IPAC-RS Comments on Draft Health Canada Guidance Document:

"Submission Requirements for Subsequent Market Entry Inhaled Corticosteroid Products for Use in the Treatment of Asthma" Dated 2 August 2007

The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) is an association of innovator and generic companies that develop, manufacture or market orally inhaled and nasal drug products (OINDP) 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 are 3M, Abbott, Aradigm, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Nektar Therapeutics, Novartis, Novo Nordisk, Pfizer, sanofi-aventis, Schering-Plough and Teva. We welcome the opportunity to provide comments on this important and emerging regulatory topic.

GENERAL COMMENTS	
1.	The current EU Points to Consider for Clinical Documentation on Orally Inhaled Products (CPMP/EWP/4151/00) provides criteria, which allow for exemption of the need for clinical studies where pharmaceutical equivalence can be demonstrated through a valid and accepted alternate means. Similar criteria should be provided in this guidance.
2.	Considering the successful harmonization (Canada and EU) for the Pharmaceutical Quality Guideline of Inhalation and Nasal Products, there is a great opportunity for harmonization of this guidance and those similar in other regions, e.g. EU and US - harmonization with the EU PtC "recommendation to update" and discussion with FDA (contemporary Chowdry podium presentations vs. 1994 guidance). This point is critical especially given the innovative approach proposed, i.e. sputum eosinophil endpoint. Innovation in this area is very welcome if a harmonized approach can be reached. The initiative outlined in this guideline to simplify requirements is welcomed but specific details require further discussion.
3.	Perspective regarding preclinical data considerations/requirements should be addressed, even if minimally, within the guideline.
4.	The guideline is specific to asthma. Further clarity for other indications (e.g. COPD) should be provided
5.	A PD study in adults (e.g. HPA axis) should not substitute for PK measures even if it is not possible to obtain a full profile.
6.	As fixed dose combination products are becoming mainstream pharmaceutical dosage forms, clarification is requested for studies for subsequent entry combination products (ICS/LABA).
7.	As noted before, clarity and perhaps explicit comment on whether the clinical data outlined would extrapolate to all populations approved for the reference product (moderate/severe asthma, adolescents, and pediatrics) and for all approved dose regimens/strengths.
8.	Requiring both a biomarker and systemic safety (either as PK or PD) equivalence studies is obviously a more rigorous hurdle than what the US requires. We would like to see consistency in what is required.

9. By cross reference to the guideline' Guidance for Industry: Pharmaceutical Quality of Inhalation and Nasal Products' there is an implication that the formulation be 'qualitatively the same and quantitatively essentially the same' as the reference product. For Dry Powder Inhaler products, in particular, the delivery device of the subsequent entry product may be substantially different resulting in greater differences in formulation. However these differences may not result in meaningful clinical differences in dose/exposure to patients. Further clarity regarding the applicability of the clinical studies outlined, where device/formulation are substantially different to the reference product, should be explored. And, if appropriate, provide further guidance on any additional clinical studies required in this circumstance.
10. Use of sputum eosinophils is not adequately validated for use as a co-primary endpoint to establish therapeutic equivalence and the proposed 3 week study duration is considered insufficient for comparing efficacy. With respect to comparative assessments of systemic exposure, serum cortisol is a less sensitive marker of systemic exposure therefore a PD study should not substitute for PK measures even if only a partial profile is obtainable.
11. In order to establish clinical therapeutic equivalence, all proposed strengths of a subsequent entry product that a sponsor wishes to register should be studied so that drugs with non-linear dose dependent pharmacokinetics can be adequately evaluated.
12. The guidance does not appear to address any additional requirements for approval if the product can or will be used in a pediatric population. Specific clinical studies for use in pediatric patients should be required if the product labeling allows for such use. At a minimum, a PK study in children 4-11 and another in children <4 years (if applicable for the product) should be considered, especially when the drug's pharmacokinetics differ significantly between adults and children.
13. This guidance indicates that it is not intended for other indications such as COPD. It is unclear how Health Canada would prevent the use of a subsequent entry ICS containing product in this manner unless this guidance is specifically and strictly limited to those subsequent entry products whose reference product are only approved in Canada for asthma (whether as a mono-therapy or in combination with another drug). Subsequent entry ICS containing products whose reference products are approved for other uses (whether as a mono-therapy or in combination with another drug) would therefore not be approved by Health Canada until appropriate guidance is made available.
14. In lieu of the history behind the development of the current proposed guidance spanning as far back as 1990, and the significant issues of concern that still exist with respect to this issue, it is recommended that further consultation with stakeholders be conducted following receipt and evaluation of the feedback received on this draft guidance document.
15. We propose that the opportunity for further public discussion with interested trade organizations and/or companies be provided on this topic. This point is particularly important, if harmonization amongst the regions is a possibility.

SPECIFIC COMMENTS ON TEXT

Line(s)	Comment and Rationale	Proposed change (if applicable)
100-108	It should be specified that the scope of this guidance does not apply to combination ICS/LABA products. Also, reference to formulations that are applicable to this guidance should be given (e.g. DPI and MDI).	
103-104	The guidance indicates that it is not intended for other indications such as COPD.	A separate guidance for other indications is required. Until such time, Health Canada should not approve a subsequent entry ICS containing product when compared to a reference product having other indications such as COPD (whether as a mono-therapy or in combination with another drug).
167-171	We are not in agreement with the use of sputum eosinophil measures as a surrogate biomarker of efficacy for establishing clinical therapeutic equivalence, as the available evidence does not yet validate its use in this manner.	
171-175	We agree with Health Canada's assessment that use of exhaled nitric oxide is not a validated marker and therefore inappropriate for establishing clinical therapeutic equivalence.	
194	"Second Entry" should be corrected to state "Subsequent Entry" as per the title of this guidance document and this sub-section in particular.	
198-200	In terms of the generation and provision of pharmaceutical development data, the guidance rightly makes no distinction between a solution and more complex ICS drug product formulation. Therefore, the reference to the TPD Guidance for Nasal and Inhalation Products should also emphasize more definitively that a detailed in-vitro package is required to establish comparability with the Canadian reference product.	
202-203	The proposed requirement for comparability data with existing spacer devices for both adults and children is commended. A subsequent	

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	entry product should not be merely allowed to cross reference data within the first entrant's approved product monograph for demonstrating equivalency with respect to the use of such devices. More specific guidance is required with respect to the number of Canadian marketed spacers/valve holding chambers that need be assessed; in addition to flow rates, delay times, age ranges or pulmonary lung function parameters to be studied. Evaluation in children less than 4 years of age should also include face masks.	
202	"evidence of compatibility" is vague.	Specify what is meant by evidence; e.g., CMC evidence, clinical evidence, etc
222	We are not in agreement with using anti-inflammatory biomarker response measures as a primary endpoint, as the available evidence does not validate its use in this manner.	
228	It would be useful to indicate the scientific basis for applying the equivalence limits of 80-125% to sputum eosinophils. There is a concern that the variability may be high and achievement of this criteria may be difficult.	Justify the use of the 80-125% and CI and likely sample sizes or allow flexibility to justify alternative criteria being applied.
228	The statement that parallel group design is more reliable than cross over design is questionable and should be further justified.	If methods are found to deal with carry-over, flexibility to use crossover designs should be allowed since this will reduce variability relative to parallel group design.
228-233	We agree that a crossover study design is inappropriate for assessing the clinical therapeutic equivalence of products which might have carryover effects.	We recommend that only a parallel group study design be allowed by the guidance.
237-241	Finding steroid naïve mild asthma patients with >3% eosinophils will be practically difficult in Europe, USA and Canada.	Clarification on the definition of 'steroid naïve' is required. The definition of steroid naïve as 'minimum 6 weeks off ICS' is not a standard definition.
237-242	The following comments and recommendations pertain to the defined study population. • The sensitivity of the proposed efficacy assessments is	

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	questioned with respect to enrolling steroid naïve patients. It's more likely that a maximum effect on both eosinophils and lung function will be seen with this population therefore the products will tend to look the same with respect to efficacy. • It is noted that a patient population with stable mild asthma is being recommended. However, the clinical efficacy criterion of improvement in mean FEV1 of at least 10% of predicted (lines 280-283) is likely to be very difficult to achieve in a mild population. The patient population may need to have moderate asthma, or the clinical efficacy criterion should be revised. • The criteria for definition of "stable mild asthma" are not defined and neither is the age group to be studied. It is recommended that the inclusion criterion for asthma severity, expressed as % predicted FEV1, be defined and consideration given to also requiring some degree of symptoms. • "Pre- and post-bronchodilator FEV1" criteria should be specified for clarity. We recommend requiring reversibility (post-bronchodilator FEV1 minus pre-bronchodilator FEV1) of ≥12%.	
246-247	With respect to the defined sample size, additional detail should be specified for clarity. For instance, highlighting the defined therapeutic equivalence bounds specified on lines 287-288 of the guidance is recommended.	
253-258	The duration of 3 weeks is insufficient for evaluation of efficacy parameters, which do not plateau in this short time. Recommended treatment duration should be a minimum of 8 weeks, with 12 weeks being preferred. This approach would also be consistent with regulatory guidance available outside of Canada (FDA's Guidance for Industry: Points to Consider: Clinical Development Programs for	

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	MDI and DPI Drug Products)	
262	"lowest dose available" is ambiguous	"lowest to be marketed dose"
262	For products with non-linear dose dependent pharmacokinetics, a study in mild asthmatics of only the lowest dose should not be sufficient to support the use of higher strength products that may be available for the reference product. Additionally, a study conducted with the lowest labeled dose may not achieve a clinically relevant difference from placebo, but still demonstrate statistical equivalence between Test and Reference. All proposed strengths of a subsequent entry product that a sponsor wishes to register should therefore be studied.	
266	Induced sputum from mild asthmatics patients would be very difficult to achieve and a large failure rate would be expected. Sensitivity and reproducibility of sputum eosinophils are additional questions/points to consider. The proposal to use anti-inflammatory markers as a novel endpoint in these studies is welcomed in order to initiate further discussion; however a specific requirement for this design is premature until further validation work is undertaken. There is some signal in the literature indicating that other factors such as age and disease duration may affect the predictability of lung function from eosiniphilia count.	The guideline should be written more flexibly to allow for alternative anti-inflammatory markers (where demonstrated to be validated) and alternative endpoints to demonstrate therapeutic equivalence should be discussed.
270-283	Requiring a difference in baseline between both actives and placebo of 50 percentage points in %total differential count seems to be a very high hurdle. Similarly, requiring a concurrent difference in change from baseline between both actives and placebo of 10 percentage points in percent of predicted FEV1 is also a very high hurdle.	A difference of less than 10 percentage points may still be clinically meaningful.
270-283	The following comments and recommendations pertain to the defined clinical efficacy criteria. • Suggest adding significance level of 0.05.	

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	• While it is agreed that a 50% difference in mean % of sputum eosinophils is appropriate for the proposed endpoint it is still not deemed appropriate for the reasons stated above concerning lines 167-171. • Sputum eosinophil measurements are not commonly performed by general practitioners who prescribe this type of product. Therefore, results of such an endpoint may not be useful for most of these prescribing physicians. • A 10% difference in percent predicted FEV1 (expressed as a percentage of predicted) from baseline to end of treatment between low dose ICS treatment and placebo after 3 weeks may not be achievable. • If the product can/will be used in children below the age of 12 years, consideration should be given to assessing PEF vs. FEV1 for children 4-11 years of age and another assessment altogether (e.g., symptom assessment) in children <4 years of age.	
280	The guideline is unclear with respect to the efficacy criteria versus placebo and the equivalence criteria relative to FEV1.	It is suggested that the non-inferiority margin be defined as half the expected efficacy.
285 - 287	The following comments & recommendations pertain to the defined therapeutic equivalence criteria. • A requirement for comparing the safety of the test and reference products is not mentioned. Demonstration of comparable safety between the test and reference products in the clinical study (ies) should be required. • The therapeutic equivalence criteria should be made clearer. The confidence interval should be expressed in the same units as the efficacy parameter, and it should be clear which of the endpoints is/are being log transformed. For FEV1, the CI should be expressed as percent of predicted (or in liters if the FEV1 criterion is changed to this unit of	

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	measure). If eosinophils as an endpoint are expressed as % of total, the eosinophil data should not be log-transformed. If the eosinophil data are expressed as absolute count, then log transformation is acceptable. • The criteria for therapeutic equivalence are stated as 80-125%; however FEV1 generally appears to be normally distributed on the absolute scale and does not require transformation. It would therefore be beneficial to define the limits of equivalence on an absolute scale. Furthermore, the 80-125% limits appear to be transposed from bioequivalence guidelines and may not be appropriate for efficacy markers. Given that the study (ies) would involve clinical endpoint data it would be sensible to base the therapeutic equivalence rule on clinical relevance. An alternative approach to calculating delta should therefore be considered. For example, establishing a limit that would represent a difference that isn't clinically relevant – or some proportion of clinically relevant difference that would give a reasonable degree of assurance that products give comparable clinical effects.	
287	Applying the therapeutic equivalence criteria to the log transformed eosinophil percentage is in line with PK bioequivalence criteria, but might result in large sample sizes to prove. For the FEV1, as an untransformed parameter, a symmetrical 90% confidence interval would be expected.	As noted above, the non-inferiority margin should be half of the minimal clinical effect, so linking this into the clinical efficacy criteria, one would expect the CI's to be approximately +/-5% of the difference.
292-329	A PD study in adults (e.g. HPA axis) should not substitute for PK measures. The use of PK studies to assess systemic absorption is strongly supported and should be required even if it is not possible to obtain a full PK profile. Specifically, the use of a serum cortisol in situations were systemic exposure is not high enough to adequately compare formulations is of concern. Available data also suggest that serum cortisol is a much better market than urine cortisol but such studies should still be supported by other larger safety studies.	

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292-329	The guideline does not specify if the PK Safety study should be undertaken in healthy volunteers or in patients.	Specify patient population. Healthy volunteers would be most appropriate due to the lower variability making comparison of formulations easier.
292-329	We support the proposals in this section. The assumption that if systemic exposure is equivalent then safety is equivalent is simple and logical.	
317-324	To truly assess PD of a chronic therapy such as an ICS, a multiple dose study should be conducted versus a single-dose study, and serum cortisol assessed at baseline and at the end of the treatment period. The length of the studies has to be sufficiently long to result in exogenous steroid exposure, should it exist (e.g. a minimum of 3 weeks is suggested as an acceptable duration of an HPA axis study).	