

# 2006: A Regulatory Odyssey

**H**ere's a favorite factoid: Of the three billion base pairs of DNA that make up your genome (or mine), just 1.1% code for the proteins that hold us together and make us run (1). At the same time, 8% of our genetic material is left over from retroviruses that infected one of our ancestors and hopped into the germ plasm to ride the DNA train into the present (2).

Think about it: If our genomes are survival messages from the past, the evolutionary equivalent of junk mail outweighs all of the letters from family, the long-anticipated checks, the college admission letters, and birthday cards—by a factor of seven or eight to one.

On some level, all information-based systems behave that way: second-class mail clutters the wicker baskets on our hall tables; draft reports and long-superseded phone lists clog our hard drives; fossilized retroviruses and abandoned genes litter our chromosomes. Without pressure from the environment, these unused gobbets of information just accumulate.

Regulations and guidances are the DNA of pharmaceutical manufacturing, the high-level instructions that govern the production of the synthetic organics, polypeptides, and other compounds that make up the modern pharmacopoeia. Over the two decades since the invention of “validation,” we have accumulated a vast literature directive, interpretation, and commentary. We, the drug makers, have evolved in conformity with the growth of this literature and the “native lore” (in Ajaz Hussain’s phrase) that goes along with it.

But the environment has changed, and it is starting to sweep away some of the commandments on which we have relied, and to change others almost unrecognizably: In June, FDA withdrew seven chemistry, manufacturing, and control (CMC) guidances at a single stroke, referring manufacturers to a raft of International Conference on Harmonization (ICH) manufacturing and quality guidances (3). These emerging world standards take science-based manufacturing and continuous improvement as a given; our standard practice remains rooted in an unvarying adherence to an ossified process derived more from trial and error than predictive insight.

This will not be an easy transition. FDA will have to reinvent itself. We will have to rethink the way we develop and manage our processes. We anatomize some of those changes in this supplement: officers of the Office of New Drug Quality Assessment describe how the agency has restructured itself to make it easier to recognize and pass reasonable, science-based, postapproval changes; an industry veteran shows how to bring the QC lab closer to the line and real time.

Both sides have made missteps, and both sides will make more. Paleoanthropologists tell us that food-sharing was one of the earliest characteristics of emerging humanity, a defining evolutionary step that might have been the mother of planning and foresight . . . of rational thought itself.

At the foundation of the new regulatory DNA is a similar requirement: the regulators promise tolerance and understanding on their part in return for data and process understanding on ours. This is, technically, within our grasp. From here on, on both sides of the regulatory divide, success may depend more on courage than anything else.



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## References

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2. J. Paces, A. Pavlíček, and V. Paces, “HERVd: database of human endogenous retroviruses,” *Nucleic Acids Research* **30** (1), 205–206 (2002).
3. US Food and Drug Administration, “Guidance for Industry on Chemistry, Manufacturing, and Controls Information; Withdrawal and Revision of Seven Guidances,” *Federal Register* **71** (105), 31194–31195 (June 1, 2006), DOCID:fr01jn06-73.