Turkish Ministry of Health
Turkish Medicines and Medical Devices Agency
Soğutozu Mahallesi,
2176. Sokak No.5
06520 Cankaya / ANKARA / TURKEY

Subject: Regulation on “Inhaled Preparations”, Reference No. 950439, Dated 25 June 2013

Dear Sir/Madam,

The European Pharmaceutical Aerosol Group (EPAG) is a voluntary non-profit consortium of pharmaceutical companies. The member companies develop pharmaceutical products that are administered via the pulmonary or nasal route of delivery, and marketed for human use in Europe.

EPAG is aware of the above-mentioned regulation concerning “Inhaled Preparations” and welcomes the opportunity to provide comments on this important regulation.

Our comments are summarized in the following two tables, consisting of i) general comments and ii) specific comments to the five requirements stated within the regulation.

i) General Comments	
1.	The regulation refers to “Inhaled Preparations.” Further clarification on the applicability to intended inhaled dosage forms is requested (e.g. oral and nasal inhalation drug products, pressurised metered dose inhalers, dry powder inhalers (DPIs), products for nebulisation, and non-pressurised metered dose inhalers).
2.	We suggest further clarification of the scope of the regulation, as well as provision of a clear differentiation of its applicable requirements to new marketing authorisation applications versus generic products (as applicable). Additionally we recommend consideration of separation between CMC and clinical regulations/guidelines.
3.	We recommend a consistent use of harmonized terminology as contained in European Regulatory Guidelines (e.g. device resistance).
4.	We suggest the inclusion of further details as to the basis for this new regulation as well as the justification of the need for the stricter requirements stated within, since they deviate from current European regulatory guidelines and current pharmaceutical industry good manufacturing practices.
5.	We request an opportunity for further public discussion/comments with affected trade organizations and/or companies on this regulation, in the interest of regional harmonization.

ii) Specific Comments	
Requirement	Comment/s
1. Requirements for manufacturing sites	While we agree that appropriate control strategies must be implemented in manufacturing processes to prevent cross contamination, we do not agree with the general requirement that states all inhaled products must be manufactured in dedicated buildings to prevent cross contamination risks. Cross-contamination concerns with potent active ingredients are not limited to inhalation products, but any pharmaceutical product where necessary protective measures, as well as cleaning validation requirements, must comply with the applicable cGMP guidelines. The toxicological and pharmacological profile of the active ingredient/s should be considered as part of a cross-contamination risk assessment[1].
2. Requirements for product authorization	The term “airway systematic “ and the phrase “In cases where the airways are not similar, results from a clinical trial must be submitted, conducted with a device containing the active substance of the product in question” are unclear. We assume this requirement may be referring to generic inhalation products and the EMA guideline CPMP/EWP/4151/00[2]. We request this requirement is further clarified/ rephrased in the regulation including clear reference/s to existing guidelines, where appropriate.
3. Requirements for devices	We do not agree with the general requirement that inhaler devices and inhalation drug products must be manufactured at the same manufacturing site. It is common practice in the pharmaceutical industry for inhalation devices to be manufactured (e.g. component injection moulding, in process control, sub/assembly processes, release testing) by certified device suppliers/manufacturers with overall product quality being ensured by the drug product marketing authorization holder (pharmaceutical company). The requirement could be considered applicable for the “filling” manufacturing step and final assembly of certain multi-dose inhalation products (e.g. pressurised metered dose inhalers, dry powder inhalers using a reservoir and metering mechanism or a pre-dispensed dose). The definition of “qualified person” needs to be clarified. We request the meaning of “all regulatory requirements” is

	clarified with inclusion of the corresponding relevant guideline references. The term in the last paragraph “Airway resistance” is unclear and requires clarification. The specific EMA guideline referenced in the last paragraph “Airway resistance requirements have been aligned with the EMA guideline” should be referenced in the regulation.
4. Requirements for product manufacturing	The expected level of capsule weight control stated under “100% weight checks” on an individual capsule level needs to be clarified (i.e. *in situ* individual capsule net fill weights or capsule fill weight checks using capsule weight-checking production machines). In general, adequate control of the encapsulation process is assured during product development and verified during process validation. Furthermore capsule fill weight is regularly monitored as in-process controls during routine commercial production. Therefore a more general requirement concerning appropriate weight checks is desirable.
5. Equivalency of products	The term “airway geometry of the device“ is unclear. We assume this requirement may be referring to generic inhalation products and the EMA guideline CPMP/EWP/4151/00[2] and the term “airway geometry” is referring to the inhalation device resistance. The requirement needs to be clarified/rephrased in the regulation including clear reference/s to existing guidelines, where appropriate.

References

[1]*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, EMA/CHMP/ CVMP/ SWP/169430/2012*

[2]*CPMP Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP), CPMP/EWP/4151/00*

On behalf of the EPAG,
Yours sincerely,

✍Yorick Kamlag

EPAG Chair

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