DDT Vol. 8, No. 13 July 2003

Multisite clinical trials in strict accordance with GMP standards?

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The notion of conducting and managing multisite clinical research trials in strict accordance with the FDA's GMP standards has received little notice to date. For those companies that do use such an approach, there is the promise of dramatically streamlining the market approval process, market entry years earlier than ever before, lower R&D costs, greater profit margins, and significantly extended exclusivity time frames. This article looks at what the future holds for global research using today's technology and provides a clear roadmap showing how to get there efficiently.

For readers that might not deal directly with government agencies regarding drug product approval process applications, here is an example.

'We explained that the question was really addressing the issue of audit trails and not whether a record is covered by part 11. We commented that, as explained in the final rule preamble, the requirement for audit trails does not apply to actions of devices but to the actions of human operators. We explained that the programmable logic controllers and data loggers that record information to required records without human intervention need not have audit trails, but they must meet other relevant portions of part 11.'

'We commented that whether or not the recording media was durable, and whether or not a system had the capacity to generate an audit trail, did not determine part 11 applicability. We explained that the question appeared to relate to a preamble comment that clarified the agency's intent that audit trails need not capture every keystroke stored in a temporary buffer [1].'

As the industry moves towards electronic submissions of applications for market approval, the issues surrounding what information is covered in 21 CFR Part 11 (this is the location in the Code of Federal Regulations for much of the drug application regulations) are continuing to evolve and, hopefully, crystallize. However, as the above quote suggests, there is still some way to go before a clear and efficient electronic method of communicating with the regulatory authorities is established. To get there requires creativity and risk taking. Towards this end, this article discusses one approach that promises to shorten the process, cut expenses, and streamline the regulatory oversight requirements for companies seeking faster, more efficient access to markets around the world.

Background

In many of the world's product approval process systems multisite clinical trials are crucial requirements before submitting a formal application to market a product. The term, multisite clinical trials, has expanded in meaning. We now see the equivalent models in outcomes research, nationalized healthcare initiatives, postmarket surveillance requirements, ongoing healthcare-related tracking systems or registries, and, what the FDA calls, 'large simple trials' [2]. Multisite clinical trials models need to provide solutions that streamline productivity and lower transactions costs for many of the businesses that make up the healthcare industry. The ability to produce standardized applications once, and have them recognized around the world, promises increased profits, lower R&D costs, and greater productivity for companies. To this end, the concept of electronic oversight is applied. Electronic oversight is a term that speaks to the ability of regulatory authorities to monitor and manage healthcare product market applications. It is inevitable that this term will become familiar to all participants in the product approval process. What this term will mean will be determined by those who help to shape it.

A centralized Network Operations Center will monitor electronically all clinical research as it is being conducted. Accountability will lie with the validity, accuracy, and reliability of the data presented. The systems approach to provide the level of integrity of clinical research data to the industry must be one that is nonproprietary, cost effective, and one that provides a high level of incentives. Uppermost among the incentives will be the opportunity to enter the marketplace at the earliest possible moment and to conduct and manage requirements in a postmarket posture.

Regulatory history in a nutshell

As recently as 1987, the FDA, although still entrenched in a paper-driven system, expressed its need to provide patients with earlier access to much needed medications. They accomplished some of their goals by using programs designed to balance the need for early patient access, with the counter-prevailing need to maintain patients' interest to participate in clinical trials. These efforts did not address the need to assure regulators that valid data were

 1359-6446/03/$ – see front matter PII: S1359-6446(03)002691-6

provided to support product safety, efficacy, and benefits. By late November 1992, the FDA implemented the Accelerated Approval Policy, which gave companies the opportunity to work with the FDA early in the clinical research phase, in exchange for approval on an accelerated basis.

Without a full understanding of a drug's characteristics, however, it becomes problematic to optimize the usage of a new drug. To complicate matters further, the Accelerated Approval Policy was theoretically advantageous to both regulatory authorities and to the industry, but, in practice, it failed miserably. The general consensus was that when the FDA was given information early on, they still had a problem relying on the validity of the data being reviewed. This resulted in some delays, and inevitably, the time savings were diminished by the lack of action by the FDA. This delay in information processing resulted in costs running as high and times running as long as if the drug had not been entered on a 'fast track' program. Again, we see little attention paid to the one issue that could have made the most impact, and that was the need to reassure regulators that the data presented were valid and reliable.

CFR 21 Part 11, finalized in August 1997, attempted to bridge the gap between a paper-driven system and the new electronic systems approach envisioned by both the industry and the FDA. An obvious focus was placed on the validation of signatures and the secure retention of records generated by electronic means. Hindsight provides clear and convincing evidence that regulatory interests in receiving accurate and reliable data have continued to be a secondary interest to steps leading to a faster and more efficient product approval process.

Electronic submissions

For many the term, electronic submissions, means ESTRI, which stands for Electronic Standards for the Transmission of Regulatory Information. Some might know this term better as the FDA ESTRI Gateway. Its purpose is to put a centralized, agency-wide gateway into the day-to-day operations for receiving regulatory submissions securely and electronically.

Several years ago, initiatives began for the electronic exchange and review of regulatory information. These included Drug Application Methodology (DAMOS), which included optical storage sponsored by a 17 member drug company consortium, the Multiagency Electronic Regulatory Submission (MERS), Market Authorization by Network Submission End Evaluation (MANSERV), Electronic Submission for Market Authorization (SEDAMM), and, of course, the ICH multidisciplinary group (ICH-M2). Each of these initiatives sought to solve the issues related to the faster and more streamlined application and review by regulatory authorities. However, none provided a level of reassurance that the data presented were accurate and reliable. Without such reassurance, there could be no way for a reviewer to move forward in the decision-making process without first investigating and performing an evaluation of the validity and accuracy of the data.

As Ronald D. Fitzmartin, from Purdue Pharma LP, in his article, 'The challenge of global electronic submission standards in the biopharmaceutical industry' [3], stated, 'The international drug development environment is characterized by tremendous pressure to reduce healthcare costs, increasing government regulations, longer product development time, and shorter marketing exclusivity.' That was in 1998. At what point, then, can we expect this timely statement to go out of fashion?

Product approval process

Requirements for the product approval process include laboratory research, clinical research, and the review and approval phases. Within the clinical research phase, there are essentially three phases: phase I, phase II, and phase III. Oversimplified, each phase is designed to provide information that the FDA can use to base its decision on whether to approve a drug. Each phase is seen to include progressively larger and larger patient populations. In completing the requirements for the clinical research phase, companies average some six or more years of time, costs, and effort to gather the data that will comprise the arguments favoring a product's approval. Upon receipt of the formal application the FDA then reviews the arguments and makes its decision. One would expect this to be a straightforward process, guided by FDA regulations and guidelines, to ensure that a complete and thorough analysis and evaluation is carried out by the government.

Without going into detail, the above description attempts to impress upon the reader that there is an underlying standard approach to market approval. It is time consuming, impacts directly on a company's market exclusivity and return on investment, and is highly dependent on the FDA making decisions in a timely manner.

Many would argue that if one receives accurate, reliable data, the ability to make decisions is optimized considerably.

Blueprint for the future

Historically, product approval in the US has been premised on a decision that gives final approval or rejection. There has been no 'conditional' approval status as such. With the advent of electronic submissions, the opportunity to consider a conditional approval presents itself (Fig. 1). Are there advantages to such a system?

The Accelerated Approval Policy of 1992 envisioned a conditional approval status that would enable companies to enter the marketplace early and to

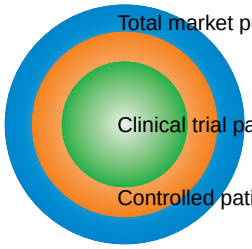

Figure 1. Graphic representation of conditional approval markets.

complete requirements in a postmarket posture. Building on that, one would expect such a system for the conduct and management of clinical research to contain the following characteristics:

- a closed, PC-based, dedicated network of computers;
- dedicated telephone lines from each research center or office;
- the typical team consisting of monitor, chief investigator, support technician, Institutional Review Board, clinical laboratory, FDA Review Committee, research investigator(s), and a repository for data

What is unique about this systems approach, as it exists today, is that it uses a streamlined audit trail capability that captures data entry at the keystroke level for each 'session', and allows visual playback, similar to playback for video tapes, keystroke by keystroke at a later date. Thus, all fields are controlled for changes that might be made and explanations are available for inspection. As a result, a central Network Operations Center approach is able to be cost-effectively placed for each clinical trial protocol.

Using this systems approach, which is not dependent on the internet and is considered to be somewhat primitive in its configuration, a company is able to gain early access to FDA personnel, and, in return, to expect the level of decision-making that would enable companies to move forward into the marketplace in a timely fashion.

Once a company receives conditional approval for a drug with a restricted marketplace, further research will allow the marketplace to be enlarged, and, over time, complete the requirements for final approval. It is the ability of the private sector to make a clinical research environment possible for regulatory oversight, which leads to timely decision-making by regulatory authorities, that sets this systems approach apart from all the others.

The audit trail mentioned above uses nonproprietary keystroke capture, which timestamps each keystroke. It files these keystrokes and permits playback, visually, keystroke by keystroke. At the end of a 'session', the directory containing the files is labeled and stored; reviewers can recall such 'sessions' at any future date. This method of tracking field changes enables audit reports to be generated and it allows convenient tracking from the 'source' to the final expert reports and application submissions to the FDA. The audit trail feature is nonproprietary, so no company has an advantage over another, which has led to industry-wide acceptance to use such a feature and has encouraged the global harmonization of research results to be recognized.

Companies that use such a systems approach will benefit on several levels. The first, and most obvious, advantage is early market entry, which could be months to years earlier for their products. Now, consider a drug company that has market approval for a product in one country. It seeks approval in a second country, and, because it will use the systems approach for meeting the requirements of the second country, it has a compelling argument for immediate, conditional approval and to conduct any requirements in a postmarket posture. It is not unreasonable to expect that the regulatory authority, with the ability to monitor not only the patients within a specific trial protocol but also those who would be purchasing the product, to be monitored as well. As the requirements are met and the results are evaluated, this surrounding marketplace is enlarged, eventually leading to final approval.

The second advantage is that the FDA, or regulatory authority that participates in such a systems approach, is reassured that the data being reviewed are accurate and reliable. The FDA knows that the data are accurate and reliable as soon as the system is formally executed, under the guidelines described above. If the data are accurate and reliable, then the decision-making process becomes efficient and timely. The phrase, 'the data speaks for itself', leaves the regulatory authority accountable for its decision-making schedule. Under the Accelerated Approval Policy of 1992, as it was envisioned, the early participation by regulatory authorities would enable both sides of the product approval application to operate as a team. This vision becomes a reality under the systems approach described above.

The third advantage is that a Network Operations Center not only enables the FDA, or regulatory authority, to actively monitor a clinical research protocol, but also it is scalable so that it can monitor all research on a global basis. The costs of such a center are easily demonstrated to be less than the costs of the present systems approaches being used and considered. This is simply because there is no present systems approach used, or being considered, that relieves the regulatory authority of the expense of validating the data presented.

In the systems approach described above, one sees that three new operations are now in place. The first requires that the Institutional Review Board receive a computer on which specific information appropriate to the responsibilities of the Institutional Review Board is present. The second

requires that the clinical laboratory information be collected and made available before entry into the laboratory's database management system. In other words, the raw results from 'runs' (laboratories will batch samples for testing and refer to these batches as 'runs') will be archived directly from the laboratory testing equipment. The third requires that the FDA Review Committee receive a computer on which specific information appropriate to the responsibilities of the FDA Review Committee is present.

These three modifications to the present clinical research data collection systems approaches used by the industry serve to speed up the overall process and allow companies to begin generating revenues years earlier than would otherwise have been possible.

Patients need access to low cost medicines. They need early access and they also need to be able to measure the risk associated with a particular product. The systems approach described above addresses these needs in surprising ways. Electronic oversight allows the tracking of patients, from the innermost circle representing clinical trial patients, to an expanded, but 'controlled', patient population, to the fully expanded market.

The Safe Medical Device Act of 1990, calls, among other things, for the tracking and monitoring of some devices over the life of the device. The entry of a patient into an Outcomes Research Protocol will most probably track and monitor that patient throughout his or her life. These are but two examples of what we can expect in the future for healthcare around the world. Patients will be tracked and monitored for regulatory purposes. It is to their advantage, as well as to the pharmaceutical companies, to begin to explore how such strategies can benefit us all.

Summary

This article reviewed some of the aspects of conducting and managing clinical research in strict accordance with GMP and offered some reasons why a shift to stricter levels of oversight and clinical research requirements might be advantageous to companies seeking market approval for their products. Electronic oversight is a term that will inevitably pervade all aspects of pharmaceutical development. We now have the opportunity to help establish those requirements for electronic oversight that best serve the industry and patients, by providing advancements in scientific research on a global scale.

References

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