Outcome of a Questionnaire within European Pharmaceutical Aerosol Group (EPAG) Companies Concerning the Implementation of the Abbreviated Impactor Measurement (AIM) Concept for the Assessment of Orally Inhaled Product (OIP) Aerosol Aerodynamic Particle Size Properties

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Summary

The AIM Concept as an augmentation of full resolution cascade impactor (CI) measurements of the aerodynamic properties of aerosols emitted by OIPs has been in existence for about ten years. A previous EPAG-based survey undertaken five years ago indicated significant interest in the approach, particularly for the screening of candidate products in early stage product development. We report the outcome of a further questionnaire with the goals of establishing: (a) the types of AIM-based equipment currently in use; and (b) insight into perceived hurdles towards full implementation within the product lifecycle. Responses were received in October 2016 from 17 out of 22 organizations from people involved directly with the *in vitro* testing of pressurized metered dose inhaler (pMDI) and dry powder inhaler (DPI) products. The survey has shown that the AIM concept has sufficient popularity within the EPAG respondent organizations to be considered a viable augmentation to existing full resolution CI methodology. The main conclusions are: (1) The Fast Screening Andersen (FSA), reduced Next Generation Impactor (rNGI) and Fast Screening Impactor (FSI) are all used as AIM-based impactor configurations for both dry powder inhaler (DPI) and pressurized metered dose inhaler (pMDI) applications; (2) AIM-based methods are used almost entirely for the early development phase of the OIP life cycle; (3) Organizations in general do not have confidence to use the AIM concept more widely in the product life cycle whilst no compendial/regulatory guidance is available to provide standard procedures and precautions/regulatory acceptance respectively.

Introduction

The AIM Concept as an augmentation of full resolution cascade impactor (CI) measurements of the aerodynamic properties of aerosols emitted by OIPs has been in existence for about ten years with a textbook describing the 'art' published in 2013[1]. A previous EPAG-based survey undertaken five years ago, and focusing on comparative efficiency between AIM- and full resolution-based CI measurements in use, indicated significant interest in the approach, particularly for the screening of candidate products in early stage product development[2]. However, progress towards the adoption of AIM into the mainstream of the product lifecycle has been slow, despite the existence of cross industry-generated guidance on how this goal may be achieved[3]. Furthermore, two recent cross-industry experiments comparing AIM-based measurements with a full resolution CI-based counterpart and designed to address comparative accuracy have demonstrated good agreement between the techniques, albeit highlighting the potential for slightly higher measures of the most pertinent sub-fraction, either fine particle mass < 5 µm aerodynamic diameter[4] or small particle mass[5], most likely arising from lower internal wall losses associated with the AIM-based apparatus. In 2016, the Impactor Sub-Team of EPAG therefore decided to perform a follow-up survey of members, this time focusing attention on the following: (a) which abbreviated impactors were in use and for the evaluation of which class(es) of OIP, (b) where in the product lifecycle was an AIM-based approach being implemented and (c) what obstacles (if any) lay in the path of full implementation as far as a regulatory submission is concerned. The results from this survey are reported here.

Survey Details

Completed surveys were received in October 2016 from 17 out of 22 organizations directly involved with the in vitro testing of OIPs. Table 1 is a breakdown of the different types of full and AIM-based equipment in use for the various OIP classes. Some organizations may use more than one technique, resulting in multiple responses in the completed survey, therefore the total number of responses for each inhaler class or configuration, does not equate with the total number of organizations responding.

The majority of responses (20 responses from 13 organisations) reported working with DPIs of which 15 and 4 responses were for the NGI and ACI respectively as their full resolution apparatus, with 1 organization employing the Multi-Stage Liquid Impinger (MSLI). 9 organisations stated they used AIM configurations and a total of 14 types of AIM configurations for this product type were in use, with the FSI being the most popular technique (7 responses), followed by the rNGI (4 responses) and the FSA (3 responses).

12 responses were for pMDI products (from 9 organisations), of which 8 and 4 responses were for the NGI and ACI respectively as their full resolution apparatus, with no organization employing the Multi-Stage Liquid Impinger (MSLI). 6 responses from 4 organisations stated they used AIM configurations for the analysis of pMDIs products consisting of the FSA (3 responses), rNGI (2 responses) and FSI (1 response).

7 organisations reported testing other inhaler types (presumably nebulizers and/or soft mist inhalers); all used the NGI as their full resolution apparatus with none undertaking measurements using AIM-based methods.

Table 1: Breakdown of Cascade Impactor Apparatuses for Aerodynamic Particle Sizing by Inhaler Class

Inhaler Class	Number of responses to Full Resolution CI types:			Number of responses to Abbreviated CI types:		
	NGI	ACI	MSLI	FSA	rNGI	FSI
DPI	15	4	1	3	4	7
pMDI	8	4	0	3	2	1
Other Devices	7	0	0	0	0	0

Notes: NGI = Next Generation Impactor; ACI = Andersen 8-stage cascade Impactor; MSLI = multi-stage liquid impinger; FSA = Fast Screening Andersen; rNGI = reduced NGI; FSI = Fast Screening Impactor

Table 2 is a summary of the different uses for AIM-based apparatuses. Almost all respondents reported using AIM-based methodology confined it to use in development with only 1 for each inhaler type reporting that they had used this approach in support of the clinical programme. No respondents reported using AIM for the purposes of QC batch release.

Table 2: Use of AIM-Based Methodology in the Product Life Cycle

Inhaler Class	Number of responses to Abbreviated CI types	Stage of Product Development		
		Development	Phase I, II or III clinic	QC Batch release
DPI	14	14	1	0
pMDI	6	6	1	0

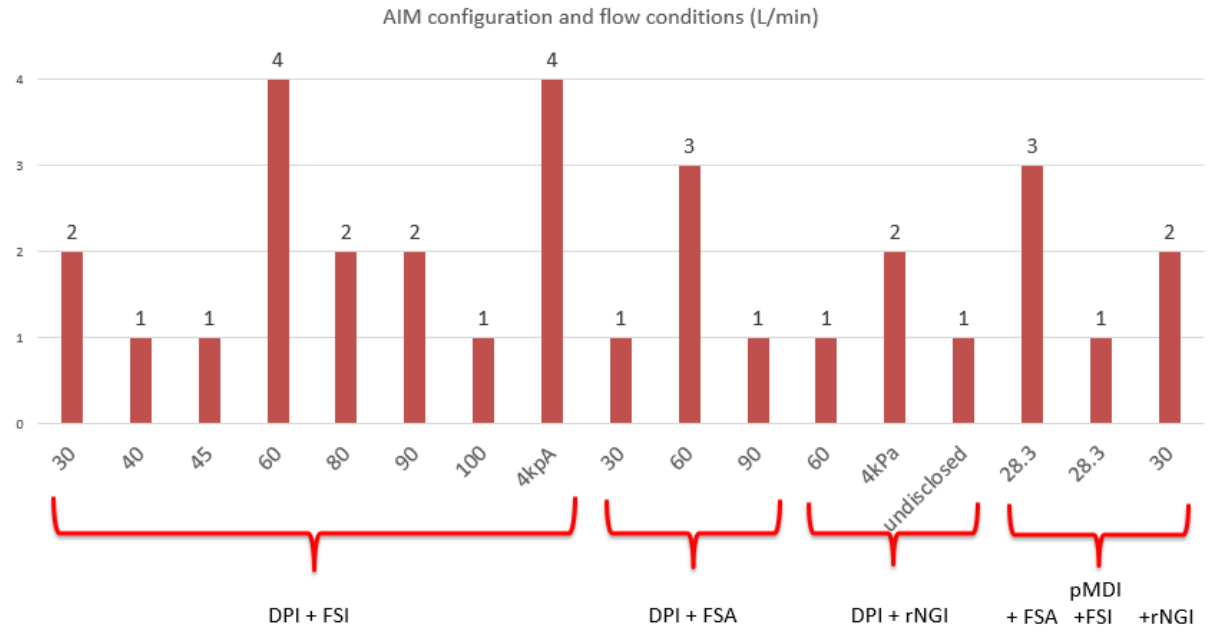

Figure 1: Different Operating Conditions for the Various AIM-Based Apparatus in Use by Respondents

Figure 1 is a summary of the different operating conditions (flow rate and pressure drop for DPI testing; flow rate only for pMDI evaluations) used with their abbreviated apparatus configurations by the different responses, subdivided into inhaler class and AIM-based apparatus type. As expected from the compendial methodologies, the most prominent conditions for DPI testing are 60 L/min or a 4 kPa pressure drop. Interestingly, the FSI was used for testing at a much wider range of flow rates than either the FSA or the rNGI, perhaps reflective of the relative ease of changing the flow rate with this apparatus. The outcomes for those evaluating pMDIs were as expected, with the flow rate for the FSA tied to 28.3 L/min to match with that of the full resolution ACI and the rNGI operated at 30 L/min, a flow rate for which an archival calibration exists.The survey also probed the prospects for organizations to do more with AIM-based methodology, in particular moving towards its inclusion in a regulatory filing for a product. As expected, no organization had used AIM in a regulatory submission to date, and none of the respondents indicated that their organization was planning to submit one in the next three years. On a more positive note, however, 5 out of the 13 responses to this question reported that there is the potential for such a submission, with 5 other respondents being more cautious and reporting maybe such a regulatory submission might happen. In terms of perceived risk of using AIM for product registration, 7 respondents considered that full resolution cascade impaction is required for submission to a regulatory agency, with a further three respondents indicating that full stack CI was required to fully characterise the product. Whereas both statements are true, it was perhaps surprising that observations were not received acknowledging the supporting role that AIM-based methods can play, with the option of full resolution CI measurements as the reference technique.

In summary, this survey confirmed the belief based on the earlier assessment of EPAG companies that AIM-based methodology has a place in the portfolio of methods available for the *in vitro* performance assessment of both pMDI- and DPI-based products. However the lack of a current regulatory submission as well as the limited prospects for one to take place within the next three years suggests that hurdles exist that are preventing this concept from becoming mainstream in the product life-cycle. We therefore deduce that the AIM concept has sufficient popularity within the EPAG respondent organizations to be considered a viable augmentation to existing full resolution CI methodology, especially for early phase studies. However, a general move towards mainstream adoption is unlikely unless there is more clarity from regulatory agencies and the pharmacopeial compendial authorities as to the acceptability of this methodology.

Conclusions

This survey has provided an update and a clearer description of the AIM-based methods currently being used across member companies within EPAG. The following conclusions can be made:

1. The FSA, rNGI and FSI are all used as AIM-based impactor configuraions for both DPI and pMDI applications;

2. AIM-based methods are used almost entirely for the early development phase of the OIP life cycle;

3. Organizations in general do not have confidence to use the AIM concept more widely in the product life cycle whilst no compendial/regulatory guidance is available to provide standard procedures and precautions/regulatory acceptance respectively.

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