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Trying to Address Probable Versus Possible Events

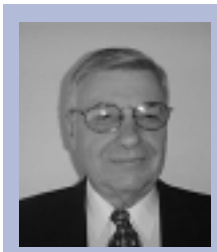
If we look back over some of the regulatory highlights in the development of the FDA, we find that virtually every step taken to increase regulatory authority was in response to some abuse in the marketplace. The 1906 enabling legislation was in answer to an ever-increasing crescendo of public outcries against adulteration, misbranding, and outright fraud in the market. That outcry was driven in part by Harvey Wiley's series of articles and press releases on toxic food additives, with the last straw delivered by the publication of Upton Sinclair's book, *The Jungle,*[1] which discussed the adulteration and fraud in the meat-packing industry in Chicago.* Although this legislation was targeted at adulteration and misbranding in commerce, its enforcement did not result in an immediate cleanup of the market; later legislation added to the enforcement authority, bringing about a significant improvement in commerce.

Similarly, the elixir sulfanilamide incident brought about premarket testing for safety, while the thalidomide fetal safety issue ushered in legislation for efficacy. Hold on: The thalidomide fetal safety issue brought about efficacy requirements? Herein lies one of the most interesting aspects of regulation; a negative action may precipitate a remedial reaction, an overreaction, or an unrelated reaction that was lying in the wings awaiting a break in the legislative process. The safety requirements following the elixir sulfanilamide tragedy were an obvious regulatory remediation. The passage of the efficacy legislation was precipitated by the thalidomide safety issue, although the existing safety regulations could have been used to address safety of fetuses.

> "VIRTUALLY ALL MODERN ANALYTICAL INSTRUMENTS ARE NOW COMPUTER BASED AND ACQUIRE PROTECTED RAW DATA FILES."

In this array of abuse reactions we find the generic drug fraud scandals of the late 1980s, which, to me, provides one of the most interesting recent regulatory reactions. These scandals included an array of fraudulent practices, including submission of fake products for bioequivalence studies, falsifying production records, etc., as well as incidents of bribery in the Agency itself. These

*Upton Sinclair wrote this book to bring to the attention of the American people the oppressive and exploitive living conditions of the immigrants working in the meat-packing industry. As he later noted, he aimed the book at the heart of America and hit them in the stomach (www.ssa.gov/history/sinclair.html).



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incidents gave rise to several different regulatory reactions. One of these, which in retrospect seems to be an obvious requirement (i.e., why weren't we doing it all along?), was the preapproval inspections to help ensure that manufacturers could in fact produce the drugs for which they had applied for marketing authorization. Several other issues brought about other remedial actions. However, the sheer scope of the fraudulent practices startled the FDA infrastructure and broke the faith in the industry–regulator climate. There is no question that blatant instances of fraud and corruption had occurred, and that the formation of watchdog groups, both inside and outside the Agency, was an appropriate preventative action. However, I feel there also was an overreaction or backlash mindset in some of the Agency perspectives; fraud had occurred in a very limited segment of the regulated industry and was not all pervasive. The overreaction arises from a paradigm shift from dealing directly with the originating provocative fraudulent event which, *de facto,* has an occurrence and detection probability, to the "what if" realm of the prevention and/or detection of any possible fraudulent event, e.g., the search for other provocative event possibilities and possible remedies stretching well beyond the scope of the originating event. This could also be summarized as a paradigm shift from preventing probable fraudulent events to attempting to prevent possible fraudulent events without regard to their probabilities or risks.

It should be noted that the generic drug fraud event was triggered by an investigator observing a discrepancy in record-keeping at one manufacturing site which, upon followup investigations at the firm's other sites, yielded additional fraudulent findings. Further investigations revealed additional instances of fraudulent practices in the industry. These findings have led to what I feel is an overreaction on record retention concepts that are stifling some innovations in record-keeping. These retentions may also confound the efficiency of future FDA investigations and findings due to the deluge of cloudy irrelevant data. In addition, these practices may reduce the adoption of new technologies, which could improve product consistency and uniformity at reduced costs. The FDA Center for Drug Evaluation and Research (CDER), in the recently announced risk-based GMP review, has undertaken a laudable initiative to revisit requirements and their enforcement for potential overreaction situations. It should also be noted that this overreaction was precipitated by records that were being kept; the highly regulated pharmaceutical industry could not successfully undertake a record-shredding frenzy to avoid detection.

The generic drug fraud record-keeping incident occurred at a very inopportune time for the move to greater use of electronic data systems in laboratories and production. Virtually all modern analytical instruments are now computer based and acquire protected raw data files. It is possible that a brilliant computer programmer could modify these files, but it is highly improbable that any analyst or operator could do so. However, analysts frequently massage these raw data files through various presentation manipulations to make the data more amenable to decision-making. These manipulations are the art and practice of analysis, and the various manipulations and massaging attempts should not be of regulatory interest. Only the raw data file and its meta data file and the final presentation file and its meta data file, which are the basis of the technical decisions, are relevant to ensure the safety, efficacy, and quality of the product. This data handling approach is used in chromatographic systems, nuclear magnetic resonance (NMR), etc. Retention of all iterations of the process of taking the raw data points through to the final presentation format is not only unnecessary, but this added data load may in fact deter future investigations due to the sheer magnitude of irrelevant data.

It is noteworthy that in FDA regulatory history, while actions have been driven by obviously blatant abuses in the marketplace, serendipitous findings of discrepancies in records, and substantiated reports from whistleblowers, distraught former employees, or concerned competitors, it is likely that serendipity and whistle-

> "GOOD AND EFFICIENT BUSINESS PRACTICES SHOULD ALWAYS PREVAIL IN MANAGING DATA STREAMS FROM ANALYTICAL AND PROCESS MONITORING INSTRUMENTS."

blowers have been the largest sources of findings of illegal activity. Although in retrospect the serendipitous findings generally appear obvious once discovered, 20–20 hindsight is not a useful guide for the design of the information systems of the industry. I do not believe that the retention of much larger amounts of records would have facilitated the serendipitous generic drug fraud finding; voluminous records may in fact have made that revelation less likely.

The revolution in pharmaceutical production led to abuses in manufacturing. This has been adequately addressed by the application of GMP and related regulatory concepts. These regulations have helped to define appropriate practices that provide a level playing field on which conscientious manufacturers can compete. The pharmaceutical industry is now being impacted by the information acquisition and handling revolution. That revolution, along with a "what if" mindset, have given rise to practices that are hindering advances in control technologies through interpretive projections; the advent of the information age and its attendant deluge of data have brought an overreaction to realities. However, this phenomenon is not limited to the regulatory side of the industry. For example, it was noted by Mitchell Hollander,[2] in his article on a late 1990s laboratory information management system (LIMS) implementation in the radiopharmaceutical R&D group at **Dupont Merck Pharmaceutical Co.** (Wilmington, DE) that the system had several problems, including: "The original system was over ambitious. There was an attempt to put strict controls on infrequently used processes, leading to complicated functions that were inflexible, difficult to understand and difficult to use properly." However, as ex-

plained in the article, the system had been designed to accommodate the GMP/GLP signature rules in the electronic format as well as other standard security safeguards, which made this aspect compliant with 21 CFR 11.

This pre-21 CFR 11 LIMS operation electronic record-keeping highlights the overreaction that frequently accompanies any situation change or revision on either side of the regulatory fence. The response to the innovation appears to be driven by what is *technically feasible* rather than by what is *technically necessary* to achieve the objective. In this instance, the computer technology allowed the development of an overly ambitious system with unnecessarily strict controls that led to "complicated functions that were inflexible" or were actually leading to LIMS paralysis. The tendency to move to the technology limits as a design basis leads to attempts to address all issues, both probable and possible, but unlikely. This approach seems to be a human failing that may be an endemic issue both in our regulated industry and their regulator counterparts. Hollander noted that in the redesign of the system, "The team felt it was important not to yield to the temptation of trying to build every conceivable control over user practices in the system" because "Experience showed this could lead to a hard-to-maintain mess." The design team also dismantled a set of custom controls for managing repeat testing since this aspect "had some of the most complicated programming logic behind it . . . it could be readily replaced by a set of 'manual' procedures." This move to a hybrid electronic LIMS, coupled with a manual entry stream, simplified the overall system operation. Good and efficient business practices should always prevail in managing data streams from analytical and process monitoring instruments. The data streams into the LIMS should be rationalized for optimum efficiency while maintaining the data integrity.

The bottom line on this business is that it is wonderful that CDER has risen to the task of visiting the regulatory environment from a risk or probable basis rather than from a seat-of-the-pants or a *technically possible* perspective for possible, but unlikely, events. The regulated industry and their scientists deserve this relief so that they can proceed with research, development, and control improvements that will reduce costs and bring improved products to our markets. Serendipity and whistle-blowers will come along to help police the process regardless.

References

1. Sinclair U. The jungle. New York, NY: Bantam, 1906 (http://sunsite.berkeley.edu/Literature/Sinclair/TheJungle).
2. Hollander M. Application of part 11 to a LIMS. Am Pharm Rev. Summer 2002:116–20 (www.americanpharmaceuticalreview.com/past_articles_f.htm).