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STATEMENT TO ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE AND OINDP SUBCOMMITTEE

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Regarding Chemistry, Manufacturing, and Controls and In Vitro and In Vivo Bioavailability/Bioequivalence Issues in Draft Guidance Documents for Orally Inhaled and Nasal Drug Products

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INTRODUCTION

This statement is submitted to the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science in connection with their meetings on 17 and 19 July 2001, respectively.

The agenda for these meetings includes a consideration of the issue of dose-response of locally acting nasal drug products, with particular application to bioequivalence studies. The ITFG/IPAC-RS Bioequivalence and Bioavailability Technical Team offers their views on this topic in section **I.2.a** (page 7) of this report. Specifically, the Team reviews its findings on this issue, submitted to the Agency in August 2000, and presents its positions developed since the August submission.

We also provide an update on the work of the other Technical Teams of the ITFG/IPAC-RS Collaboration to inform the committee members of the progress made since the last meetings of these committees in 2000, to outline the full scope of our concerns with the draft Guidances for OINDP, and to highlight areas where additional research has been undertaken or proposed by the industry.

EXECUTIVE SUMMARY

- In January 2000, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) and scientists of the Inhalation Technology Focus Group (ITFG) of the AAPS initiated an extensive scientific collaboration to address important issues in the FDA's draft Guidance documents for orally inhaled and nasal drug products (OINDP).[1]

- Over 100 individuals from more than 25 companies and institutions are participating in the ITFG/IPAC-RS Collaboration.[2] The Collaboration involves several Technical Teams and Working Groups, addressing the issues of *in vitro* and *in vivo* tests for bioavailability and bioequivalence (BA/BE) studies, dose content uniformity (DCU) specifications, particle size distribution (PSD) tests and specifications, tests and methods used for control of product quality, leachables and extractables testing, and supplier quality control for orally inhaled and nasal drug products.

- ITFG and IPAC-RS are interested in data-based, scientifically justified Guidances for the development and registration of OINDP. In order to contribute constructively to the development of such Guidances, the ITFG/IPAC-RS Collaboration collected and analyzed relevant data and proposed modifications to the FDA draft Guidance documents.

- Since its inception, the ITFG/IPAC-RS Collaboration prepared and submitted seven scientific reports to the FDA and members of the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science, attended two meetings with the Agency regarding the findings and recommendations contained in the DCU and BA/BE reports, and made public presentations during the April 2000 meeting of the OINDP Subcommittee and the November 2000 meeting of the Advisory Committee. Copies of the reports submitted by the ITFG/IPAC-RS Collaboration are publicly available through the FDA dockets and are also posted at http://www.ipacrs.com/submissions.html. We respectfully request that the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science consider conclusions, recommendations and proposals presented in these reports.

- We are grateful for the time and attention the Agency has accorded to the consideration of the BA/BE and CMC issues for OINDP and we commend the Office of Pharmaceutical Science for its continuing interest in and support of this process. We are hopeful that through the meetings of the OINDP Subcommittee, Advisory Committee for Pharmaceutical Science, the Product Quality Research Institute (PQRI), and other appropriate fora, the work of the ITFG/IPAC-RS Collaboration will be carefully considered and taken into account by the Agency during its revision of the draft Guidances. If this happens, we believe that both the FDA and the pharmaceutical industry will be better able to respond to the needs of patients by expediting the availability of new OINDP products while maintaining appropriate standards of safety, efficacy and quality.

SUMMARY OF RECOMMENDATIONS

As demonstrated in the following sections, the ITFG/IPAC-RS Collaboration has investigated a number of open CMC and BA/BE issues in the draft Guidances and looks forward to a careful discussion of its findings by the Agency and other appropriate bodies, such as PQRI, the OINDP Subcommittee, and the Advisory Committee for Pharmaceutical Science. The Collaboration is grateful for the Agency's consideration of its work and proposals. We summarize our general positions below.

Regarding the BA/BE draft Guidance:

- Pertinent data should be gathered and evaluated to address the potential risks in the proposal that *in vitro* tests alone would be adequate to demonstrate the bioequivalence of generic nasal solutions for local nasal therapy.

- Further investigation of PSD profile comparison methods should be undertaken in order to identify appropriate means to compare Reference and Test products and to evaluate what test metrics have clinical relevance for nasal and inhaled delivery.

Regarding the CMC draft Guidances:

- The parametric tolerance interval DCU test developed by IPAC-RS in collaboration with ITFG scientists should be considered by the Agency as a replacement for the approach to DCU specifications in the current draft Guidances for OINDP.

- The mass balance specification requirement should be removed from the CMC Guidances for OINDP. If appropriate, additional dialogue on PSD specifications and the utility of mass balance should take place as part of the process of revising the draft Guidances.

- The revised CMC Guidances for OINDP should include a leachables qualification program, including reporting and toxicological qualification thresholds for leachables. Further, the approach to establishing reporting and qualification thresholds and the thresholds proposed by the Collaboration should be evaluated and carefully considered by toxicologists and chemists from the FDA, industry, and other interested parties.

- The revised CMC Guidances for OINDP should include a statement recognizing the value of a cGMP guideline for component suppliers, and acknowledging that if sufficient supplier control mechanisms are in place, appropriate reductions in testing of the finished product will be considered.

- The revised CMC Guidances for OINDP should avoid requiring redundant or irrelevant routine testing of finished products. The Guidances should recognize that most appropriate tests for the quality control of commercial products should be selected based on the product development data.

We believe that through additional work in the identified areas, the draft Guidances for OINDP could be significantly improved, which would offer a win/win/win solution for the Agency, industry and patients.

REVIEW OF ITFG/IPAC-RS WORK AND PROPOSALS

At the 26 April 2000 meeting of the OINDP Subcommittee, the ITFG/IPAC-RS Collaboration presented[3] its concerns regarding a number of CMC and BA/BE issues in the FDA draft Guidances and made a commitment to collect and analyze relevant data in order to contribute constructively to the revision of the draft Guidances. A comprehensive review of the ITFG/IPAC-RS work carried out through November 2000 was presented to the Advisory Committee for Pharmaceutical Science on 15 November 2000.[4] Following is a brief update on the work and progress of the Collaboration since these meetings. Copies of the scientific reports prepared by the ITFG/IPAC-RS Collaboration are posted at http://www.ipacrs.com/submissions.html, and are also available through the FDA dockets for the draft Guidances.

I. IN VITRO AND IN VIVO TESTS FOR BIOEQUIVALENCE STUDIES

1. Key Concerns with Draft BA/BE Guidance

The BA/BE Technical Team of the ITFG/IPAC-RS Collaboration reviewed the draft Guidance for Industry: *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, reviewed and analyzed available literature and data, and has prepared and submitted to the FDA three technical papers.[5] The papers outline the key concerns with the draft BA/BE Guidance and propose possible approaches for the way forward.

2. BA/BE Work to Date

2.a. Dose-Response and Transfer of Indications for Locally Acting Nasal Drug Products

In the paper entitled *Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at 26 April 2000 OINDP Advisory Subcommittee Meeting*, submitted to the Agency in August 2000, the Team addressed the Agency's questions regarding clinical studies for locally acting nasal drugs.[6] Based on the review of published data, the Team arrived at the following conclusions:

- The approach to collection and presentation of data, and selection of primary and secondary endpoints described in the draft *Guidance for Industry Allergic Rhinitis: Clinical Development Programs for Drug Products* (April 2000)[7] may be an appropriate model for differentiating between several doses of Test/Reference product in a 2 week clinical study using endpoint comparisons including onset of action, and mean change from baseline for

patient-rated total nasal symptom score over the entire double-blind period. Replication or substantiation of these results in either an Environmental Exposure Unit or Days-In-The-Park study may be appropriate. The products should be equivalent at all pre-defined timepoints. The standards used to establish statistical equivalence must have been shown to be of some clinical relevance.

- 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. There is a need for the draft BA/BE Guidance to further develop the statistical requirements for this study if it is to be used for equivalence testing and link appropriately to the guidance on Allergic Rhinitis referenced above, without confusing the issues of equivalence and comparability. At present the Team is not aware of an alternative method that can be relied upon to establish equivalent local delivery.

- A pre-existing indication for Perennial Allergic Rhinitis, Perennial Non-allergic Rhinitis 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.

Since the last Advisory Committee meeting, the BA/BE Team has sought additional information to answer the questions posed in connection with dose response studies, *in vivo* study waivers for locally acting nasal products, and test metrics for *in vitro* as well as *in vivo* comparisons. This effort continues to reinforce the earlier findings that the development of robust clinical protocols, the availability of reliable metrics, and the establishment of relevant *in vitro* test platforms are lagging behind present regulatory needs.

Because of this lack of firm information upon which to base sound regulatory policies, the BA/BE Team has analyzed the problem from the standpoint of risk management. The idea is to focus thinking and scientific investigation toward those critical elements whose uncertainty should be given priority as the development of guidances progresses. This analysis has brought forward three risk areas that are present with locally acting nasal sprays in the context of dose response and clinical equivalence:

- primary local effect;
- local side effects; and
- systemic side effects resulting from absorption of a fraction of the locally applied preparation.

While the first two risk areas can possibly be grouped together and dealt with in a single trial, the third must be treated independently. In fact, the types of clinical trials needed to address each risk area may be very different in nature and construction. It cannot, therefore, be presumed that an *in vitro* test that correctly correlates with the local actions will also be predictive of the systemic outcome.

Although the Team agrees that development and validation of an appropriate model for assessing dose-response as a model of *in vivo* equivalence (in terms of local efficacy and local side effects) is an important element in development of equivalence standards for this group of products, the BA/BE Team believes that the highest risk area in the establishment of product equivalence is the systemic absorption component. We suggest that the design of studies to assess systemic availability and equivalence between nasal solutions for local action deserves the highest level of attention.

2.b. Role of In Vivo and Vitro Tests for Bioequivalence Studies

In the 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,* the Team described and supported its two general position statements that (i) *in vitro* testing is essential for pharmaceutical product equivalence and should be included as part of the BA/BE Guidance for all nasal and oral inhalation products, but is not currently sufficient for BE approval without establishing *in vivo* BE; and (ii) 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.

One of the Team's hypotheses expressed in that paper is that:

> *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.*

Following the submission of the paper, the Agency requested that this position be substantiated with additional data. In response to this request, the Team conducted further research to supplement its previous survey of the scientific literature in regard to this position. This investigation is described in the Team's third paper, *On the Risks of Eliminating In Vivo Studies for Nasal Solutions for Local Action,* which was submitted to the Agency in April 2001.

The scope of the survey was expanded to include opinions of international regulators and examples from orally inhaled systems, since many of the underlying concepts, design requirements and performance attributes of drug/device combinations for orally inhaled products parallel closely those demanded of nasal solutions and nasal suspensions. Unfortunately, even after this thorough evaluation of the available literature and information, the Team was unable to identify references that could provide an unequivocal foundation for either the Team's or the Agency's positions in regard to the bioequivalence of nasal solutions.

The Team has found, however, that there is a lack of documentation from well-controlled, replicate trials that demonstrate (i) the correspondence between the proposed *in vitro* tests and *in vivo* measures of safety and efficacy; (ii) the discriminatory capability and reliability of the proposed *in vitro* tests as surrogate markers for clinical safety and efficacy parameters; and (iii) that the *in vitro* tests uniformly apply to all classes of drugs under review, *i.e.,* nasal solutions and suspensions for administration via spray or aerosol for local action.

Furthermore, there is clear evidence of a lack of agreement among regulators, as reflected in the current draft CPMP guidance on bioavailability and bioequivalence. This EU guidance proposal does not differentiate between nasal solutions and nasal suspensions for local use (section 5.1.8 (a) of CPMP/EWP/QWP/1401/98). Moreover, it requires pharmacodynamic or comparative clinical studies for locally acting nasal products. Additionally, there is general acknowledgement among scientific and clinical experts regarding the need for more work before the *in vitro-in vivo* correlations necessary to support waivers of clinical testing for this group of drug/device products can be made.

Because there is not sufficient data to show that *in vitro* testing methodologies are an adequate substitute for *in vivo* studies, the Team believes that the Agency should reconsider the draft Guidance's biowaiver provision for nasal solutions for local delivery. In addition, more specific and relevant data must be generated in order to ensure that the final guidance reflects best practices in regulatory science.

2.c. Development of Risk Management Framework

The BA/BE Team believes that the current lack of definitive information and expert consensus regarding the validity of current *in vitro* testing as a guarantee of *in* vivo outcome is a risk situation, with unknown clinical efficacy or safety consequences, to the users of nasal pharmaceutical products. However, the current draft Guidance does not acknowledge this risk, and does not, therefore, fall within the risk management framework elaborated in the 1999 Report from the Task Force on Risk Management to the Commissioner.[8]

The Team has outlined three possible risk management approaches (*i.e.,* risk avoidance, risk stratification, and risk comparison) that may be incorporated into the Guidance until relevant data on the sufficiency (or insufficiency) of *in vitro* testing to demonstrate bioequivalence of nasal solutions is generated.

The Team is a committed stakeholder in this process and is interested in exploring with the Agency the manner in which the appropriate risk analysis and risk assessment can be brought into the text of the draft Guidance. The Team is interested in collaborating with the Agency to define appropriate measurement systems and reliable test conditions which could be adopted to address the risk factors objectively.

Furthermore, correct methods of numerical analysis and valid comparison metrics should be developed, which will ensure that a uniform state of minimized risk is maintained. In the meantime, the Team strongly recommends that any consumer risk should be avoided by

requiring that all nasal solution, as well as suspension, products meet both the *in vitro* and *in vivo* BE criteria suggested in the draft Guidance.

3. Team's Current Activities

In light of the current lack of data regarding appropriate *in vitro* tests to establish equivalence of nasal solutions, the Team will propose to explore the following hypothesis through PQRI:

> *sole reliance on the in vitro tests outlined in the draft BA/BE Guidance may not be sufficient to establish bioequivalence, including equivalent systemic absorption (for safety purposes) between two Q1/Q2-equivalent nasal solution products which exert their efficacy through local action.*

In parallel, the BA/BE Team will also develop a risk management framework for addressing risks of elimination of *in vivo* studies for nasal solutions.

4. Next Steps Regarding In Vitro and In Vivo Tests in draft BA/BE Guidance

The Team is grateful that the Agency has recognized the value of gathering and evaluating relevant data through PQRI and addressing the risks inherent in FDA's biowaiver provision for nasal solutions for local delivery.

II. DOSE CONTENT UNIFORMITY (DCU) SPECIFICATIONS

1. Overview of Key Concerns with DCU Specifications in FDA Draft Guidances

At the 26 April 2000 meeting of the OINDP Subcommittee, the DCU Working Group committed to examine the suitability of the DCU specifications recommended by the FDA Guidances and to explore alternate approaches to setting DCU specifications that would ensure consistent and uniform dosing for each drug product. As a first step in these investigations, the Working Group committed to collect industry data and to evaluate 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.*

FDA has also acknowledged that the current approach to DCU specifications in the draft CMC Guidances may need to be re-evaluated. At the April meeting, the Agency posed the following questions[6]:

> *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?*

2. DCU Work to Date

In the spring of 2000, the DCU Working Group conducted an industry-wide survey of DCU data. The initial analysis of the collected data was presented in a technical paper submitted to the Agency and the members of the OINDP Subcommittee on 31 July 2000.[9] In the paper, the Working Group concluded that the database indicates that orally inhaled products do not in general comply with the DCU specification in the FDA's draft Guidances and that 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. These findings were reported at the November 2000 meeting of the Advisory Committee for Pharmaceutical Science[4].

Since the fall of 2000, the DCU Working Group has been exploring alternate approaches to DCU specifications and has developed a new DCU test, which is grounded in general statistical considerations, quality standards set by the draft Guidances, and the capabilities of modern inhalation technology. The new test follows the parametric tolerance interval approach propounded by Dr. Walter Hauck. The test also builds upon certain aspects of the approach put forth by the Pharmacopeial Discussion Group of ICH. The main features of the test developed by the Working Group can be summarized as follows:

- The new DCU test is based on a parametric tolerance interval approach, which uses information contained in a sample more efficiently than the DCU tests in the FDA draft Guidances. This increased efficiency allows the test to provide an improved level of consumer protection (in the statistical sense), while at the same time mitigating the producer risk compared to the FDA draft Guidance tests.

- Quality is defined in terms of the proportion of doses in the batch that fall within a specified target interval.
- To ensure the pre-defined batch quality, the new test uses three acceptance criteria: for the sample mean, sample standard deviation, and the so-called acceptance value. These acceptance criteria ensure that the mean dose is close to the label claim, that dose variability is controlled and that the frequency of outliers is limited.
- Control of through-life trends is achieved through a stratified sampling plan that allows simultaneous evaluation of both between-container and through-container-life uniformity of multi-dose products using a single test.
- The test establishes a uniform minimal quality standard regardless of the dosage form (*e.g.,* MDI, DPI, multi-dose, unit-dose, sprays), yet allows the producer to select the testing schedule most appropriate for their product.
- The improvements accomplished by this test are due to the use of a parametric approach (rather than the non-parametric approach of the draft Guidances) and an increased sample size.

3. Current Activities

The IPAC-RS companies and the DCU Working Group under the leadership of prominent industry experts have undertaken an unprecedented effort to develop a test that could replace the DCU tests in the draft CMC Guidances. In this process, the DCU Working Group has consulted with ITFG scientists, academicians and representatives of the Agency.

The Working Group expects to submit a written proposal on the alternative DCU test to the Agency in the fall of 2001. The Working Group believes that the proposed test will benefit the Agency, the industry and patients by establishing a long-term solution to the control of DCU in OINDP, by ensuring consistent quality standards for such products, and by facilitating the development and CMC approval of new orally inhaled and nasal medicines.

4. Next Steps Regarding DCU Specifications

We acknowledge and appreciate the Agency's attention to the critical issue of DCU. We encourage members of the OINDP Subcommittee and Advisory Committee for Pharmaceutical Science to consider our forthcoming DCU proposal for an alternative approach to DCU testing. To facilitate the evaluation of the new test by the Agency and other relevant parties, we encourage a broad scientific discussion of the merits of the proposed test. In this spirit, the IPAC-RS proposes to hold, in coordination with all interested parties, a public workshop on the newly developed test, once the written proposal of the DCU Working Group is submitted to the FDA docket.

III. PARTICLE SIZE DISTRIBUTION (PSD) TESTS AND SPECIFICATIONS

A. PSD CMC Specifications

1. Overview of Key Concerns with PSD in FDA Draft CMC Guidances

The PSD Working Group's key concerns regarding the current draft CMC Guidances for OINDP are related to the requirement that:

the total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per actuation basis.

The PSD Working Group strongly objects to the inclusion of the mass balance specification in the CMC Guidances because:

- As a specification for the finished product, the mass balance specification requirement uses PSD mass balance as a measurement of emitted dose rather than a characteristic of the particle size distribution;
- Control of emitted dose is accomplished through a separate test (dose content uniformity);
- The use of mass balance may be valuable as a control of system suitability, but is not justified as a drug product specification;
- The limits on mass balance used for control of system suitability should be established in validation studies and not arbitrarily set by a CMC Guidance;
- The definition of mass balance should not be based on the label claim (LC) because the label claim is not necessarily defined by the total mass of drug collected on all stages and accessories. For example, LC for DPIs that use pre-metered blisters or capsules can be based on the amount in the blister or capsule rather than the amount emitted by the device. Since capsule/blister residual is not quantitated during particle size determinations, obtaining 100% LC mass balance is not possible; and
- The initial analysis of the industry data has demonstrated that general compliance with the requirement as given in the draft CMC Guidances may not be feasible.

2. Work to Date on PSD issues in CMC Draft Guidances

At the 26 April 2000 meeting of the Subcommittee, the PSD Working Group committed to collect industry PSD data to investigate the suitability of the mass balance requirement. In a paper[10] that was subsequently submitted to the FDA and the members of the OINDP Subcommittee, the Working Group concluded that:

the initial assessment of the database indicates that orally inhaled products do not in general comply with the proposed mass balance requirement in the draft CMC Guidances (85-115% LC) and that the proposed requirement 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 Working Group also used the collected database to carry out an initial investigation of the utility of the requirement in the draft CMC Guidances that 3 to 4 stage groupings be used for PSD specification.

3. Current Activities

The PSD Working Group would like to receive clarification from the Agency on the intention of the mass balance requirement and to explore alternate ways to address the Agency's concerns. The Working Group has prepared a proposal for PQRI to investigate this issue and to make a data-based recommendation for the CMC Guidances.

4. Next Steps Regarding PSD CMC Specifications

We respectfully request that the OINDP Subcommittee and the Advisory Committee consider the PSD Working Group's previous submission[10] in support of the recommendation that the mass balance specification requirement be removed from the CMC Guidances. If appropriate, additional dialogue on PSD specifications and the utility of mass balance should take place, possibly through PQRI.

B. PSD as In Vitro Test for Bioequivalence Studies

1. Key Concerns with PSD in Draft BA/BE Guidance

The draft BA/BE Guidance recommends that in order to establish bioequivalence, the Test and Reference products have to demonstrate equivalent PSD profiles. The method for profile comparisons recommended by the draft BA/BE Guidance is based on chi-square differences. However, this method has a number of limitations, as reflected in the Agency's question to the OINDP Subcommittee in April 2000 regarding the appropriateness of the chi-square comparative approach.[6]

Some of the limitations of the chi-square method are the following:

- In the chi-square method recommended by the draft BA/BE Guidance, cascade impactor or multistage liquid impinger data is used to calculate chi-square differences between Test and Reference profiles. The use of alternate methods of particle sizing is precluded by this approach.

- A decision regarding equivalence or inequivalence of profiles is made based on the comparison of chi-square ratios to a pre-defined critical equivalence limit. The selection of this equivalence limit at present is arbitrary.

2. Work to Date on PSD Issues in BA/BE Draft Guidance

Using industry data, the PSD Working Group carried out an initial investigation of alternate analytical techniques, such as that based on bootstrapping, that may improve the discriminating ability of profile comparisons, and provide consistency in the approach used for various products and measuring devices. The Working Group also believes that methods using different metrics, or weighting factors, should be investigated, as they may better reflect the clinical relevance of different portions of the particle size profile when making a decision regarding bioequivalence of two products.

3. Current Activities

The PSD Working Group prepared a proposal for investigating through PQRI the following hypothesis:

A method for comparing particle size distributions of the Test and Reference product may be developed such that it does not depend on particular product type or particle sizing equipment, and may include metrics that relate to clinical relevance of various particle sizes.

4. Next Steps Regarding PSD BE Issues

The PSD Working Group recommends that further investigation of the profile comparison methods be undertaken in order to identify appropriate means to compare Reference and Test products and to evaluate what test metrics have clinical relevance.

IV. LEACHABLES AND EXTRACTABLES TESTING

1. Overview of Key Concerns with Leachables and Extractables in CMC Draft Guidance

At the April 2000 OINDP Subcommittee meeting and at the November 2000 meeting of the Advisory Committee for Pharmaceutical Science, the Leachables and Extractables Team committed to preparing a data-based technical report and recommendations on leachables and extractables. In March 2001, the Team submitted its paper entitled *Leachables and Extractables Testing: Points to Consider*[11] to the Agency and the members of the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science. In this technical paper, the Team identified several areas of the draft CMC Guidances regarding leachables and extractables that could benefit from clarification or further development, and made recommendations regarding these areas.

2. Leachables and Extractables Team Work to Date

To address key areas of concern in the draft CMC Guidances, the Team conducted industry-wide surveys of current practices utilized by pharmaceutical companies as well as suppliers of components for finished drug products. The Team also collected leachables and extractables data and conducted literature reviews, where appropriate. In its work, the Team drew on the collected data and the expertise of leading analytical chemists, product development scientists and toxicologists. The recommendations contained in the *Points to Consider* paper are based upon relevant data and best industry practices. In particular, the Team recommended that the CMC Guidances should:

- state that toxicological qualification be performed only on leachables.
- include reporting and qualification thresholds for leachables. These thresholds should be based on relevant data and best industry practices. *Points to Consider* recommends that toxicological evaluation should only be performed on those leachables that exist above a data-supported threshold. The paper proposes a reporting threshold of 0.2 μg/day and a qualification threshold of 5 μg/day, and provides support and justification for these thresholds.[12]
- provide a definition of *correlation*. The Team suggests that a *correlation* is established when each leachable in the drug product can be assigned <u>qualitatively</u>, directly or indirectly, to an extractable.
- clarify which *critical components* should be tested in control extraction studies. The Team recommends that *critical components* include only those device components that are in contact with the formulation or the patient's mouth or nasal mucosa.

- include a description of the toxicological evaluation process. The Team proposes a complete toxicological evaluation process (including reporting and qualification thresholds for leachables) in *Points to Consider*.

- clarify the process for extractables and leachables testing. The Team offers alternate language and flowcharts, for possible inclusion in the draft CMC Guidances, that provide clarification of this process.

3. Current Activities

The Team will submit to PQRI a proposal to investigate the Team's recommendations, and in particular the development of reporting and qualification thresholds for leachables.

4. Next Steps Regarding Leachables and Extractables

The Leachables and Extractables Team recommends that the Guidances for OINDP incorporate a leachables qualification program, including reporting and toxicological qualification thresholds for leachables. Further, the Team strongly recommends that the approach to establishing reporting and qualification thresholds, and the thresholds proposed by the ITFG/IPAC-RS Collaboration be evaluated and carefully considered by toxicologists and chemists from the FDA, industry, and academia. The Team looks forward to such considerations through the PQRI process.

V. SUPPLIER QUALITY CONTROL

1. Overview of Key Concerns with Supplier Quality Control in CMC Draft Guidance

The current draft CMC Guidance documents in several instances require excessive testing of the finished product in an attempt to control changes in the supply chain. The Supplier Quality Control Team of the ITFG/IPAC-RS Collaboration believes that the appropriate way to control quality of incoming components is through a comprehensive system of supplier quality control.

2. Work to Date on Supplier Quality Control

As reported at the April 2000 meeting of the OINDP Subcommittee and the November 2000 Advisory Committee meeting, the Supplier Quality Control Team, which includes representatives of pharmaceutical as well as supplier companies, conducted a survey of current cGMP practices among the suppliers of pharmaceutical device components. The survey identified existing practices that could be used as a standard for the supplier industry and areas that would benefit from the development of comprehensive cGMP guidelines.

3. Current Activities

The Team is exploring the feasibility of an industry-wide initiative to undertake the development of a cGMP guideline for suppliers of pharmaceutical device components.

4. Next Steps Regarding Supplier Quality Control

The Team encourages the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science to recommend that the Agency consider inserting into the revised 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.

VI. TESTS AND METHODS FOR CONTROL OF PRODUCT QUALITY

1. Overview of Key Concerns with Tests and Methods in CMC Draft Guidance

The draft CMC Guidances require a large number of tests on the finished drug product, some of which are redundant or add little value to the assurance of product quality. The Tests and Methods Technical Team of the ITFG/IPAC-RS Collaboration outlined its concerns at the April 2000 OINDP Subcommittee meeting and the November 2000 meeting of the Advisory Committee for Pharmaceutical Science.[3,4]

2. Tests and Methods Team Work To Date

In 2000, the Team committed to collect industry data on key tests recommended by the draft CMC Guidances and to prepare and submit a technical report to the FDA containing the Team's findings and recommendations. In May 2001, the Team completed its work on the MDI tests of greatest concern to the Team and submitted a paper entitled *Recommendations for Tests and Methods*[13] to the Agency. The paper focused on the following tests: water content, shot weight, plume geometry, pressure, spray pattern, particle size distribution, dose content uniformity, and impurities and degradants. The paper provided a critical assessment of the value that these individual tests add to the development and control of a new product.

In general, the Team recommended that a fixed list of control tests may not be appropriate for all products. Furthermore, the Team proposed that the draft CMC MDI/DPI Guidance:

- should support the concept of characterizing a new product in development and applying that information to select appropriate control tests for the commercial product; and
- should eliminate redundant control tests which do not add meaningful information about product quality.

Through scientific evaluation of industry and literature data, the Team made specific assessments regarding the relative value and usefulness of the investigated tests. For example:

- **Some tests provide little or no value in the development phase or as tests for control of product quality,** *e.g.,* spray pattern, plume geometry, pressure (propellant/co-solvent formulations only).
- **Some tests are useful for product characterization during the development phase, but for certain products may be irrelevant for control of product quality,** *e.g.,* water content, control of relative humidity and temperature on particle size distribution.
- **Some tests may be useful for control of product quality**: water content (if development studies demonstrate product sensitivity to moisture); shot

weight (only to verify quality of incoming components, and as a diagnostic tool).

The Team is therefore assessing tests in such a way that they are able to offer recommendations on *how* to select tests needed to characterize a new product and to control a finished manufactured product. The overall goal is to maximize the value of characterization and control testing, and minimize redundant testing and testing that does not provide meaningful information about product quality.

3. Current Activities

The Team is considering development of proposals that could be submitted to PQRI based on the concepts and the findings in *Recommendations for Tests and Methods.*

4. Next Steps Regarding Tests and Methods

The Team encourages the Agency, the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science to consider the conclusions in *Recommendations for Tests and Methods.* This paper confirms the Team's belief that the revised CMC Guidance should reflect the concept that appropriate control tests for the commercial product should be selected based on the product development data. The Team is hopeful that its findings will assist the Agency in eliminating redundant or unnecessary testing recommendations in the draft CMC Guidance documents.

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 Guidance documents in facilitating the development and approval of new products. We are encouraged by the Agency's effort to address open CMC and BA/BE issues in developing the Guidances for nasal and orally inhaled medications.

We agree that development and validation of an appropriate dose-response model of in vivo equivalence (in terms of local efficacy and local side effects) is an important element in development of equivalence standards for this group of products but note that in order to manage the potential risk for systemic side effects, there is also a need to establish clear protocols for assessing equivalence of systemic absorption. We commend the Agency on ensuring that pertinent data are evaluated to address the potential risks associated with selecting particular *in vitro* and *in vivo* models to demonstrate the bioequivalence of nasal solutions and suspensions for local nasal therapy.

We hope that the Agency continues to work toward resolving all of these important CMC and BA/BE regulatory science issues by utilizing existing avenues for interactive, scientific dialogues, including, as appropriate, the OINDP Subcommittee, the Advisory Committee for Pharmaceutical Science, PQRI, an FDA/USP/AAPS workshop on OINDP regulatory issues, or meetings with representatives of the ITFG and IPAC-RS. Further discussion will ensure that the OINDP Guidances bring maximum value to regulators and industry, and most of all, to patients and physicians.

We appreciate the opportunity to submit this statement to the Agency and the members of the OINDP Subcommittee and 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 on these important documents based on all currently available scientific evidence.

NOTES

[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.*
These draft Guidances are available at http://www.fda.gov/cder/guidance/index.htm.

[2] The IPAC-RS member companies include: Aradigm, AstraZeneca, Aventis, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Inhale Therapeutics Systems, IVAX, Kos Pharmaceuticals, Pfizer, and Schering-Plough. ITFG scientists from the following companies and institutions have contributed to the work of the ITFG/IPAC-RS Collaboration: Bespak, BI Roxane, Dura Pharmaceuticals, Inspire Pharmaceuticals, Lovelace Respiratory Institute, Magellan Laboratories, Microdrug Development, Pfeiffer, Presspart, Primedica, Sciarra Laboratories, RWJ-PRI, Trudell Medical, University of Rhode Island, Valois, 3M Pharmaceuticals.

[3] ITFG/IPAC-RS presentations to the OINDP Subcommittee on 26 April 2000 are available at http://www.fda.gov/ohrms/dockets/ac/00/slides/3609s1.htm.

[4] The ITFG/IPAC-RS presentation to the Advisory Committee for Pharmaceutical Science on 15 November 2000 is available at http://www.fda.gov/ohrms/dockets/ac/00/slides/3657s1.htm.

[5] 1) *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* (August 2000),
2) *Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at 26 April 2000 OINDP Advisory Subcommittee Meeting* (August 2000), and
3) *On the Risks of Eliminating In Vivo Studies for Nasal Solutions for Local Action* (April 2001).
These papers are available at http://www.ipacrs.com/bio.html.

[6] The list of questions presented to the OINDP Subcommittee on 26 April 2000 is available at http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3609q1.pdf

[7] Draft Guidance for Industry *Allergic Rhinitis: Clinical Development Programs for Drug Products* (April 2000), available at http://www.fda.gov/cder/guidance/2718dft.pdf

[8] *Managing the Risks from Medical Product Use: Creating a Risk Management Framework.* Report to the FDA Commissioner From the Task Force on Risk Management. (U.S. Department of Health and Human Services, FDA, May 1999).
http://www.fda.gov/oc/tfrm/riskmanagement.html.

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[9] *Initial Assessment of the ITFG/IPAC Dose Content Uniformity Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration* (July 2000), available at http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_reports.htm.

[10] *Initial Assessment of the ITFG/IPAC Aerodynamic Particle Size Distribution Database* (August 2000) available at http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_reports.htm.

[11] *Leachables and Extractables Testing: Points to Consider* (March 2001) available at http://www.fda.gov/ohrms/dockets/ac/00/reports/3657_reports.htm.

[12] Note that for certain classes of potential leachable compounds with special toxicological concerns [*i.e.,* nitrosamines, polynuclear aromatics (PNAs), mercaptobenzthiazole, *etc.*] much lower reporting thresholds, and appropriate qualifications and risk assessments may be required.

[13] *Recommendations for Tests and Methods*and *Appendices* (May 2001) are available at http://www.ipacrs.com/tests.html.