

Implementation Challenges for ICH’s New M7 Guideline on Mutagenic Impurities Will Present Themselves at Both the Development and Post-Approval Levels

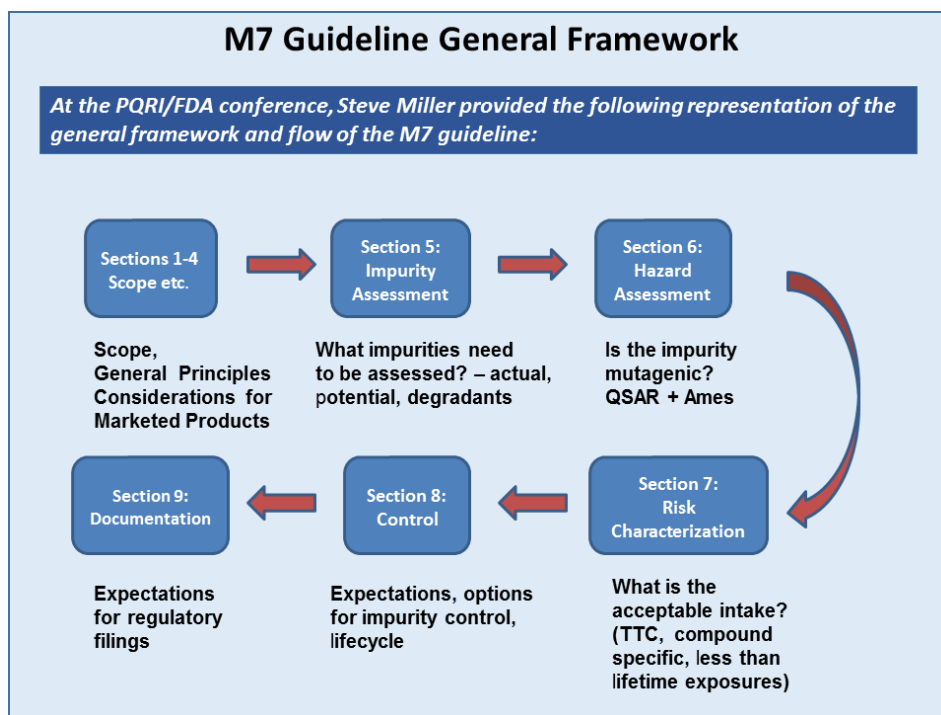
Among the challenges that will present themselves to pharma companies in implementing ICH’s new M7 guideline on mutagenic impurities is the use of quantitative structure-activity relationship [QSAR] predictions in assessing the risks during development and for post-marketing changes.

The expectation in the guideline is that two orthogonal QSAR systems plus the standard Ames test be applied where mutagenicity may be at issue both for products in development and those undergoing higher-risk-to-patient changes. QSAR represents a sophisticated set of physicochemical and statistical tools that some companies may have little or no experience with and will need to bring in-house and validate.

Mutagenicity risks should be evaluated, the guideline instructs, for post-approval changes involving new synthetic routes, new product degradants, or different dosage levels.

M7 was finalized at the ICH meeting in Minneapolis, Minnesota in June, and the Step 4 guideline was released in July. EMA formally adopted the guideline in late September. FDA and Japan’s Ministry of Health, Labor, and Welfare (MHLW) are expected to follow suit soon.

The primary final content of ICH’s elemental impurities guideline Q3D was also reached at the June meeting. The Step 4 version is expected to be released shortly ([IPO October 23, 2014](#)).



The 23-page M7 guideline is divided into nine numbered sections: • introduction • scope • general principles • considerations for marketed products • drug substance and drug product impurity assessment • hazard assessment elements • risk characterization • control, and • documentation.

Following these nine sections are additional pages that include notes regarding lab methods and calculations, and a table of examples of clinical use scenarios with different treatment durations for applying acceptable intakes. Also included is a glossary of terms used in the guidance, references, and two appendices covering the scope of scenarios for application of M7 and “case examples” to illustrate potential control approaches.

At a conference on “evolving product quality” cosponsored by the Product Quality Research Institute (PQRI) and FDA in mid-September in Washington, D.C, Office of New Drug Quality Assessment (ONDQA) CMC Lead Steve Miller, who served as a member of the M7 expert working group (EWG), discussed the general principles in the guideline and shared his insights on: • impurity assessment • impurity control, and • implementation challenges. [Miller’s complete remarks are provided in the full IPQ story.]

Miller addressed a conference session on international harmonization, at which Novartis Analytical Science and Technology Group Quality Operations Global Head Mark Schweitzer, the industry rapporteur on ICH Q3D, provided a Q3D review and discussed its implementation challenges (*ibid.*).

Other presenters at the session included: • BMS’ Mark Rosolowsky, who provided an overview of the most pressing harmonization issues now on the table • FDA’s Sharmista Chatterjee and BMS’ Ambarish Singh on the EMA/FDA QbD application pilot • BMS’ Peter Kitz on international inspection collaboration, and • Novo Nordisk’s Andrew Chang on the post-approval change management problem.

[A full review of Miller’s presentation and the discussions that ensued at the PQRI conference session appeared in the [October 2014 IPQ Monthly Update](#). By special arrangement, excerpts of IPQ’s extensive coverage of the September PQRI/FDA conference are being made available to the PQRI community. IPQ provides in-depth coverage of emerging drug and biotech CMC and GMP issues and developments with a mission of helping advance and harmonize the quality regulatory process globally. For information on how to take advantage of IPQ’s introductory company/organization license fees for 2015, contact Wayne Rhodes (rhodes@IPQPubs.com, (202) 841-9720) or Julia Zimmerman (zimmerman@IPQPubs.com). For more on IPQ, visit our website at www.IPQPubs.com.]

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