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Serving Two Masters: Reconciling EMEA/GAMP 5 and FDA/cGMP Phase 1

Quality by Design can help satisfy both the results-focused outlook of the EMEA and the process-focused outlook of the FDA

Reconciling the requirements of the US Food and Drug Administration and the European Medicines Agency (EMA) can be a headache for large, well-established biotech organizations and a matter of survival for early-stage companies on a short financial leash. It's a delicate balance: companies do not want to maintain expensive and burdensome dual systems for meeting the requirements of both agencies, nor do they want to under-invest to the point that their investigational new drugs are rejected by either agency.

The FDA's July 2008 release of "Guidance for Industry: cGMP for Phase 1 Investigational New Drugs" (cGMP1)—whose EMA counterpart is "Good Automated Manufacturing Practices, version 5" (GAMP 5)—points up the dilemma anew. In the absence of an explicit harmonization document, the best approach to the problem is to understand the philosophical differences between the two agencies, examine the differences in the documents in light of those philosophical differences, and consider the most promising avenue for reconciling them: Quality by Design (QbD).



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PHILOSOPHY: SAFETY VERSUS ACCESS

To some extent, all regulatory agencies are involved in a dynamic tension between competing and often incompatible goals. The EMA and the FDA are charged by their respective governments to both ensure public access to drugs and ensure the safety of those drug products. If the agency focuses on maximizing the public's access to potentially beneficial drugs, it adheres to a policy of promotion, helping to ease the approval and the testing process. If, on the other hand, safety is the agency's

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primary focus, it tends to restrict access by maximizing pre-release analysis and testing.

For historical, legal, and political reasons, the FDA has traditionally emphasized safety (resulting in a relatively small, but presumably safe, pharmacopeia), whereas the EMA has tended to maximize access, allowing patients and their physicians greater flexibility in making their own determinations of safety. As a result, the EMA is generally seen by the industry as cooperative, helping to get drugs to market, whereas the FDA is often viewed as obstructionist, reducing access in the name of safety.

Not surprisingly then, the EMA focuses on the final drug product as tested in Phase 1 (and other phases), while the FDA spends considerable energy and regulatory capital examining the active pharmaceutical ingredient (API) and raw materials that precede the final product. In effect, the EMA tests for purity, and the FDA audits and back-traces for the same assurances. In other words, the EMA emphasizes the end product, and the FDA emphasizes the process.

Critical Differences

This fundamental philosophical difference between the two agencies—a focus on access and end product at the EMA versus safety and process at the FDA—help account for some important differences between GAMP 5 and cGMP1 in three critical areas: requirements for validation, QA/QC policy, and process monitoring.

The GAMP 5 guidelines have "automated" built into the name and the philosophy—they envision process and system (computer) validation as integrated entities. An automated process is tested with an installation, operational, and performance qualification to be certain that the automated

procedure has been properly installed, tested, and used.

By contrast, the FDA's cGMP1 document assumes a manual process with only tangential reference to the reality of automated process systems (covered by the FDA in a separate document, 21 CFR Part 11, which defines system validation and provides guidelines for it). In keeping with the agencies' philosophical differences, the EMEA stresses bottom-line performance, while the FDA stresses the process itself (procedurally and with automation). Under GAMP 5, a Phase 1 investigator would validate the results of an automated analysis system as a functioning analytical unit. Under cGMP1, an investigator would validate the analytical process and, perhaps, depending on risk, separately validate the analytical system that conducts the procedure.

Similarly, the EMEA focuses on quality assurance (QA)—the general overview questions—regarding a study: does it produce a reliable result with appropriate quality oversight? While still emphasizing QA, the FDA approach puts equal weight on the quality control (QC) process, including all aspects of production and operation as well as the final QA overview. The EMEA would potentially rely more heavily on a final quarantine and testing for the release procedure, whereas the FDA would augment it with step-by-step reviews of the manufacturing and clinical testing plan.

As for process monitoring, the EMEA GAMP 5 de-emphasizing of process differs significantly from the FDA's process analytical technology (PAT) initiative. Potentially, PAT provides near continuous and self-correcting

cybernetic monitoring of a procedure, method, practice, or course of action. The result is, again, greater reliance at the FDA on analysis at all phases, with a contrary reliance at EMEA on the final result rather than the interim steps that lead to that result—in short, process understanding versus process outcome.

The Path to Harmonization: QbD

The FDA's PAT initiative is just the first of three components of Quality by Design, a rigorously science-based approach to drug safety. QbD integrates an understanding of design space, a risk-based approach to compliance, and PAT monitoring. Together, those three elements can help satisfy both the results-focused outlook of the EMEA and the process-focused outlook of the FDA:

- Design space is defined in ICH Q8 as “the multi-dimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.”¹ Successfully defining the design space means achieving a full understanding of the various permutations of input variables and process parameters that ensure an in-specification product. Design space analysis establishes flexible operating parameters within which fluctuations are permitted, thus satisfying the FDA's emphasis on quality control.
- A full understanding of the mul-

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tiple, complex interactions among variables makes it possible to predict the outcome from particular permutations. It is then possible to ensure an acceptably low risk of failing to achieve the desired clinical attributes, thus opening the way for a risk-based approach to compliance.

- PAT's continuous and cybernetic monitoring of process parameters automates process control, satisfying EMEA's emphasis on testing and quality assurance.

Thus QbD promises to effectively harmonize the safety goals of the FDA with the access goals of the EMEA, without compromising either.

Even more promisingly, QbD can ultimately satisfy the QA bent of the EMEA and the QC emphasis of the FDA in a way that improves both. The ability to design-in product and performance characteristics from the beginning rather than deriving them through testing after the fact more efficiently meets EMEA's results and testing-focused requirements. Meanwhile, the analysis of design space satisfies the FDA's thirst for process understanding, while avoiding cumbersome re-filings every time a process parameter is changed. Biotechs that adopt QbD will not only be able to meet the differing EMEA and FDA requirements, but do so in a way that could significantly lighten their regulatory burden. ♦

REFERENCES

1. International Conference on Harmonization. Q8, Pharmaceutical development. Geneva, Switzerland; 2005.

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