CROSS-INDUSTRY Organizations

# A review of the European Pharmaceutical Aerosol Group (EPAG) technical subteams

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The activities, structure and objectives of the European Pharmaceutical Aerosol Group (EPAG) were reviewed in *Inhalation* in June 2011. This article provides further insight and summarizes the EPAG technical subteams. These have been established to provide scientific, quantitative data to support the recommendations and proposals that EPAG provides for a range of applications, such as improving and developing testing methodologies and responding to draft regulatory guidance.

EPAG subteams have a very successful record of work, much of which is published externally. The external publications include peer reviewed journal articles and conference posters. Many of these publications can be found on the EPAG website: (http://www.epag.co.uk/epag/Default.asp).

Subteams include relevant experts who can contribute to the issues at hand. To achieve this, the subteams are open to non-EPAG member companies, suppliers, service providers, regulatory representatives, academics and others. The subteams operate to approved "terms of reference" (ToR) and deliverables. Once the deliverables have been completed, the subteam ceases to function but may be reactivated if suitable issues arise at a future time. A list of active and completed subteams is shown in Table 1 and various subteams are described here:

## Inhaler mis-use

This team assessed aspects of inhaler mis-use by the patient and the ways these aspects could be tested within the laboratory. The output from this group was a paper entitled "Guidance on inhaler use and mis-use" that was published in PharmEuropa (14.3, 2002).

## Stability reduced testing

Blinded data sets from companies were analyzed statistically by this team to determine if a reduced matrix would be able to forecast the same predicted shelf life outcome. A number of issues were found that currently make reduced stability testing for inhalers products difficult. A paper analyzing inhaler dose content uniformity from a statistical perspective was published in Drug Delivery to the Lungs-XI, (2000), pp.117-122.

## Nebulizer

This subteam conducted a series of practical studies and literature assessments to assist in the preparation of the first Ph. Eur. Monograph - Preparations for nebulisation: characterisation (2.9.44). The studies that were conducted were published in Pharm - Europa Scientific Notes and contributed to the successful issuance of the monograph (effective January 2012).

## Lactose

This team's focus was on lactose monohydrate as used in DPI formulations, specifically working to agree on a harmonized list of specific tests/test methods used to characterize α-lactose monohydrate during development as well as for product QC testing. This was in preparation to challenge and influence the proposed Pharmacopeia monograph on "lactose for inhalation." However this proposed monograph seems to have been withdrawn and no further work is needed at this time.

## Quality by design

This team looked at the practical application of QbD principles in inhaler product development. The application was modelled for a pMDI although the processes could be applied to other types of inhalers. An industry survey on the status of applying QbD for inhalation product development was conducted in November 2006, and the results of the survey were presented at RDD Europe in May 2007.

## Impactor

The impactor subteam has the longest history and has dealt with a wide variety of investigations, too many to mention here. Its current activities and deliverables are shown in Table 2.

**Table 1**

**EPAG subteams**

| Status | EPAG Subteam | | | | |
|---|---|---|---|---|---|
| **Active** | Impactor | Device | Nasal | Electrostatics | |
| **Completed** | Inhaler mis-use | Stability reduced testing | Nebulizer | Lactose for inhalation | Quality by design |

## Device

This is one of the newest subteams. Its initial objective is to prepare a road map showing the key aspects to consider during development of an inhaler and the ways they interplay with product development stages.

## Nasal and electrostatics

The Nasal subteam is developing test methodologies for a new Ph. Eur. Nasalia monograph. The initial focus is on aerodynamic particle size methodology for aqueous sprays to measure that which is "potentially" respirable. The Electrostatics subteam is attempting to unravel many of the issues associated with electrostatics when developing inhaler products. The key activities are: an industry survey, evaluating issues and solutions, a literature review and issuing best practices.

## In summary

EPAG has established several subteams to scientifically investigate issues: (a) that present considerable problems in the context of oral and nasal inhaler evaluation, (b) evaluate whether further knowledge is needed, and (c) aid decision making with supportive data of high quality. The subteams are open to relevant experts who have a demonstrable interest or knowledge in the topic under scrutiny. The subteam process has had an enviable record of producing results and publications. EPAG would welcome suggestions of topics that could become future subteam activities. For more information, please visit www.EPAG.co.uk.

**Table 2**

**Current activities of the cascade impactor (CI) subteam**

| Activity | Deliverable |
|---|---|
| 1. Report the first phase of the CI sample volume study in connection with medium resistance DPI testing | Studies recently published, see AAPS PharmSciTech (2012) DOI: 10.1208/s12249-012-9797-0 |
| 2. Undertake the second phase of the CI sample volume study with low and high resistance DPIs | Conference proceedings presentation and peer-reviewed journal article in 2013, extending the work in Activity 1 |
| 3. Fundamental assessment of CI start-up kinetics | Computational fluid dynamics models for both the ACI and NGI under "start-up" conditions for DPI testing |
| 4. Experiments to understand non-uniformity of deposition behavior in the Andersen cascade impactor | Assessments with monodisperse fluorescent particles as tracers to evaluate deposition patterns for selected stages; Contrast with behavior in the NGI |
| 5. Explore the importance of volumetric flow-time profiles in context of DPI testing | Round-robin trial of standard flow-time measurement equipment for assessment of flow rate rise times for different DPI and pMDI products |
| 6. Continue experimental work in support of the Abbreviated Impactor Measurement (AIM) concept | Understand the limitations and precautions needed for AIM implementation across all oral inhaler classes; Support preparative work for AIM incorporation into the pharmaceutical compendia |
| 7. Summarize the findings of the cascade impactor stage mensuration project that were published in AAPS Pharm. Sci. Technol. in 2010 | Stimulus-to-revision article in PharmEuropa Sci Notes and Pharm Forum to inform pharmaceutical compendia committees on current best practices |
| 8. Survey EPAG member companies on current impactor usage | Update and publish survey undertaken shortly after introduction of the NGI comparing uses of the CIs recognized in the pharmacopeia compendia |