

## Biotech Warning! Your Compliance is Required



### 21 CFR Part 11

Compliance is coming, and the implications for Canada's biotech industry are huge.

If you're not sure what that means, read on because it could be the single most important factor influencing time-to-market: attempts by the United States Food and Drug Administration (FDA) to require biotech companies to submit selected information in electronic format. If recent initiatives demonstrate anything, it won't be long until the FDA only accepts submissions in electronic format.

Consider this a not-too-distant early warning. Some think this could happen as soon as next year. This warning, however, is not intended to incite fear, but to demonstrate that compliance is an opportunity, not a threat. For the swift and the bold, it is an opportunity to innovate and gain a competitive edge. It is an opportunity to significantly shorten time-to-market, decrease submission costs and increase shareholder value.

Biotechs need to know the benefits of electronic submission programs and what makes a good e-submission program. But they should also know why, in the near future, they won't have a choice and will be required to be 21 CFR Part 11 compliant.

#### Background

First published in 1997, *Title 21, Code of Federal Regulations, Part 11* (21 CFR Part 11, or Part 11) outlines procedures and controls for ensuring authenticity when electronic records and signatures are used. Biotechs that comply with 21 CFR Part 11 criteria can replace cumbersome paper records and signatures with electronic records and signa-

tures, allowing them to streamline FDA submissions.

Part 11 does not actually require companies to adopt electronic processes, but it regulates the procedures for those that do.

However, this all changed in May 2002 when the FDA proposed its first regulation to *require* submission of information by electronic means.

If passed, certain labelling submitted for review with new drug applications, certain biological licence applications, abbreviated new drug applications, supplements, and annual reports would only be accepted by the FDA if submitted in an electronic format compliant with Part 11 guidelines.

The FDA temporarily backed away from this regulation in September 2002 because of concerns expressed by the biotech industry — specifically, that certain interpretations of Part 11 were restricting the use of electronic technology and the regulation would significantly increase the costs of compliance.

Since then, the issue has been in constant flux as the FDA has issued and withdrawn several Part 11 guidance reports.

#### It is Only a Matter of Time

Had it been finalized, the regulation would have been the first time the FDA required submission of information by electronic means. It would also have been the FDA's first regulation issued under U.S. President George W. Bush's E-Government initiative.

When the regulation was first introduced, U.S. Health and Human Services Secretary Tommy G. Thompson said, "This is part of the larger effort President Bush has ordered to use electronic data technologies

to improve the federal government's efficiency and our service to Americans."

With direction coming straight from the top, it really is only a matter of time until all FDA submissions will have to be in an electronic format that complies with Part 11 regulations.

#### Why Wait?

Given the efficiencies of e-submission programs over traditional, paper-based programs, and the inevitability that the FDA will only accept e-submissions in the near future, there is no good reason why a biotech should wait to become Part 11 compliant.

Ignoring — for a moment — that compliance will be forced upon biotechs in the near future, let's look at the advantages of an e-submission program and judge it on its own merits.

#### Reduces Submission Costs

First and foremost, an effective e-submission program reduces the cost of producing FDA submissions. Fewer resources are required to assemble, copy and organize necessary documents. Given the volume of printing required for a paper-based submission, there is a substantial cut in printing charges. There is also a significant reduction in shipping costs.

At first these cost savings may seem trivial, but anyone who has been responsible for organizing and shipping boxes and boxes — containing tens of thousands of pages from laboratories all over the world — to the FDA will tell you the cost savings are very substantial.

## Likelihood of a Faster Review

There is no guarantee that electronic submissions will result in a faster review, but they are greeted favourably by the FDA because they are easier to process. Paper submissions document the entire drug-development process, from clinical trial data to formulation and manufacturing information. Simultaneously working with multiple volumes of paper is laborious and time-consuming for an FDA reviewer. With electronic submissions, the reviewer can easily jump between sections.

In fact, when the FDA introduced its first requirement for Part 11 compliance concerning labelling changes for New Drug Applications (NDAs), Biologics License Applications (BLAs) and Abbreviated New Drug Applications (ANDAs), its rationale was that it would enable more rapid and accurate review of the labelling content. This part of the review process involves conducting word-for-word comparisons to ensure accuracy and currency of the information submitted.

FDA deputy commissioner Dr. Lester Crawford, PhD, acknowledged the benefits of the regulation when it was introduced, citing the capacity for computer matching to perform faster, more precise comparisons.

## Simultaneous Submission to the Largest Markets

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which includes representatives from regulatory authorities and industry in the U.S., Europe and Japan, has been working toward standardizing key parts of drug approval submissions for its member states. It has created two submission formats for the purposes of standardization: the common technical document (CTD) and the electronic common technical document (eCTD).

The eCTD is now accepted in Europe and the U.S. It is expected to be accepted in Japan next year. By implementing an e-submission program based on Part 11 and the eCTD, a biotech company will gain the ability to simultaneously submit to the three largest pharmaceutical markets in the world.

## Keys to a Strong e-Submission Program

Implementing an e-submission program won't cause a massive shock to the system because 80 per cent of what Part 11 calls for is good business practice anyway. Generally, an e-submission program needs to be accurate and reliable. It needs to show who created the information, who has access to it, who can view it and who can change it.

The four most important elements to implementing a successful e-submission program are planning, people, process and technology. Based on the technical requirements and benefits to be gained by an e-submission program, it is recommended that biotechs start planning as soon as possible for the changes required. To delay while the rest of the industry – including the regulatory agencies – moves forward constitutes a missed opportunity.

It is crucial for an e-submission program to have trained personnel who have bought into the project. It is also important to ensure that the project team is balanced between IT staff and the regulatory and business staff. IT's primary role is to address issues related to Part 11, but it is not advisable to let IT drive decisions without reflecting on your organization's business issues. The project team also needs to work externally with the FDA, as it requires consultations four to six months ahead of a planned e-submission.

E-submission programs and document management systems are all about data attribution, so process should reflect this. A biotech company needs strong, accessible standard operating procedures and manuals that reflect how the company does its business. The FDA will also require proof that the company follows its own procedures. Standard operating procedures need to be in a non-corruptible form, and it should be demonstrated that they are easily accessible by the required staff.

As expected, technology also plays an important role in e-submission programs. The computer systems need to enhance, not hinder, a reviewer's ability to deal with an electronic document. It is essential that those systems enable proper online book-

marking and hyperlinking. If you send the FDA an electronic submission that is not compliant, it will be sent back and cause delays. Your computer systems should also include an audit trail feature that allows data to be tracked through every stage of the information-sharing and information-flow process.

Risk assessment must be accounted for as well. This is the potential of the computer systems to affect product quality and record integrity. An e-submission must provide documented evidence, to a high degree of assurance, that the computer systems perform their intended functions accurately and reliably in their associated operating environments. It also needs to provide an infrastructure that will ensure the computer systems will be supported by sufficient documentation throughout their functional lifetime.

Compliance is coming, and in the near future all biotech companies will be forced to implement e-submission programs. For this reason, biotechs need to start thinking about compliance now. Those that act now will not only prepare for the inevitable, but also benefit from the advantages and gain a significant competitive edge.



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