The Good Cascade Impactor Practice (GCIP) Concept: A systematic approach to risk management of erroneous measurements in the assessment of inhaler emitted aerosol aerodynamic particle size distributions (APSDs)

Jolyon P. Mitchell
Jolyon Mitchell Inhaler Consulting Services, Inc.

Introduction

Despite their labor-intensive nature, the multi-stage cascade impactor (CI), including the multi-stage liquid impinger (MSLI), remains the mainstay for the assessment of emitted aerosol aerodynamic particle size distribution (APSD) for orally inhaled products (OIPs). When combined with an appropriate chemical assay technique for the recovered drug product(s) under investigation, these apparatuses enable the mass of each component of the aerosol to be size-classified in terms of its mass-weighted aerodynamic diameter. In the OIP quality control environment, the complexity of the method can be a contributory cause of measurements that are deemed to be out-of-specification (OOS). The Good Cascade Impactor Practice (GCIP) concept is a means whereby the risk of such an occurrence can be minimized by following a logical process through which errors caused by the operator (MAN), the apparatus itself (MACHINE), the assay method (ANALYSIS or MEASUREMENT) and finally the formulation/delivery device (MATERIAL) are identified and controlled. This article explains what GCIP has currently evolved to become and provides advice on implementing this regimen in the OIP test laboratory.

Origins of GCIP

Serious consideration for the need of a regimen that enables the user of the CI method to isolate the many sources of potential error in routine measurements of OIP quality originated in discussions held in the early 2000s by a group of experts brought together from industry, academia and the regulatory agency (US Food and Drug Administration [FDA]) through the Product Quality Research Institute (PQRI). The underlying concern was the belief by industry that the FDA-suggested limit of ±15% label claim for the sum of the mass of active pharmaceutical ingredient (API) recovered from the measurement apparatus (mass balance) in its 1998 draft guidance on Chemistry, Materials and Controls for pressurized metered dose inhaler (pMDI) and dry powder inhaler (DPI) testing[1] was too severe, given the capability of the measurement procedure.[2] Although these discussions were unsuccessful at widening the mass balance limits, the resulting discussions about the underlying CI methodology achieved the following goals:

1. Potential sources of OOS results arising from MAN, MACHINE, MEASUREMENT and MATERIAL were identified (Figure 1);

2. The likelihood was evaluated of each of these sources of error to affect either mass balance and/or the APSD measurement itself;

3. A basic failure mode analysis (fault tree) was developed as a guide to users of the CI method faced with an OOS result (Figure 2).

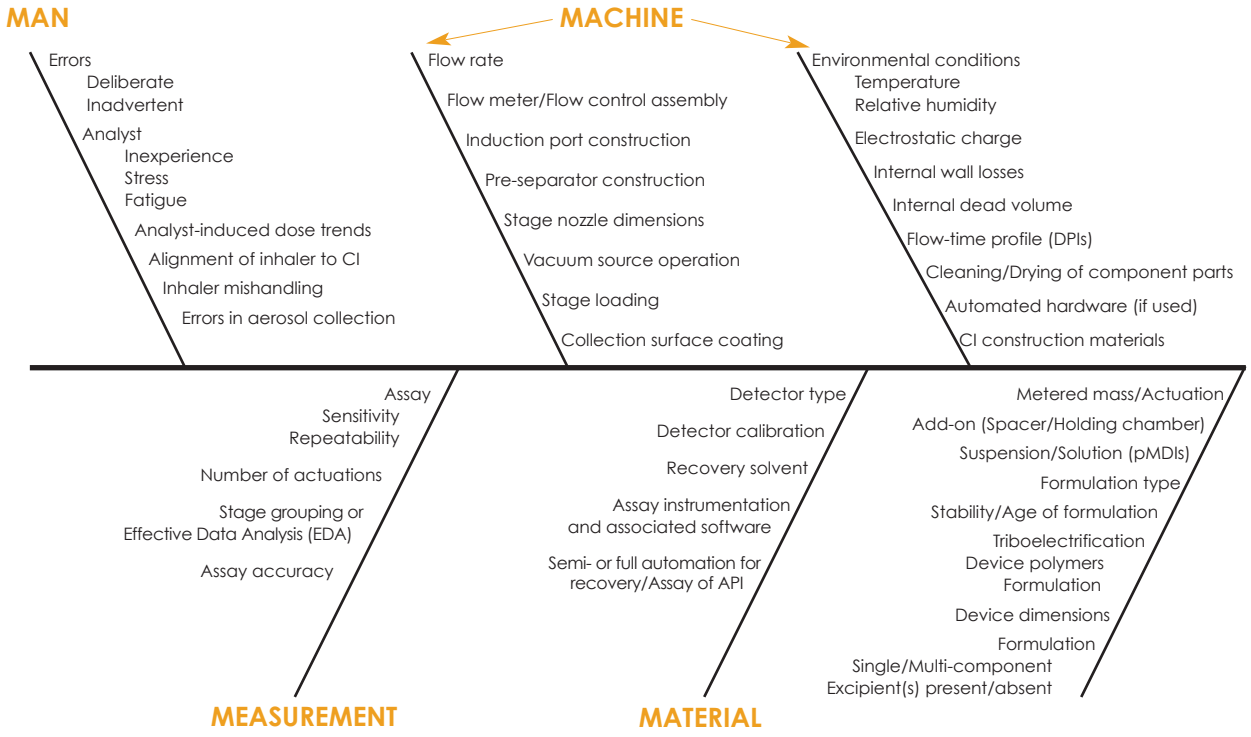
This PQRI-led assessment of the robustness of the CI method laid the foundation for a logical approach for users to identify and rectify causes that could contribute to inaccurate and/or imprecise CI-based measurements.

GCIP evolution

The next step in understanding how a GCIP regimen might function was an assessment to evaluate the intrinsic variability associated with the CI method.[3] This initiative was led through the Cascade Impactor

Figure 1

Sources of potential error in APSD measurements identified by the PQRI study[2]



Working Group of the International Pharmaceutical Consortium on Regulation and Science (IPAC-RS). The outcomes, also based on the Ishikawa diagram shown in Figure 1, revealed the intricate network of underlying causes of APSD variability, with the potential for several multi-way statistical interactions. Significantly more quantitative information was shown to exist about MACHINE-related causes than about MAN-, MEASUREMENT- or MATERIAL-derived influences. The following specific recommendations are highlighted as pertinent to the formation of a GCIP regimen:[3]

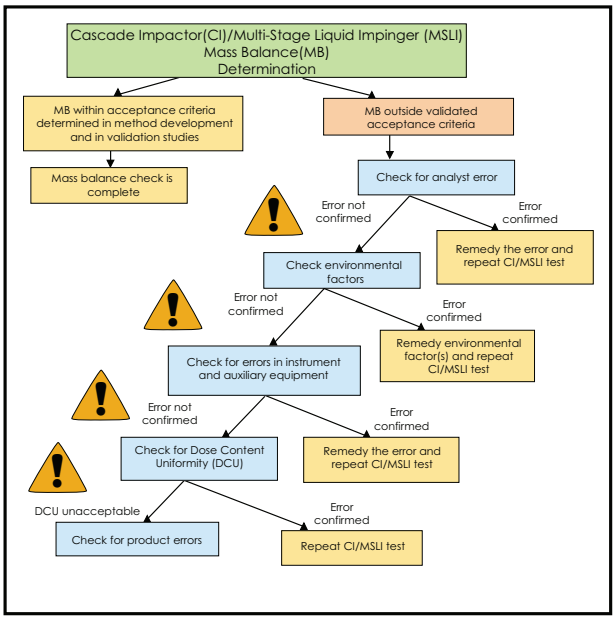
1. MAN – Operator training in the correct assembly and disassembly of the CI system is essential. In some CI designs (notably the Andersen 8-stage [ACI] and Westech W7 impactors), it is possible to assemble stages in the incorrect order, and unless each stage is numerically identified on an external surface, the misassembled CI cannot be distinguished from a correctly-assembled impactor;

2. MAN – The need for operator training in the correct handling of the OIP being tested, including aerosol introduction into the apparatus, is also self-evident. For example, pMDI suspension formulations must be shaken and primed in accordance with the manufacturer instruction. More generally for this class of OIP, the time delay between shaking and actuation, the timing between individual actuations in the likely event that more than one actuation is needed per measurement, as well as alignment of inhaler mouthpiece with the induction port of the apparatus, can each affect APSD results;

3. MACHINE – Translation of API mass deposition data into the APSD depends on the individual stage "cut-off" sizes (effective cut-off diameters [ECDs] in accordance with the Marple-Liu theory of inertial size-separation.[4] Assertion of CI accuracy previously had to be determined by a lengthy calibration of

Figure 2

Failure mode analysis identified in the PQRI study for mass balance OOS results from the CI method[2]



each stage with monodisperse particles of known aerodynamic diameter.[5] Nowadays, stage mensuration using a combination of calibrated optical image analysis equipment and mechanical "stop-go" gauges provides acceptable traceability to the international length standard[6] through the stage effective diameter that is related to the area mean and median diameters of the individual nozzles;[7]

4. MACHINE – Reduction of potential sources of measurement bias that can be easily assessed are: avoidance of particle bounce and re-entrainment by the use of an appropriate stage-coating procedure for the formulation type (i.e., dry powder or liquid droplets) and number of inhaler actuations being delivered;[8,9] removal of leakage into the apparatus caused by faulty seals;[10] correct flow rate setting at the entry to the apparatus;[11] avoidance of premature deposition from DPIs by reducing the sample volume below the 4 L limit recommended in the pharmacopeial compendia;[12] selection of appropriate environmental conditions (temperature and relative humidity), especially for the evaluation of nebulizer-generated aqueous droplets;[13] and minimization of electrostatic charge accumulation on the inhaler and measurement apparatus.[14,15]

These findings provided stimulus for the idea that there may be scope to focus on the MAN and MACHINE components as the core component of a GCIP regimen. On the other hand, issues to do with either MEASUREMENT or MATERIAL aspects are more likely to be specific to the OIP product, and therefore less amenable to a general approach to risk management as a preventative for poor quality CI data.

More recently, the CI Working Group of the European Pharmaceutical Aerosol Group (EPAG) undertook an assessment of the feasibility of introducing GCIP as a means to help establish so-called "in-use" specifications in relation to the manufacturer design for the various compendial apparatuses.[10]

Figure 3 is a schematic illustration of the relationships they considered to be capable of being developed to define in-use suitability, focusing on the ACI and Next Generation Pharmaceutical Impactor (NGI) systems.

The following ideas were viewed as being needed at the heart of a GCIP regimen:

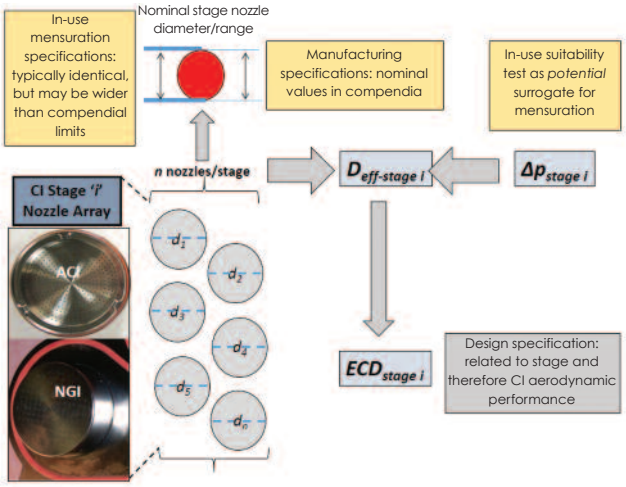
1. Confirmation, on receipt of a new CI, of conformance with the manufacturer specifications, comprising the nominal values of nozzle diameter with associated tolerance for a given impactor stage (from which the acceptable range of effective diameter values of new impactors can be calculated);

2. Confirmation, on receipt, of conformance with the compendial-specified dimensions of a new Ph.Eur./USP induction port and manufacturer specifications for a new pre-separator (if used);

3. Visual checks, to be made before each use, for defects that have been acquired in service to surfaces

Figure 3

The relationships between specifications for critical dimensions associated with CIs; d= diameter; D_{eff} = effective diameter; ECD = effective cutoff diameter; Δp = differential pressure



of the induction port and pre-separator (if used) that come in contact with OIP-generated aerosols;

4. Verification of the absence of leaks, carried out before each use, a process which can be accomplished by the measurement of the time-dependent pressure rise across the full CI system sealed at the inlet entry, after drawing a partial vacuum (applies to new or used CIs);

5. Setting of the volumetric flow rate that is correctly undertaken at the entry to the induction port before each use;

6. Periodic establishment with time-in-service of stage nozzle measurements from which effective diameter values for a used CI can be calculated.

This EPAG-led assessment went on to maintain that checks for leakage and the correct setting of volumetric flow rate at the entry to the induction port should be part of the procedure ***before every use of a CI system.***

Several of these ideas had already been identified by either or both of the PQRI-led[2] and IPAC-RS-led[3] assessments previously mentioned, lending additional support to their incorporation as part of GCIP.

The future of GCIP

A recently published Stimulus Article addressing the prospect for incorporating stage mensuration of CIs into the compendial literature as part of GCIP came to the attention of the current Aerosols sub-committee of the General Chapters Committee of the United States Pharmacopeia (USP) during its current (2010-2015) term of office.[16] Although this article was confined to considerations concerning the means of CI qualification with use to the manufacturer specification, its adoption of GCIP as a governing concept to

reduce risk of APSD measurement inaccuracy with repeated use has provoked discussion as to whether there is a place in the USP for an informative chapter (>1000 series) covering GCIP. At the same time, the removal of much of the data analysis section in the latest issue of the normative Chapter <601>, which describes CI-based methods for pMDI and DPI inhaler APSD assessments,[17] has provided an opportunity to incorporate basic data interpretation common to both types of OIPs, possibly as part of a chapter associated with GCIP. At the present time, feedback is being sought from the various cross-industry groups previously mentioned as to the possible content for such a chapter, before coming to a decision whether or not this approach is appropriate.

Concluding remarks

This overview has summarized the potential that exists to implement the GCIP concept as a management tool for purposes of minimizing the risk of measurement "failures" originating from man, machine or analysis during the aerodynamic size characterization of aerosols from OIPs. Discussions are ongoing concerning its possible inclusion as part or all of an informative chapter in the US Pharmacopeia on the CI method in support of the normative methodology already included in Chapter <601>. Regardless of what transpires at the pharmacopeial level, the user can already make use of the information provided herein to develop a regimen that will isolate potential methodology-based faults. Implementation of "in-house" GCIP can thereby enable efforts to be focused on the most important factor affecting the measurement outcome, which is the quality of the OIP being tested.

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Jolyon P. Mitchell is an Affiliate Professor at the Daniel K. Inouye College of Pharmacy, University of Hawaii, and owns Jolyon Mitchell Inhaler Consulting Services, 1154 St. Anthony Road, London, Ontario, N6H 2R1, Canada, Tel: +1 519 472-5364, jpmitchell@rogers.com.