthcoming draft BA/BE Guidance for orally inhaled drug products. The Team expects that its work will assist the Agency in finalizing the draft BA/BE Guidance for nasal aerosols and sprays and also be useful to the Agency in its preparation of the draft BA/BE Guidance for orally inhaled drug products.

III.2. CMC SPECIFICATIONS TECHNICAL TEAM

1. *Specifications Team Membership*

Scientists and other individuals from the following companies/institutions are members of the CMC Specifications Technical Team:

| | |
|----------------------|----------------------------|
| Aradigm | Inhale Therapeutic Systems |
| AstraZeneca | Inspire Pharmaceuticals |
| Aventis | IVAX |
| Boehringer Ingelheim | Kos Pharmaceuticals |
| Dura Pharmaceuticals | Magellan Laboratories |
| Eli Lilly | Schering-Plough |
| Glaxo Wellcome | 3M Pharmaceuticals |

2. *Specifications Team's Approach*

(i) **Dose Content Uniformity (DCU) Working Group**

The DCU Working Group believes that orally inhaled and nasal drug products are amenable to the principles set forth by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). In particular, the ICH Harmonised Tripartite Guideline on "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (Q6A) provides a process for establishing specifications.

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).

The DCU Working Group notes that the draft FDA CMC Guidance documents recommend a single, one-size-fits-all specification for dose (spray) content uniformity (DCU/SCU) that does not take the principles outlined in ICH Q6A into due consideration. For example, the FDA draft CMC Guidances do not seem to acknowledge the relevance of development or production performance data. Further, the DCU Working Group finds it unjustified that products that have been shown to be safe and efficacious by clinical trials should be considered unacceptable solely because they do not comply with pre-established in vitro specifications. Based on the collective experience, the Specifications Team is investigating the following question:

Can the current state of OINDP technology generally comply with the DCU specifications in the draft FDA CMC Guidances?

The Team has developed and initiated an industry-wide survey designed to collect blinded DCU/SCU data from companies that are developing and/or marketing an orally inhaled or nasal drug product worldwide. The objective of the survey is to generate a comprehensive database which can be used to examine the actual DCU/SCU capabilities of these types of drug products. The database generated from this survey will provide the Team with a means of investigating the above question. In addition, the database generated may enable the DCU Working Group to investigate alternate approaches to DCU specifications. Alternate specifications, if proposed, will be based upon a statistical analysis of the survey database. Statistical analysis of the blinded data will be performed by statisticians from several participating companies. A one-size-fits-all specification is neither presumed nor rejected a priori.

The Team has also agreed on the following position:

The format of the specifications in the draft Guidances should be based upon sound statistical practices such that they can be translated into a quality requirement.

An adequate specifications format is important for many reasons. For example, a flaw with the DCU test in the draft CMC Guidance is that the requirement that no observed value may be outside a fixed limit rewards minimalistic testing since the probability to pass increases with decreasing sample size. This is in contrast to a requirement on a distribution parameter (for example a mean or a standard deviation) for which a larger sample size provides a better estimate and therefore a more accurate quality assessment.

The Team proposes to work with the OINDP Subcommittee, the Agency and an independent statistician to consider the following potential options for an alternate DCU specification:

- ICH Uniformity of Dosage Unit Pharmacopeial Harmonisation effort
- Dr. Walter Hauck's Approach
- ISO 2859-1 Approach
- Other Approaches

(ii) Particle Size Distribution (PSD) Working Group

The PSD Working Group, like the DCU Working Group, believes that the process outlined in ICH Q6A for establishing specifications should apply to inhaled drug products as well as other dosage forms.

The PSD Working Group proposes that for each product, the specification should be developed on the basis of sound scientific principles and data collected during the development process as well as from testing of the commercially manufactured product. Wherever possible, internationally accepted compendial methods should be applied to the characterization of PSD. They should be validated for the specific product, or alternative methodologies need to be justified and validated. The metrics for the PSD measurement should be based on clinical safety and efficacy experience, process capability and other historical data obtained during the development. Statistics with specifications that assure failure of batches containing unsatisfactory product but do not cause excessive failure of batches that would not pose significant safety or efficacy risks, should be applied.

The PSD Working Group notes that the draft CMC Guidance documents indicate that the total mass collected in the particle size determination should be +/- 15% on a per actuation basis. The PSD Working Group believes that mass balance criterion should be a system suitability requirement for particle size distribution testing, not a specification. The PSD Working Group believes that both the specifications and the methods need to be developed individually for each OINDP. The Specifications Team is investigating the following question:

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

The PSD Working Group has developed and initiated an industry-wide survey designed to collect blinded PSD data from companies that are developing and/or marketing an orally inhaled or nasal drug product anywhere in the world. The objective of the survey is to obtain a comprehensive database which can be used to examine the actual PSD capabilities of OINDP products and analytical methods. The PSD data collected through this survey will be used to:

- Evaluate the position that the mass balance specification in the draft CMC Guidance documents should be changed to a system suitability requirement; and
- Test the PSD specification format proposed in the draft CMC Guidances (e.g., investigate if fewer than 3-4 stage groupings can provide equivalent control).

3. *Specifications Team's Commitment*

To date, more than 12 companies participating in the ITFG/IPAC Collaboration have initiated the process to provide DCU data for more than 45 drug products and PSD data for more than 40 drug products. The Team is committed to offering its technical reports, collected datasets, and recommendations to the Agency and the OINDP Subcommittee for consideration during the Subcommittee's deliberations. In addition, the Team is committed to working with and supporting the Agency, the OINDP Subcommittee and independent statisticians consulting the Agency to develop a method for establishing DCU specifications.

The Team expects that it will need approximately three months to collect the data and make an initial assessment. Depending on the results and discussions with the Agency and the OINDP Subcommittee, additional time may be required for further data analysis.

III.3. CMC TESTS AND METHODS TECHNICAL TEAM

1. *Tests and Methods Team Membership*

Scientists and other individuals from the following companies/institutions are members of the CMC Tests & Methods Technical Team:

| | |
|-------------------------|-----------------------|
| Aradigm | IVAX |
| AstraZeneca | Kos Pharmaceuticals |
| Agouron Pharmaceuticals | Eli Lilly |
| Aventis | Magellan Laboratories |
| Boehringer Ingelheim | Schering-Plough |
| Dura Pharmaceuticals | Sciarra Laboratories |
| Glaxo Wellcome | 3M Pharmaceuticals |
| Inspire Pharmaceuticals | |

2. Tests and Methods Team's Approach

The Team has carefully reviewed the draft CMC Guidances and proposes for the FDA's consideration tests that are meaningful, scientifically justified and add appropriate control of the product. The Team has identified the following issues in regard to tests and methods:

- 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.
- In many instances, the language in the draft CMC Guidances is ambiguous.
- 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.
- Additionally, the Team is prepared to work with the OINDP Subcommittee and the FDA to facilitate the harmonization of FDA, USP, and ICH.

In general, the Team's process is as follows. The current draft CMC Guidance for MDIs requires over thirty different tests that purport to control product quality at different stages of the product's life. Team members identified seven tests that the Team believes should be addressed differently:

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

In a series of meetings and teleconferences, the Team developed working position statements for these tests. Team members are in the process of collecting data. Based

on the data analysis, the Team will, if appropriate, revise its position statements and make final recommendations.

For example:

Water

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.

Spray Pattern

The Team believes that Spray Pattern testing for finished MDI drug products is redundant to the dimensional analysis conducted during component release testing.

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.

Pressure Testing

The Team believes that pressure testing of MDIs should not be required for single propellant/co-solvent systems. The Team will continue investigating the relationship between pressure testing and propellant ratio in blends.

Particle Size Distribution

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 Guidances 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 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.

Plume Geometry

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

To date, the Team has not reached any final conclusions regarding these tests, but is working on collecting and analyzing the relevant data. If the data show that the existing testing requirements are neither meaningful nor scientifically justified, then the Team will request an opportunity to recommend relevant, technically defensible, alternative methods to the OINDP Subcommittee and the Agency.

Additional Clarification

For the dose content uniformity test, members seek a clarification of the draft Guidance language:

Dose Content Uniformity

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

The Team is also undertaking similar analyses for the other dosage forms and anticipates identifying a number of issues 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. *Test and Methods Team’s Commitment*

The Team is committed to reviewing and evaluating the data collected, and retaining or revising its positions as necessary. The Team realizes that the abundance of data and tests involved will require a lengthy process of investigation. However, the Team believes that in the next three to four months it can prepare a technical paper containing its recommendations regarding some of the key MDI tests. Additional time will be required for further data analysis on tests for the other dosage forms.

The Team believes that its reports and datasets will assist the Agency in eliminating redundant or unnecessary testing in the draft CMC Guidance documents. In addition, the Team will suggest alternate language for the draft CMC Guidance documents that would make testing criteria specific to particular dosage forms.

III.4. CMC LEACHABLES AND EXTRACTABLES TECHNICAL TEAM

1. *Leachables and Extractables Team Membership*

Scientists and other individuals from the following companies/institutions are members of the CMC Leachables/Extractables Technical Team:

| | |
|----------------------|----------------------------|
| Aradigm | Glaxo Wellcome |
| Aventis | Presspart |
| AstraZeneca | Kos Pharmaceuticals |
| Boehringer Ingelheim | 3M Pharmaceuticals |
| Dura Pharmaceuticals | Schering-Plough |
| Valois | Inhale Therapeutic Systems |

2. *Leachables and Extractables Team's Approach*

The Team has examined the sections of the draft CMC Guidances which address the areas of extractables and leachables in detail. The Team agrees with the Agency that control of extractables and leachables is important for ensuring the safety and quality of inhalation drug products. Through its review and deliberations, the Team has focused on four general topics, and identified specific areas that either beg clarification, or raise questions for which an examination of relevant data could lead to a reassessment of the requirements in the draft CMC Guidances.

The Team has identified the following issues for review and further investigation: (i) analytical characterization of extractables (control extraction studies), (ii) analytical characterization of leachables, (iii) safety qualification of leachables, and (iv) routine extractables testing. The Team's questions and concerns relating to the issues, and the Team's approach to addressing these issues are described below.

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

Questions and Concerns:

- Several areas of the draft Guidance documents related to control extraction studies beg clarification. It is the opinion of the Team that the Guidance documents should provide clear, concise guidance on the requirements for control extraction studies.
- The draft CMC Guidances require detailed characterization of critical components. The Team requests that the Agency clarify this issue. With respect to identifying potential leachables, is it necessary to conduct control extraction studies on critical components which do not contact the

formulation or the patient's mucosa? With respect to control of component performance, would not functional testing and supplier qualification be most appropriate?

Team's Approach:

- The Team will suggest alternate language for the draft CMC Guidance documents in order to clarify the specific requirements for analytical characterization studies of extractables for each of the relevant dosage forms.

(ii) Analytical Characterization of Leachables

Questions and Concerns:

- The term "correlation" with respect to leachables and extractables data is not clearly defined in the draft CMC Guidances.
- If a correlation can be made between the identity and profile of component extractables with leachables, is there a need for drug product leachables acceptance criteria and routine leachables testing? Have there been instances where extractables have not correlated with leachables? If so, what were the circumstances?

Team's Approach:

- The Team will prepare a review of available leachables data and examine it for correlation with the corresponding extractables data. The Team will propose a working definition of "correlation" based on the data collected.

(iii) Safety Qualification of Leachables

Questions and Concerns:

- What are current industry practices for establishing safety of leachables?
- What are appropriate mechanisms of on-going control of leachables once safety is established?

Team's Approach:

- The Team will survey current industry practices and will propose a strategy for safety qualification of leachables based on best practices.

(iv) Routine Extractables Testing

Questions and Concerns:

- Is quantitative testing of extractables an appropriate mechanism to control composition of all components?
- Are there alternative processes of control?

Team's Approach:

A review of existing extractables data will be prepared in order to assess the suitability of routine extractables testing to ensure component composition, function and safety. The data will be examined for correlation with the known composition of the relevant plastic and elastomeric components. Potential alternate process(es) for control of component composition will be reviewed and submitted for consideration to the Agency.

3. Leachables and Extractables Team's Commitment

The Team is committed to offer data-based technical reports and recommendations to the Agency and the OINDP Subcommittee for consideration during the Subcommittee's deliberations within three to four months as follows:

- (i) The Team will propose alternate language to clarify the specific requirements for leachables and extractables for each of the relevant dosage forms.
- (ii) The Team will prepare a review of available leachables data and examine it for correlation with the corresponding extractables data. The Team will propose a working definition of "correlation" based on the data collected.
- (iii) The Team will propose a strategy for safety qualification of leachables based on best practices.
- (iv) 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.

III.5. CMC SUPPLIER QUALITY CONTROL TECHNICAL TEAM

1. *Supplier Quality Control Team Membership*

Scientists and other individuals from the following companies/institutions are members of the CMC Supplier Quality Control Technical Team:

| | |
|----------------------|---------------------|
| Aradigm | Kos Pharmaceuticals |
| AstraZeneca | Presspart |
| Aventis | Pfeiffer |
| Bespak | 3M Pharmaceuticals |
| Boehringer Ingelheim | Schering-Plough |
| Dura Pharmaceuticals | Valois |
| Glaxo Wellcome | |

2. *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, 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. 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.

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 requesting the assessment of performance at supplier companies 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.

3. *Supplier Quality Control Team's Commitment*

The members of the Team are committed to addressing the shortcomings of their suppliers. As a result of the Team's findings, and recognizing the existence of certain shortcomings, 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 these suppliers, which, as indicated in the Team's survey results, needs to be improved. The Team believes that implementation of cGMP guidelines for component suppliers will improve the quality and compliance of component suppliers at all levels of the supply chain, and in turn offer increased assurance of the quality of the finished product.

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.

IV. CONCLUSION

IPAC and ITFG share the FDA's goal of assuring the highest levels of safety, efficacy and quality of orally inhaled and nasal drug products and making these products available to patients in the most expeditious manner. We strongly support the Agency's development of guidance for nasal and oral inhalation drug products. We recognize the value of having guidance documents to facilitate the development and approval of new nasal and oral inhalation medications. However, much debate and differing views surround CMC and BA/BE issues relating to orally inhaled and nasal drug products. These differences need to be resolved through the process of a science-based dialogue so that the OINDP Guidances can bring maximum value to regulators and industry, and most of all, to patients and physicians.

The FDA's creation of the OINDP Subcommittee has initiated a process to explore differing views and make new information available that will benefit regulators, industry and patients. The OINDP Subcommittee presents an important opportunity for pharmaceutical scientists and the pharmaceutical industry to help make new information available. The ITFG and IPAC are strongly encouraged by the Agency's creation of the OINDP Subcommittee. The numerous pharmaceutical scientists participating in the ITFG/IPAC Collaboration are working together to combine scientific and technical expertise to facilitate consensus building on CMC and BA/BE issues for orally inhaled and nasal drug products. The ITFG/IPAC Collaboration is committed to offer its findings to the OINDP Subcommittee and the Agency as key scientific issues relating to OINDP are deliberated and revisions to the draft Guidance documents are considered. Further, the members of the Collaboration look forward to the views of the Subcommittee and Agency, and if possible, the Collaboration will provide relevant information on issues raised by the Subcommittee and the Agency but not currently being addressed by the Collaboration.