COMMENTS FROM THE INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM ON REGULATION AND SCIENCE (IPAC-RS) ON EMEA RECOMMENDATION ON THE NEED FOR REVISION OF (CHMP) POINTS TO CONSIDER ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP) (CPMP/EWP/4151/00)

INTRODUCTION
IPAC-RS is an international association of companies that develop, manufacture or market orally inhaled and nasal drug products for local and systemic treatment of a variety of debilitating diseases such as asthma, chronic obstructive pulmonary disease and diabetes. Current members of IPAC-RS include 3M, Aradigm, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kos, Nektar Therapeutics, Novartis, Novo Nordisk, Pfizer, sanofi-aventis, Schering-Plough and Teva. IPAC-RS is grateful for the opportunity to provide the following comments on the EMEA Recommendation on the Need for Revision of (CHMP) Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00)
GENERAL COMMENTS
IPAC-RS commends EMEA for issuing the above-referenced document and the inclusion of other dosage forms beyond pressurized Metered Dose Inhalers.
While the intention of the original Points to Consider (PtC) was to provide clinical guidance, there are significant pharmaceutical development expectations described there. The CHMP should consider cross-referencing to pharmaceutical aspects (specifically, as described in the Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005 Corr)) rather than duplicating them in the PtC, except where necessary for the context of the clinical guideline.
The scope of applicability of PtC should be clarified, e.g. locally vs. systemically acting drugs.
IPAC-RS agrees with the necessity to evaluate the factors included in *3. Discussion* and sees these items as key elements for the PtC.
The PtC should place greater focus on clinical designs. For example, it would be helpful if the PtC provided considerations for designing clinical trials for various classes of drugs, providing clear instructions as to acceptance criteria and ranges, types (PK, PD) and durations of studies.

The Recommendation focuses on the issue of therapeutic equivalence but is related to the 1993 guideline on 'Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products', which addressed the phase-out of existing CFCs, and addressed the preclinical requirements (in its section 3) and approaches to the assessment of clinical safety of products (in its section 4.2). These topics should be incorporated into the revision of CPMP/EWP/4151/00. In particular, the following points should be covered:

- Preclinical testing of new combinations of excipient and active or combinations of actives (a cross reference to CHMP/EMEA/CHMP/SWP/258498/2005 may be appropriate).
- Assessment of the effect of a change in formulation or delivery device on the systemic pharmacokinetics of/exposure to the active substance(s) (and possible consequent need to either reconsider the suitability of the safety margins defined in non-clinical testing and/or redefine dose of the product).
- Some guidance on circumstances in which post-marketing surveillance studies, as outlined in CPMP/180/95, would be expected.

CPMP/EWP/4151/00 provided guidance on the need for a clinical programme for well-known active substances (section 2.2). This section of the document implied that in-vitro testing and/or pharamacodynamic/pharmacokinetic studies may be used as a surrogate for clinical studies in certain circumstances. However, the current version of that document does not provide sufficient information relating to the standards to be applied to declare similarity between products. For in-vitro testing, the document should identify key parameters to be tested (as per EMEA/CHMP/QWP/49313/2005Corr) and how to set acceptable margins to define equivalence for each. The document should be clear regarding whether these margins relate to standards that are applied as a prelude to clinical testing or to a scenario in which in-vitro testing is an acceptable alternative to clinical testing.

IPAC-RS suggests that EMEA explore with the industry further considerations beyond a revised PtC, e.g., by arranging a discussion of Interested Parties regarding the comments submitted to EMEA either before or after close of the commenting period.