IPAC-RS

COMMENTS

on a Note for Guidance on
Requirements for Pharmaceutical Documentation for
Pressurised Metered Dose Inhalation Products
(CPMP/QWP/2845/00) version released for consultation Nov. 2000

Submitted by
The International Pharmaceutical Aerosol Consortium
on Regulation and Science (IPAC-RS)

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I. EXECUTIVE SUMMARY

- The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) issued a draft Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurised Metered Dose Inhalation Products (CPMP / QWP / 2845 / 00) on 16 November 2000 for consultation.

- The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), an association of companies with expertise in metered dose inhalation product design and manufacture, reviewed the draft Note for Guidance and herein provides suggestions for its further refinement.

- In general, IPAC-RS agrees with the content of the draft Note for Guidance and recognizes its contribution to improving public health. These comments highlight instances where the draft Note for Guidance could be clarified and improved, and make recommendations for revised language, especially in those parts of the Guidance which deal with Development Pharmaceutics, the Method of Preparation, and the Control of the Finished Product.

- IPAC-RS looks forward to the final Note for Guidance, and hopes that its suggestions can be incorporated therein.

II. INTRODUCTION

IPAC-RS is an association of companies that develop, manufacture or market orally inhaled and nasal drug products for local and systemic treatment of asthma, chronic obstructive pulmonary disease, rhinitis, migraine, diabetes and other debilitating diseases. The members of IPAC-RS include: Aradigm, Armstrong Pharmaceuticals, AstraZeneca, Aventis, Boehringer Ingelheim, GlaxoSmithKline, Inhale, IVAX, KOS, Eli Lilly, Pfizer, and Schering-Plough. The members of IPAC-RS are committed to improving public health by facilitating the availability of safe, effective and quality inhaled and intranasal drug products.

Patients rely on inhalation drug products for the safe and effective treatment of diseases. The pharmaceutical industry and the EMEA share a common goal – to respond to the needs of patients for these medications by expediting the availability of new products to market while maintaining appropriate standards of safety, efficacy and quality. IPAC-RS strives to contribute constructively to the development of scientifically driven standards and regulations for inhaled and intranasal drug products.

IPAC-RS commends the CPMP and the Quality Working Party on the development of this draft Note for Guidance and its overall approach. We recognize the value of having this guidance as an aid to facilitate the development and approval of new inhalation medications. IPAC-RS also appreciates the opportunity to provide input on the draft Note for Guidance to assist the CPMP in producing a final version that will provide sponsors with a thorough, yet flexible approach to the development and registration of these important dosage forms.

We hope that through our comments we may assist the EMEA in developing a final Note for Guidance that will clarify for industry the aspects of pharmaceutical performance and quality that the EMEA considers important to control and, consequently, assist developers in understanding more clearly the EMEA's expectations. Such a Note for Guidance will enable industry to avoid unnecessary drug development delays and will better serve patients by facilitating the prompt approval of safe and effective new inhalation drug therapies.

III. THE GUIDANCE SHOULD NOT BE RETROACTIVE

IPAC-RS fully supports the development of this draft Note for Guidance. In general, we find that the draft Note for Guidance is comprehensive and, in most areas, describes appropriate procedures for drug product development and quality control. However, it is important that any new guidance not be applied retroactively to existing products or those nearing approval. Sponsors of products that have been approved since the 1993 CFC replacement guidance, or are nearing approval in the near future, have relied on that Guidance in their development. For these reasons, we agree with the draft Note for Guidance that "all new products should be labelled with the delivered dose," however we consider the retrospective application of the draft Note for Guidance to "existing products" inappropriate.

In particular, we are concerned that any change in the expression of dosage – from metered to delivered – for existing products will result in inconsistency and consumer and / or physician confusion. We would recommend therefore that the final sentence of Section 2 be rewritten as follows (proposed new language in bold):

> In order that consistency is achieved in the future, all new products should be labelled with the delivered dose ~~but for existing products current practice in each member State should be followed~~. **The only new products to be labelled with the metered dose will be those resulting from the reformulation (CFC transition) or the redevelopment of an existing product (*e.g.*, introduction of breath-operation or combination of existing single products) labelled with the metered dose.**

IV. REFINEMENT OF THE GUIDANCE ON *PT IIA COMPOSITION OF THE MEDICAL PRODUCT/ DEVELOPMENT PHARMACEUTICS*

We propose that it is adequate to perform one-time development studies on a single batch in most cases where a product characteristic such as priming, rather than a batch-dependent characteristic, is under evaluation. Furthermore, we would also propose that additional guidance be given, such that where multiple strengths or pack sizes are under development, performance can be assessed using a bracketing approach, as long as it can be demonstrated that no strength or pack-size related effects are apparent.

A. *Moisture content* (Section 3.1)

We agree with the principle expressed in Section 3.1 that moisture content should be investigated and that a specification should only be included for products that have demonstrated sensitivity to moisture. We recommend the following wording for clarity (proposed new language in bold):

> The effect of moisture content on product performance during stability should be ~~investigated and if necessary controlled because of the possible effect on stability~~ **evaluated. A specification would only be required for those products that have demonstrated sensitivity to moisture.**

B. *Delivered dose* (Section 3.2)

The draft Note for Guidance states that the uniformity of the delivered dose has to be evaluated by "the test described in the European Pharmacopoeia." This wording leaves it unclear whether this applies to the European Pharmacopoeia protocol or apparatus, or both. The European Pharmacopoeia protocol is not intended as a protocol which can be used by manufacturers to release product. The draft Note for Guidance would be clearer if it stated explicitly that the protocol for release testing, although based on the European Pharmacopoeia protocol, would be appropriate for a drug product. Therefore, we would propose that the first paragraph of this section be reworded to say (proposed new language in bold):

> The uniformity of the delivered dose ~~has to be evaluated by the test described in~~ **should be evaluated for compliance with the requirements of** the European Pharmacopoeia. In addition, the average value obtained should be within ±15% of the labelled dose if the labelled strength of the product is expressed as delivered dose (ex actuator).

Moreover, the draft Note for Guidance is inconsistent in that it directs testing in accordance with the European Pharmacopoeia (in the first paragraph of Section 3.2) – which requires testing at the beginning, middle, and end of the labelled claim per container – while also requiring testing at the beginning and end of the labelled claim per container (in the third paragraph of Section 3.2). We believe that, for quality control, it is appropriate to perform the latter testing on the appropriate number of containers.

Also, the statement "retention in the mouthpiece should be addressed" is ambiguous. The use of "evaluated" rather than "addressed" would be more appropriate. Therefore, we suggest that the last two sentences of the first paragraph in Section 3.2 be replaced with (proposed new language in bold):

> For products labelled with the metered dose, limits are derived ~~taking into account~~ **by evaluating** the retention in the mouthpiece and consequently wider limits are accepted. ~~Retention in the mouthpiece should be addressed and in line with the delivered dose.~~

Furthermore, we recommend that "intensively validated" in the last sentence of the second paragraph of Section 3.2 should be replaced by "validated." By definition, validation provides evidence in accordance with the principles of Good Manufacturing Practices (GMP) that the process leads to the expected (required) results. Thus, the addition of "intensively" is superfluous. Accordingly, the sentence would read:

> The production process should be ~~intensively~~ validated regarding these parameters, in connection with the uniformity of the delivered dose.

Clarification is also required on the meaning of "at least three canisters of different batches," *i.e.*, whether three canisters from each batch or one canister from each of three batches are tested.

C. *Fine particle dose* (Section 3.3)

It is reasonable that the test for aerodynamic particle size is performed on the minimum number of actuations required to achieve appropriate analytical sensitivity. Additionally, defining the number of actuations required to obtain a meaningful result should be commensurate with delivered dose consistency in order to define throughout batch or between batch differences. Hence the qualification "but should not normally exceed the number recommended as one dose" in the second paragraph of Section 3.3 is unnecessary. Instead, we recommend adding the following (proposed new language in bold):

> The number of ~~actuations~~ **doses** used ~~in this test~~ **for determination of the particle size distribution** should be ~~the minimum required to achieve appropriate analytical method sensitivity~~ **as minimal and as close to the**

> **patient dose as possible,** ~~but should not normally exceed the number recommended as one dose~~ **taking analytical sensitivity and delivered dose uniformity into consideration.**

For clarity, we recommend that the first two sentences of the fifth paragraph in Section 3.3 be rewritten as follows (proposed new language in bold):

> From ~~the data derived from the batches~~ **a combination of batch release and stability data and data for batches** used clinically, it is necessary to define a lower and an upper limit for the fine particle dose (FPD) ~~for release purposes~~ **to be applied in the release and end-of-life specifications**. ~~This~~ **The release** specification must be maintained throughout the life of the product unless an alternative shelf-life specification ~~has been validated clinically~~ **is supported by a review of all available stability data, which may include clinical batches. In line with ICH guidelines, this should be based on long term 25°C/60%RH data.**

Furthermore, we suggest that data from additional batches, *e.g.*, initial data from stability and production batches (where available), should also be included for the purposes of setting a specification, in order to introduce normal variability. Variability of FPD will be greater than that of dose, therefore wider specification limits than for dose should be applied.

We support the process by which an appropriate FPD specification is established based on clinical safety and efficacy experience, but additionally we would suggest the inclusion of wording with regard to consideration of normal batch manufacture and stability data in line with International Conference on Harmonization (ICH) guideline Q6A.

If a single stage impactor is used as currently allowed by the European Pharmacopoeia, it is not clear how the FPD, as defined by the European Pharmacopoeia, can be calculated. Clarity is requested on this guidance regarding the use of single stage impactors.

Perhaps most importantly (with respect to this section), FPD is a specific term used in the European Pharmacopoeia to define the mass of drug in an emitted dose less than 5 μm. Further guidance is needed with respect to single stage impactors, where this specification is unworkable. We would propose that a flexible approach be adopted such that, as an alternative, the fine particle mass be defined as the mass of drug in the emitted dose.

The reference to clinical validation of shelf-life specification should be changed to "justified," so as to ensure that consumers' access to new medications is not delayed while sponsors conduct stability studies.

Also, reference is made to stability data to ensure confidence that the FPD is consistent "through the volume of the container over the shelf-life of the product." We would propose

that this be reworded to offer more flexibility in the approach to such determinations (proposed new language in bold):

> In determining routine compliance with this specification it will only be necessary to evaluate data from the beginning of the nominal content of the containers tested providing that sufficient data have been generated ~~in~~ **during product** development ~~and on stability~~ to give confidence in the ~~FPD~~ **performance** of the product**, including aged product,** through the volume of the container ~~over the shelf life of the product~~.

Finally, we recommend that the wording of this section be standardized so that "impinger/impactor" is used consistently.

D. *Priming* (Section 3.4)

Clarification is again required on the meaning of "at least three canisters of different batches," *i.e.*, whether three canisters from each batch or one canister from each of three different batches are tested. We see priming as a product characteristic and not as a batch characteristic.

E. *Extractables* (Section 3.5)

We agree that the toxicological implications of extractables should be considered. However, cross-referencing to discussion of the toxicological implications in Part III may be more appropriate, with only a summary of relevant points presented in Part IIA. To the extent this discussion remains, we suggest that the terminology be revised. We also recommend that a definition of extractables and leachables be included in the Note for Guidance, and that the title of this section be changed accordingly. Therefore, we propose the following language for the beginning of Section 3.5 (proposed new language in bold):

> **3.5 ~~Extractables~~Leachables**
>
> **Extractables are compounds that can be extracted by solvents, and leachables are compounds that leach as a result of contact with the formulation.**

Also, the draft Note for Guidance would be improved by allowing monitoring up to the point of equilibrium, or alternatively, to the end of the proposed shelf-life of the product.

F. *Use of spacers* (Section 3.6)

We strongly support that comparative in-vitro data for the fine particle dose should be generated on the pMDI, with and without spacer, and this will suffice to demonstrate the physical compatibility of the spacer and the pMDI. The spacer is not an integral part of a medicinal product, and its properties, including the effect of cleaning, are better described in a technical documentation for a CE mark. However, if the cleaning procedure for the spacer and the Metered Dose Inhaler (MDI) are to be addressed in this Note for Guidance, consideration should be given to replacing this paragraph with a separate section, *i.e., 3.9 Cleaning Procedures.*

G. *Breath actuated devices* (Section 3.7)

The draft Note for Guidance requires data to demonstrate that all target patient groups are capable of triggering the breath actuated device. We believe this is best evaluated as part of the clinical program, during patient handling studies.

H. *In-use performance (Section 3.8)*

This section seems to contemplate assessment by equilibrating the product at the relevant conditions and then testing immediately. However, the verbiage should distinguish between temperature related testing of inhaler performance and stability storage, as follows (proposed new language in bold):

> The effect of low and high temperatures on the ~~valve~~ performance **of the inhaler** ~~and on the fine particle dose (FPD)~~ should be assessed.

Also, more guidance is required to clarify what is meant by "simulated conditions," particularly with respect to low and high temperatures.

V. REFINEMENT OF THE GUIDANCE ON *PT IIB METHOD OF PREPARATION*

The draft Note for Guidance asserts that manufacture of MDIs is considered to be a non-standard method of manufacture, and thus the data requirements for a Marketing Authorization Application are increased. We would contend that, while the products are complex, the methods of manufacture are no longer considered to be non-standard within the pharmaceutical industry. The technology for manufacturing is well developed. For example, similar product manufacturing processes are used by both innovators and generics. Hence, we recommend that the first paragraph of this section be reworded as follows (proposed new language in bold):

> Manufacture of pMDIs is considered to be ~~a non-~~standard method of manufacture (see CPMP Note for Guidance on Process Validation). Data demonstrating the validity of the process should be **collected, but need not be** submitted in the marketing authorisation dossier. Data should be ~~provided on three consecutive batches at production scale prior to approval. However, data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches and by a history of consistent manufacture of products by an essentially equivalent process.~~ **collected to demonstrate the robustness of the process at pilot scale and to justify the range of batch sizes proposed for routine manufacture.** ~~In the latter case, post-approval, additional process validation should be generated on 3 production batches~~.

VI. REFINEMENT OF THE GUIDANCE ON *PT IIC 1/2 CONTROL OF STARTING MATERIALS*

With respect to the justification for a suitable particle size specification developed for the active ingredient, clinical batches provide only a limited data set on which to base the specification. We suggest that the particle size specification for the active ingredient should be based on the range that has been demonstrated to lead to finished product that is within specification. Therefore, the sentence would read (proposed new language in bold):

> For suspension formulations, a suitable multipoint particle size specification should be developed for the active ingredient justified by reference to**, but not exclusively,** batches used clinically. **Justification can also be found, for instance, in the range that has been demonstrated to lead to finished product that is within specification.**

We also note that the International Pharmaceutical Aerosol Consortia for Toxicity Testing of propellants HFA 134a and HFA 227 are filing separate comments on this section of the draft Note for Guidance.

VII. REFINEMENT OF THE GUIDANCE ON *PT IIC 3 CONTROL OF PACKING MATERIALS*

The draft Note for Guidance requires provision of details on "dimensions, dimensional tolerances and materials of construction." However, in order to eliminate the inclusion of superfluous detail, we recommend that the draft Note for Guidance is amended to require only dimensions of the critical component that may influence the performance or manufacture of the product. The revised language would be (proposed new language in bold):

> The specification for each component of the inhaler should be presented to include ~~details of dimensions, dimensional tolerances and materials of construction~~ **dimensions of the critical component that may influence the performance or manufacture of the product**.

Also, we do not agree with the need for data to show compliance as this is a GMP issue. It is more appropriate to confirm the compliance of the components used during clinical and stability evaluations of the product with the component specifications.

However, we agree that control of leachables in the drug product is more appropriate by control of extractables at the component or bulk material level rather than at the product level, and that the correlation between component (extractables) and product levels (leachables) should be evaluated during development. If levels of leachables are below that which would give rise to any safety concern, we propose such testing may be eliminated altogether.

Finally, appearance testing should be sufficient to demonstrate the integrity of internal coatings. Accordingly, the last paragraph of this part of the draft Note for Guidance, addressing *"PT IIC 3 CONTROL OF PACKING MATERIALS,"* should be reworded as follows (proposed new language in bold):

> If the aerosol canisters have an internal coating, specifications for this should be given. The integrity of the inner surface should be ~~demonstrated in stability testing protocols~~ **confirmed by appearance testing during product development**.

VIII. REFINEMENT OF THE GUIDANCE ON *PT II E CONTROL TESTS ON THE FINISHED PRODUCT*

We suggest that the requirements for the finished product specification be clearly defined where a specific need arises. For instance, the use of "Ph.Eur." in parentheses after selected tests should clearly indicate whether the test is merely included in the Ph.Eur. or the test should be applied as defined in the Ph.Eur., including the application of the acceptance criteria.

All tests should be listed avoiding the use of *"etc.,"* thereby qualifying the needs of certain tests, particularly with regard to assay. We believe that the appropriate assay tests for MDIs are delivered dose and FPD. These tests are individually listed. However, the assay of the drug per canister may be appropriate for a solution aerosol where the delivered dose is controlled by shot weight, but is not an absolute requirement for the specification where adequate in-process control on drug per can is applied and the delivered dose is controlled in the specification. Similarly, a specification for related impurities should be defined where there is evidence of degradation, but may be omitted where justified on the grounds of product stability.

We do not believe that the test of "Number of deliveries per inhaler" provides any additional information over that provided by the Uniformity of Delivered Dose test. Therefore, we suggest eliminating this test, since the test measures the last dose. Also, the test for foreign particulate matter has been described in national pharmacopoeia only. IPAC-RS is not aware of investigations which show that this test describes a batch characteristic. Therefore, this test should be eliminated from this section, as it is more appropriately considered a development pharmaceutics issue.

We consider that some wording from ICH Q6A (CPMP/ICH/367/96) would provide clarification regarding the justification of the specifications. The third paragraph of this section of the draft Note for Guidance refers only to justification of limits at end of shelf-life, which differ from those applied at release. Also, periodic testing is permitted, providing adequate justification is given. However, the draft Note for Guidance only refers to three particular tests (particulate matter, leak rate, and microbial purity) and not other tests, for example, related impurities. We recommend that the draft Note for Guidance be amended to be more generic in this regard. Given that the draft Note for Guidance elsewhere refers to alternative FPD testing, elaboration should be given here on the data to be presented to justify the use of any alternative methodology. We also note that testing for foreign particulates should be performed during development and validation, but not at release.

Therefore, we propose the following revised wording for Section 7 (proposed new language in bold):

The quality characteristics to be controlled in the Finished Product Specification should be chosen to control the quality of the drug product on a routine basis rather than to establish full characterization, and should focus on those characteristics important in ensuring the safety and efficacy of the drug product. Similar performance specifications will be required for both solution and suspension formulations.

In addition to the normal quality characteristics **of appearance and identity** ~~to be controlled~~ in the Finished Product ~~tests e.g. identity, assay, related substances, etc.,~~ Specification, the following **tests** should be included:

7.1. Moisture Content (if relevant)

7.2. Delivered Dose and Uniformity of Delivered Dose ~~(Ph.Eur.)~~ **(if tested, the product should comply with the Ph.Eur. requirements for uniformity of delivered dose and number of deliveries per inhaler)**

7.3 Fine Particle Dose ~~(Ph.Eur.)~~

~~7.4 (Foreign) Particulate Matter~~

~~7.5~~ **7.4** Leak Rate

~~7.6~~ **7.5** ~~Number of deliveries per inhaler (Ph.Eur.)~~ **Related substances (if relevant)**

~~7.7~~ **7.6** Microbial purity ~~(Ph.Eur.)~~

The tests and limits included in the Finished Product Specification should be justified with appropriate reference to relevant development data, pharmacopoeia standards, data for batches used in clinical studies and data from production batches (where available). Parameters more appropriately controlled outside of the specification, such as the in-process control of canister fill weight, should also be justified. Additionally, a reasonable range of expected analytical and manufacturing variability should be considered by examination of batch analysis data.

Where a separate shelf life specification limit is requested for any parameter, this should be clearly stated and justification provided. **For the critical product performance parameter – fine particle dose – the proposed release and end of life limits should be supported by data for batches used in clinical studies, and results from long term stability studies and, as appropriate, accelerated stability studies.**

Periodic testing for ~~particulate matter,~~ **specific tests may be considered where sufficient data are presented to demonstrate that the batches would meet the requirements for these tests if tested, for example,** leak

rate, ~~and~~ microbial quality**, and related substances** ~~may be considered if adequate justification is provided~~.

IX. REFINEMENT OF THE GUIDANCE ON *PT II F* STABILITY

We propose that bracketing and matrixing should be encouraged for stability studies with inhalation products. There is no significant difference between these dosage forms and others for which the industry and authorities routinely accept such approaches.

The test conditions required to evaluate product performance under typical storage conditions encountered during product distribution and patient use are provided by ICH guidance. The proposed requirement to carry out cycling stability studies for 6 months is not an ICH requirement. It is unlikely that a product used twice daily will need to be studied for a period far exceeding normal use. Thus, cycling studies performed out to 6 weeks, rather than 6 months, would be more appropriate. The concordant revised language would read (proposed new language in bold):

> In addition to standard testing conditions, temperature cycling should also be performed for a minimum period of six ~~months~~ **weeks**.

For temperature cycling, the important factor is the number of cycles, not the total time. In any case, we would recommend that additional guidance be included on appropriate temperature cycling conditions (*e.g.*, 5-40°C, 12 hours), including periodicity. In addition, we recommend that the draft Note for Guidance should state that cycling data on a minimum of 1 batch per product strength should be sufficient.

The parameters examined in the fourth paragraph of this section should be the specification tests listed in Part IIE, with the exception of those that are not relevant to stability. Additionally, we recommend the inclusion of guidance that, where there is no change in a parameter on storage, only limited frequency of testing is required. We therefore recommend that the wording be amended to this effect (proposed new language in bold):

> ~~Besides the normally parameters eg. assay, related substances, microbiological purity etc., the~~ **The** parameters ~~described in Section II E of this Note for Guidance~~ **investigated during the stability trials** should ~~be included in the stability trials~~ **include the specification tests described in Part IIE of this Note for Guidance, with the exception of identity. Additionally, where there is no change in a parameter on storage, only limited frequency of testing is required.**

Finally, it is not clear why stability studies out of the overwrap should be performed through to container exhaustion. Such testing should instead be to label claim, not to container exhaustion.

X. REFINEMENT OF THE GUIDANCE ON *SUMMARY OF PRODUCT CHARACTERISTICS*

The statement about clinical justification of use of a spacer, under *Posology and method of administration*, should be clarified to be in line with statements in Section 3.6 *Use of spacers* of this draft Note for Guidance, referring to *PT IIA DEVELOPMENT PHARMACEUTICS*.

Also, in the December 1999 Guideline on Summary of Product Characteristics, it is stated under Section 6.6 that, "Only information necessary for the pharmacist or other health personnel to prepare the product for administration to the patient should be included here. Instructions on handling of the product by the doctor, other health personnel, or patient should be included in Section 4.2 *Posology and Method of Administration.*" This section of the draft Note for Guidance should be in accordance. The instructions for use should also cover disposal of the product, *e.g.*, instruction not to incinerate.

The discussion of cleaning instructions in the Note for Guidance should be amended to also refer to the frequency of cleaning, as follows (proposed new language in bold):

> If applicable, a detailed description of the cleaning instructions **and cleaning frequency** for the spacer and / or MDI has to be given.

If the spacer is not an integral part of a medicinal product, then its properties, including the effect of cleaning and cleaning frequency, are better described in a technical documentation for a CE mark.

XI. ORGANIZATIONAL REFINEMENTS

The organization of the draft Note for Guidance, in many places, does not clearly set forth the EMEA's recommendations. We recommend that the draft Note for Guidance be somewhat reorganized so as to assist industry in understanding the EMEA's expectations for the registration of future inhalation spray products. For example:

- The implication from the opening paragraph of Section 3 is that the justification of the specification should be presented in Part IIA, rather than in Part IIE where it is usually presented. The text refers to presenting "sufficient data ... to support the specifications proposed." Much of what is listed in this section can be given as development pharmaceutics information, and we suggest that the second sentence be moved to Section 7 of the draft Note for Guidance and changed to read (proposed new language in bold):

> Sufficient data should be provided to support the ~~specifications proposed~~ **patient instructions proposed** ~~or~~ **and** to give adequate assurance that those performance characteristics which are not be routinely tested *e.g.*, priming and testing to exhaustion have been adequately investigated. **The justification of the specification should principally be addressed in Part IIE.**

- In addition, we believe that the reference in the last sentence of Section 3 to "Similar performance specifications will be required for both solution and suspension formulations" is also better placed in Part IIE, found in Section 7 of the draft Note for Guidance.

- The comments on process validation presented in the second paragraph of Section 3.2 are out of place and would be better placed in Part IIB, found in Section 4 of the draft Note for Guidance.

- We suggest that temperature cycling, now addressed in Section 8 of the draft Note for Guidance, should come under *PT IIA DEVELOPMENT PHARMACEUTICS*, addressed in Section 3 of the draft Note for Guidance, as it would not be performed for all primary stability batches.

XII. CONCLUSION

We recommend that the EMEA utilize an appropriate technical process to assemble the best available medical, pharmaceutical and academic expertise, from within and outside the EMEA, to make recommendations for a final version of the Note for Guidance for Requirements for Pharmaceutical Documentation for Pressurised Metered Dose Inhalation Products. We believe that a consensus-building process that addresses, among other things, scientific, technological, and quality control issues for MDI products is critical to the future development of these products.

We support the development of guidance for inhalation drug products and appreciate the EMEA's efforts in developing the draft Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurised Metered Dose Inhalation Products. We hope our comments will be of value to the EMEA and we look forward to the publication of a final Note for Guidance that will effectively serve the current and future needs of the inhalation drug product industry. Finally, IPAC-RS appreciates the opportunity to contribute constructively to the development of this and future EMEA guidances.

XIII. GLOSSARY

CE mark	Conformité Européenne mark (logo demonstrating conformance with the European Union Council Directives concerning Medical Devices)
CFC	Chlorofluorocarbon
CPMP	Committee for Proprietary Medicinal Products of the European Agency for the Evaluation of Medicinal Products
EMEA	European Agency for the Evaluation of Medicinal Products
FPD	Fine Particle Dose
GMP	Good Manufacturing Practices
HFA	Hydrofluoroalkane
ICH	International Conference on Harmonization
MDI	Metered Dose Inhaler
Ph.Eur.	European Pharmacopoeia
pMDI	Pressurised Metered Dose Inhaler
Q6A	ICH Guideline *Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
RH	Relative Humidity