



COMPLIANCE NEWSLETTER

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# Compliance enforcement trends for the health care industry

## Quality Risk Management, a Retrospective

Long ago (2005), Quality Risk Management was implemented as an [ICH Guideline](#), after which almost all guidelines acquired a “risk-based approach”. In 2008, GAMP defined its “Risk-Based Approach” to computer validation via GAMP5. It doesn’t look like there is any activity to further develop the concept.

Most would agree now, that quality measures should be commensurate with the appraised risk, but this was not the mind set before 2005. Quality measures were conceived, e.g. Part 11, which pushed the industry to stretch technological limits, until a relaxed interpretation came in 2003, (during the rise of the QRM concept). We should be thankful that QRM has brought some realism to quality goals. It has been fully embraced in the practices of most regulatory bodies, where it is used to manage priorities with limited resources in a transparent manner.

Adopting QRM has introduced a formal documentation and management of risks into regulatory submissions, computer validation, and partially into operations. The FDA still accepts however, informal risk management methods, as declared in its [Guide to QRM](#): “The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.” What is acceptable should include at least

a determination of the appraised risks and the persons or organizations responsible for managing them.

The FDA frequently forces firms to make such appraisals in Warning Letters, such as when data integrity issues are observed; “A current risk assessment of the potential effect of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse in data integrity, and risks posed by ongoing operations.” It is clear that the responsibility lies with the firm and not with the regulators.

In the QRM interpretation of GAMP5 for computer systems, there must exist at least a System Risk Assessment, and in most cases a Functional Risk Assessment. The outputs of these activities are employed for guiding the design effort and later testing the system. Unlike technical risk assessments, there usually is no data or knowledge of the probabilities associated with these patient-, compliance-oriented risks, and pessimistic or worst-case assumptions are usually made. After countermeasures are completed, a lower residual risk value is usually assigned to the perceived risks.

The final QRM step is to review risks and monitor controls. Post-release operations are expected to include this in scope. Whether risks are updated with new information seems to be an open end in the concept.

Considering validated computer systems, one could expect that the initial risk assessments could be updated after years of productive use. However, the Operation Appendices of GAMP5, particularly O8, Periodic Review, do not explicitly include an update of risk assessments for mature systems, and the GAMP Good Practice Guide: Operation of GxP Computerized Systems only mentions in Appendix 3, that the periodic review “provides an opportunity to reconsider risk throughout the Operation Phase of the system”. It is commonly observed that validated systems typically have risk assessments which have grown with the system via the addition of new risks during subsequent release cycles, but still include original risks assessments. An often incomprehensible collection of identified risks can be the result. For the auditor, a Functional Risk Assessment may appear to document a risky system. This is at least one area where QRM could be developed further.

## FDA's New Mission: Promoting Domestic Manufacturing

The FDA has requested \$400 million in additional funding to indirectly [promote domestic manufacturing](#), and thereby fit-in with Trump's political agenda. A number of initiatives are vaguely described, and some have been previously announced. Apparently new is:

- Supporting domestic compounders, by fostering outsourcing facilities, via lowered market barriers, training, and other support in cooperation with state regulators;
- New Medical Data Enterprise – this database initiative should capture the data of 10 million patients to provide “near-real-time evidence evaluation” for both clinical and post-marketing studies at US healthcare facilities;
- Knowledge / Content Management Platform – This facilitator for drug development would be shared with innovators to speed-up the regulatory process.

While most of the listed initiatives do not explicitly favour domestic manufacturing, and global players could conceivably participate, it is clear that regulatory oversight will be sharing with industrial interests the top priorities at the FDA.

## Warning Letters of Interest

Only limited access to new WLs was available in February, while the FDA prepares the site for another year. Available, and of relevance, is the WL sent to Spanish [Casmara Cosmetics](#), an OTC drug manufacturer. The inspection occurred last May, before the implementation of the MRA, and the firm received an import ban just before the MRA went into effect. This inspection was not apparently a joint inspection with the EMA; no compliance report has been posted on the [Eudra GMDP website](#).

Included in the specified corrective measures are 2 risk appraisals of released product on the US market: risks associated with inadequate testing of active ingredients before product release; risks associated with product for which the stability of the active ingredients is not tested.

Similar WLs to OTC drug manufacturers were issued in [China](#) and in [South Korea](#), also resulting in import bans. At Indian, [Alchymars ICM](#), an API manufacturer, the FDA stopped short of an import ban, despite data integrity lapses.