

**IPAC-RS Comments on the Health Canada Draft Guidance Document  
 “Submission Requirements for Subsequent Market Entry Steroid Nasal Products for Use in the Treatment of Allergic Rhinitis” 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 appreciate Health Canada’s efforts to develop a guidance document in this important area and welcome the opportunity to provide the following comments.

Lines	Comment and Rationale	Proposed change (if applicable)
General	Requiring both a biomarker and systemic safety (either as PK or PD) equivalence study is more rigorous than what the US requires. We would like to see consistency in what is required.	
181-183	We recommend that the ingredients sourced for production of the subsequent entry product also be required to meet similar quality standards as those used in the manufacture of the innovator’s product as differences could have implications with respect to product safety (e.g. impurity profile)	
227	We do not agree that an Environmental Chamber study is a suitable alternative for establishing the clinical therapeutic equivalence of a subsequent entry product unless it were validated as being truly reflective of the drug’s response in a real world setting. The guidance therefore needs to detail how such an approach would need to be validated.	
241-244	We do not agree that allowances should be made to justify the absence of pollen counts. Without such measurement it is unclear how a sponsor would confirm that study patients were in fact exposed to the particular allergen of concern.	
249	The phrase “Placebo is not required for the run-in period” is ambiguous.	Please change to “Placebo dosing is not required for the run-in period”
254-257	The frequency of clinical efficacy evaluations made in establishing the therapeutic equivalence of a test product should be at least as stringent as that required for approval of the reference product.	
261-263	The instantaneous assessment post-drug would not therefore be a trough evaluation. Is this truly the intent of this statement? Is the goal to demonstrate a quick onset of effect? From a steroid this seems unlikely.	
287-292	We do not agree that use of the lowest labeled dose in this study offers the best sensitivity for	

	establishing therapeutic equivalence. It is important to distinguish between statistically significant differences and clinically relevant differences. A study conducted with the lowest labeled dose that could not achieve a clinically relevant difference from placebo could demonstrate statistical equivalence between Test and Reference. It is therefore recommended that the study be conducted with the approved adult starting dose of the reference product.	
303-304	Regarding safety assessments, detailed physical nasal examinations should be required for all studies.	
311	What happens/does it mean if the test is numerically worse than reference but not statistically different? Why should this be an issue? Also, this is a little strict, given a non-inferiority design is not required to assess onset. Where is room for random variability? Especially given maximal effect in these drugs can take a week? Please clarify in the guidance.	
319	The draft document mentions "...baseline of at least one unit is considered clinically meaningful." "At least a 1-point difference" in change from baseline between actives and placebo in TNSS may be viewed as a strong effect. In addition, this appears to be inconsistent with the justifiable meaningful differences of 0.20 in individual symptoms such as congestion.	Please change to "...baseline of at least 0.8 is clinically meaningful."
330	The phrase "Test values can be better but not worse than those of the reference product." is unclear. Please clarify if this should be "numerically worse" or "statistically". Note this does not allow for small differences in the 'wrong' direction – which can happen even in a non-inferiority study.	
333	The phrase "90% confidence interval (C.I.) of the T/R ratio mean change of the TNSS from baseline..." is unclear. Shouldn't the ratio be adjusted for placebo similar to the asthma guidelines?	
334	The draft document mentions "on log transformed data" What is the need for doing a log-transform on TNSS data?	
336-337	Demonstration of clinical therapeutic equivalence in both a SAR and PAR population should be required for approval. It is unclear how therapeutic equivalence for treatment of PAR can be assumed when this has only been demonstrated in a SAR population? If this approach were justified, it does not explain why an innovator of a first entry new drug must study this in both populations to demonstrate the product's efficacy. Additionally, to merely assess the safety of a drug on the basis of a short term clinical study of 2-3 weeks duration in patients with SAR is questionable given chronic use of intranasal corticosteroids for the treatment of PAR can occur over several months. It is therefore recommended that sponsors of subsequent entry products also be required to run long-term safety studies in PAR subjects for drug approval if the innovator's label includes both uses.	
363-365	The PK and PD studies described in the draft guidance have very different objectives and are not interchangeable. We do not agree that a 6-week HPA axis study in adults would substitute for PK measures. It is also not clear what the threshold would be for determining whether PK studies are	

	<p>feasible. The guidance as currently provided merely states this requirement as 'too low to allow for reliable analytical measurement'. As worded, this could allow sponsors to believe that they need not even attempt to develop a suitably sensitive analytical method before defaulting to a PD study. It should therefore be specifically stated that sponsors must develop or find the most sensitive "state of the art" assay possible.</p>	
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