An Assessment of the Comparative Efficiency of Abbreviated versus Full Resolution Cascade Impactor Measurements: A Survey of European Pharmaceutical Aerosol Group (EPAG) Members

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Summary

The Impactor Sub-Team of EPAG has conducted a survey amongst its member organizations to assess quantitatively the magnitude of time savings that are being realized with Abbreviated Impactor Measurement (AIM) cascade impactors (CIs) compared with full resolution systems in their own day-to-day operations. Eight different organizations responded to the survey, with information relating to the laboratory assessment of an assortment of pressurized metered dose inhalers (pMDIs) with and without valved holding chamber (VHC) add-on devices and dry powder inhalers (DPIs). Nebulizing systems were not represented. The magnitude of efficiency gains linked to the use of AIM-based methodologies was very dependent on the organization concerned, resulting in large variability in the aggregated data. Nevertheless, the efficiency gains per particle size distribution measurement using AIM-based methods were estimated to be 67% and 39% with and without HPLC assay time included respectively. It was therefore concluded that there are tangible gains to be made in overall CI method efficiency if an AIM-based option is introduced. This survey should be repeated in 5-years time, when it is to be hoped that more respondents, especially those evaluating OIP formats other than DPIs can be encouraged to participate.

Introduction

The successful adoption of the abbreviated impactor measurement (AIM) concept that was developed to address the complexity and therefore time-consuming nature of measurements of aerodynamic particle size-related metrics by the compendial full resolution CI systems (1) will in part be determined by the magnitude of savings associated with improved operational efficiency (2). The present generation of AIM-based systems has been available for about 5 years, so it seemed timely for the Impactor Sub-Team of EPAG to conduct a survey amongst its member organizations to assess quantitatively the time savings that are being realized compared with full resolution CIs in their own day-to-day operations. This report is the result of that survey.

Methods

Ten different organizations responded to the survey, some with information relating to the laboratory assessment of more than one OIP type (Table 1). The names of the responding organizations are blinded in the interest of confidentiality, and are therefore identified in the Tables by a participant number. All but one organization were based in Europe, the exception being located in North America.

Table 1: Participating Organizations and OIP Types Tested by AIM-Based CI Methods

Organization Code	OIP Type*	Abbreviated (AIM) cascade Impactors†	Full Resolution cascade Impactors‡
1	pMDI + VHC	FSA	ACI
2	DPI – no dilution	FSA	ACI
	DPI - dilution		
3	DPI	FSI – single DPI	NGI – single DPI
	DPI	FSI – 10 DPIs	NGI – 10 DPIs
4	DPI	FSA	ACI
5	pMDI	FSA	NGI
	DPI		
6	DPI	FSI	NGI
7	DPI	rNGI	NGI
8	DPI	FSI	NGI
9	DPI	FSI	NGI
10	DPI	FSI	NGI

* pMDI = pressurized metered dose inhaler, DPI = dry powder inhaler, VHC = valved holding chamber
† FSA = Fast Screening Andersen CI (Copley Scientific, Nottingham, UK); FSI = Fast Screening Impactor (MSP Corp., St. Paul, MN, USA); rNGI = Next Generation Impactor reduced to enable AIM-based measurements to be made
‡ ACI = 8-stage Andersen non viable CI; NGI = Next Generation Pharmaceutical Impactor.

Table 2: Full Resolution CI Systems

Organization Identification Code	1	2	2	3	3	4	5	5	6	7	8	9	10
Inhaler Description	pMDI + VHC	DPI - no dilution	DPI - dilution required	DPI	DPI	DPI	pMDI	DPI	DPI	DPI	DPI	DPI	DPI
Apparatus	ACI	ACI	ACI	NGI - 1 unit	NGI - 10 units	ACI	NGI	NGI	NGI	NGI	NGI	NGI	NGI
Time to assemble apparatus (min)	5	20	20	2	11	10	5	10	5	10	35	10	5
Time to verify apparatus (min)	2	5	5						3		29		
Leak test						2				2		10	2
Pressure drop						2						5	2
Other test (please specify): collect sample		5	10										
Combined Verification	2	10	15			4			3	2	29	15	4
Time to recover (wash etc) sample from IP and PS (min)	30	10	10	25	100	10	5	10	5	5	35	6	4
Time to recover (wash etc) sample from CI stages & filter	20	10	10	25	50	12	20	20	9	12	36	15	8
Time for preparation (e.g. flasks; solvent; dilution; HPLC vial	8	30	60	48	75	20	5	10	11	2	40	155	20
Time for HPLC run and evaluation (min)	180	180	280	5	23	116	360	375		90	481	150	120
Time to clean/wash apparatus (min)	3	15	15	5	15	30	15	15	6	10	46	60	10
Time for documentation (min)	5	20	25	120	180	20	30	30	1	30	59	15	5
Total time without HPLC element (min)	**71**	**105**	**140**	**230**	**454**	**102**	**80**	**95**	**40**	**69**	**251**	**261**	**52**
Total Time (min)	**253**	**295**	**435**			**222**	**440**	**470**		**161**	**761**	**426**	**176**
No. Actuations used	5-10	5	10	5	5		2	1		1	5	6	2
Additional comments on time efficiency	Use bag to collect sample faster than flask method			5 min for HPLC evaluation: no data for overnight run time	23 min for HPLC evaluation: no data for overnight run time	add 10 min if verification fails and re-assembly is needed; 20 min for evaluation of HPLC records	90 min evaluation time for HPLC records	90 min evaluation time for HPLC records	HPLC time not provided	8 tests/day/analyst	Time to recover is combined IP + PS + stages and filter		Sample rockers; auto diluters-methods optimised

Table 3: Abbreviated CI Systems

Company	1	2	2	3	3	4	5	5	6	7	8	9	10
Inhaler Description	pMDI + VHC	DPI - no dilution	DPI - dilution required	DPI	DPI	DPI	DPI	DPI	DPI	DPI	DPI	DPI	DPI
Apparatus	FSA	FSA	FSA	FSI - 1 unit	FSI - 10 units	FSA	FSA	FSA	FSI	mod NGI	FSI	FSI	FSI
Time to assemble apparatus (min)	2	10	10	2	11	5	5	5	4	10	18	5	2
Time to verify apparatus (min)	2	5	5						3		29		
Leak test						2				2		10	5
Pressure drop						2						5	
Other test (please specify): collect sample		2	2										1
Combined verification	2	7	7			4			3	2	29	15	6
Time to recover (wash etc) sample from IP and PS (min)	10	10	10	25	100	10	5	10	5	0	30	6	4
Time to recover (wash etc) sample from CI stages & filter (min)	8	4	4	25	25	5	10	10	3	12	30	15	12
Time for preparation (e.g. flasks; solvent; dilution; HPLC vial filling) (min)	3	20	25	46	55	15	5	5	5	2	14	110	20
Time for HPLC run and evaluation (min)	75	120	140	4	13	60	220	235		84	260	70	35
Time to clean/wash apparatus (min)	2	10	10	5	10	15	10	10	4	5	26	45	10
Time for documentation (min)	5	20	20	110	140	15	20	20	1	30	31	5	10
Total time without HPLC element (min)	**30**	**74**	**79**	**217**	**354**	**65**	**55**	**60**	**25**	**59**	**149**	**186**	**58**
Total Time (min)	**107**	**201**	**226**			**129**	**275**	**295**		**145**	**438**	**271**	**99**
No. Actuations used	5	2	2	5	5		2	1		1	5	6	1
Any additional comments on time efficiency can be made here	Use bag to collect sample faster than flask method			4 min for HPLC evaluation: no data for overnight run time	13 min for HPLC evaluation: no data for overnight run time	add 5 min if verification fails and re-assembly is needed; 20 min for evaluation of HPLC records	40 min evaluation time for HPLC records	40 min evaluation time for HPLC records	HPLC time not provided other than with FSI it is 50% of the time needed for the NGI	no recovery and analysis of API on IP or PS: 12 tests/day/analyst	Time to recover is combined IP + PS + stages and filter	HPLC column lifetime extension is important	Optimization still needed:Flow rate check only

There was a good mix of abbreviated and full resolution CI systems in use. DPIs and pMDIs were represented, the latter with and without valved holding chamber (VHC) add-on device. No data were, however, reported for nebulizing systems. Each respondent was asked to complete a questionnaire that was designed to go through the measurement process on a step-by-step basis, requesting an indication of the duration taken by a typical laboratory staff member involved regularly with these measurements. Since assay for the active pharmaceutical ingredient(s) involved with the OIPs being evaluated was by high performance liquid chromatographic (HPLC) methods, it was recognized that many laboratories run the aggregated samples from the previous day's measurements overnight, so the total time per test was calculated (a) without allowing for assay time and (b) including the total assay time per CI measurement group of samples. These data are presented in Tables 2 and 3 for the full resolution and abbreviated systems respectively. All timings are in minutes per operation. The aggregated data (timings in minutes; mean ± SD) are compared in Table 4.

Table 4: Aggregated Reponses from All Participants for All Types of OIP

Step in the Measurement Process	Full resolution CI Mean ± SD (FULL)	Abbreviated CI Mean ± SD (ABB)	Absolute Improvement Using AIM [*R*]	Efficiency Gain Using AIM [*E*] (%)
1. Apparatus Assembly	11.4 ± 9.0	6.8 ± 4.7	0.60	**67**
2. System suitability (verification)	9.3 ± 9.1	8.3 ± 8.7	0.89	**20**
3. Preparation of flasks etc.	37.2 ± 42.0	25.0 ± 30.3	0.67	**49**
4. Sample recovery from IP and PS	19.6 ± 26.3	17.3 ± 26.2	0.88	**14**
5. Sample recovery from stages/filter	19.0 ± 12.2	12.5 ± 8.9	0.66	**52**
6. Cleaning of apparatus post use	18.8 ± 16.8	12.5 ± 11.5	0.66	**52**
7. Documentation of data	41.5 ± 51.8	32.8 ± 42.3	0.79	**27**
8. HPLC assay	196.7 ± 147.6	109.7 ± 81.7	0.56	**79**
TIME WITHOUT HPLC ASSAY	**150.0 ± 118.4**	**108.5 ± 94.4**	**0.72**	**39**
TOTAL TIME WITH ASSAY	**363.9 ± 181.8**	**218.6 ± 105.7**	**0.60**	**67**

Unsurprisingly, the aggregated data for each type of CI measurement had large variability, because each organization has their own independent approach to manage each step of the process, and there was large divergence from one respondent to another in the timings attributed to some activities, for example documentation. The mean time taken for each step in the process using the chosen AIM based CI (t_{abb}) or the corresponding full resolution CI (t_{full}) was compared as a ratio, *R,* in accordance with:

$$[R = (t_{abb} / t_{full})]$$

from which the mean efficiency gain (*E, %*) was determined as:

$$E = \{[1/R] - 1\}100$$

Values of *E* on a step-by-step basis ranged from 14% to 72%. The corresponding values of E using AIM-based methods were 67% and 41% for the measures of total time with and without the HPLC assay included respectively. The relatively small efficiency gain of 14% associated with sample recovery from the pre-separator (PS) and induction port (IP) is to be expected, as for a given OIP type, either the IP alone or IP with PS would have been present whether or not the measurement system was abbreviated. Values of *E* (%) are summarized on organization-by-organization basis in Table 5. This way of approaching the analysis of the survey confirmed that the magnitude of efficiency gains linked to the use of AIM-based methodologies was very dependent on the organization concerned; for instance the company reporting the largest improvement (organization 1) claimed to realize more than a doubling of throughput (*E* = 138%), whereas the corresponding gain in efficiency reported by organization 3 (reporting the least positive change) was only 6%. Although organization 10 reported reduced efficiency with their AIM-based method when HPLC time was excluded from consideration, their abbreviated method was sub-optimal.

Table 5: Efficiency Improvement (*E*) for each organization and product type[†]

Organization Code	1	2	2	3		4	5		6	7	8	9	10
Product	pMDI with VHC	DPI no dilution	DPI with dilution	DPI	DPI	DPI	pMDI	DPI	DPI	DPI	DPI	DPI	DPI
Full Resolution CI	ACI	ACI	ACI	NGI	NGI	ACI	NGI	NGI	NGI	NGI	NGI	NGI	NGI
Abbreviated CI	FSA	FSA	FSA	FSI	FSI	FSA	FSA	FSA	FSI	rNGI	FSI	FSI	FSI
***E* (%) without HPLC**	**138**	**43**	**79**	**6**	**28**	**56**	**45**	**59**	**59**	**16**	**69**	**41**	**-11[‡]**
***E* (%) with HPLC**	**138**	**47**	**92**			**72**	**59**	**59**		**11**	**72**	**56**	**79**

[†] where values of *E* with HPLC are not shown, the assay timings were not provided for confidentiality reasons
[‡] optimization of abbreviated method not yet complete

There were no obvious trends in *E* that could be attributed to choice of either full resolution or abbreviated CI type. There was an indication that those organizations testing pMDIs and related products achieved average or better than average efficiency gains. However, as only 2 respondents were associated with this category a firm conclusion could not be made. Data from organization 3 that reported step timings for single and multiple (10) CI measurements suggests that further efficiency improvements with their AIM-based method are possible when multiple determinations are made. Inclusion of HPLC-based assay times had little, if any, impact on overall efficiency.

Conclusions

This survey provides a snapshot of industry-wide practice in the implementation of AIM-based CI methodology after approximately 5-years of commercial availability of abbreviated impactor systems. Widely differing practices associated with both abbreviated and full resolution CI methods resulted in a large amount of variability in the grouped statistics. Notwithstanding this limitation, efficiency improvements in the region of 30% to 60% were widely reported irrespective of OIP type (pMDI, pMDI + add-on device, DPI), with almost all respondents reporting some degree of improved efficiency with respect to overall measurement time, the exception representing a sub-optimal abbreviated method. The lack of data relating to the testing of nebulizing systems for API size distribution by a CI-based method is a limitation, as is the relatively low numbers of respondents reporting the evaluation of OIP variants other than DPIs. In retrospect, it is difficult to gather information of this type due to confidentiality considerations, especially when the abbreviated CI methods are being used for new products, rather than those for which registrations already exist. Nevertheless, it can be concluded that there are tangible gains to be made in overall CI method efficiency if an AIM-based option is introduced. This survey should be repeated in 5-years time, when it is to be hoped that more respondents, especially those evaluating OIP formats other than DPIs can be encouraged to participate.

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