

December 15, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

RE: Docket 2006N-0464 - Electronic Submission of Regulatory Information, and Creating an Electronic Platform for Enhanced Information Management; Public Comment - Hollister-Stier Comments for Consideration

The FDA requested public comment on Docket 2006N-0464 in the Federal Register of November 21, 2006. Below are Hollister-Stier Laboratories' responses to the questions posed. Hollister-Stier is a manufacturer of biological products (allergenic extracts) as well as a contract manufacturer of both biologics and drugs. Hollister-Stier does not intend to participate in the Public Hearing scheduled for December 18, 2006.

A. Electronic Submissions

1. Transition from Paper Submissions to Electronic Submissions

- "If you are not voluntarily submitting such applications electronically, what are the reasons?"

We currently have one Drug Master File submitted electronically with CBER. We have four other Drug Master Files with CBER, one DMF with CDER, and 21 existing approved BLA applications which have been paper-filed. The one DMF filed electronically is being used as a test of the electronic system. Until such time that internal eCTD software is implemented, likely no other submissions will be made electronically, as the acceptance of electronic media is different for CBER (linked PDF) and CDER (eCTD XML only).

- "Are you electronically submitting any portion of your premarket application? Is the portion specific to product type or premarket application?"

We don't have premarket applications, but existing annual reports and amendments continue to be paper (other than the one CBER DMF that is electronic).

- "What are the major impediments to an all-electronic submission?"

The lack of a document management system capable of producing the electronic XML backbone for file creation is currently our limiting factor. CBER continues to allow hyperlinked-PDF files, but CDER has quit accepting DMFs in that format and only accepts XML based eCTD submissions.

- "How can FDA best address these impediments?"

Since Hollister-Stier is not equipped with an eCTD capable document management system, continuing to accept some filings in hyperlinked PDF system through both divisions (CBER and CDER) would be beneficial.

- "Are there certain types of premarket applications or portions of applications that would be more difficult to submit electronically? Why?"

We mostly provided CMC information in Module 3 of the CTD, and none of these would be more difficult to submit electronically. Sponsors with large clinical databases, however, will likely have more difficulty.

- "Are there specific issues related to electronic submission of a premarket application that are unique to small companies, academic institutions, and government agencies? If so, what are they and why are they unique?"

We are considered a small company (under 500 employees), and our major impediment is the cost of document management systems currently available in the marketplace. This is not unique among entities that have less capitol resources.

- "In addition to the sponsors of premarket applications, are there other sectors of FDA regulated industry that would have to make adjustments in business practices in an all-electronic submission environment? Please describe any such adjustments?"

As a contract manufacturer, we are not the sponsor of an application, but supply information to the sponsor for inclusion in their application. We have to be able to support sponsors in an electronic manner, so at this point we do not need XML eCTD file structures to support their document needs.

- "In your opinion, what internal expertise is needed for firms to make the transition to an all-electronic premarket submission? Do firms have this expertise?"

Firms need to have Regulatory professionals that understand the specific eCTD requirements and are computer-savvy enough to deal with the IT infrastructure issues. In our experience, IT personnel don't understand the regulatory requirements which make implementation difficult. Our firm is starting to get this expertise, but it is largely based on review of existing guidance. XML programmers could be utilized for the programming, but this is labor intensive compared to automated systems designed to create these files.

- "Is the labor market ready to accommodate industry's demand for such expertise to convert applications in an all-electronic submission environment?"

The labor market is not ready to accommodate applicant's demand. Regulatory professionals that also have the IT technology knowledge are difficult to obtain, and compensation packages for the most capable are beyond the reach of smaller companies and academic/government institutions. While there are IT personnel available, without knowledgeable Regulatory personnel to train them on assembling a submission, this resource is less helpful.

- "Are there enough entities available to provide such services or tools in support of this effort? If not, how long would it take for these services to become available?"

There are sufficient services and tools available in the marketplace, but cost makes them prohibitively expensive. Because submissions are a life-cycle, outsourcing support only makes short-term sense. Companies over the long-term have to make the tools available to allow in-house life-cycle management.

- "How would an all-electronic submission environment benefit you?"

Electronic submissions improve the ability of people throughout the company to see what has been submitted without having to find paper documents. It will also provide improved change history throughout the life of the submission.

- "Would an all-electronic submission environment change your ability to initiate in a timely manner the studies supporting your regulatory submission?"

In the short-term, electronic submissions take longer to prepare. While document creation time is unchanged, document assembly takes additional resources. In the long-term, once document management systems are in place and personnel are trained on their use, it should take less time to prepare submissions, and ultimately decrease timelines.

2. Cost

- "What do you estimate as the cost burden to you if all premarket applications and related documents are filed electronically? What is the breakdown of cost?"

The cost burden is largely in up-front capital and labor costs. Purchasing, installing, and training personnel on a document management system would be required before filing documents electronically. Initial costs can start at \$50k - \$150k for software, with installation and training consuming several thousand man-hours. This is likely a total cost burden starting at \$200k+. Once the system is in place, the cost of electronic applications is less than existing paper submissions.

- "Would these costs differ depending on the type of entity providing services related to the application?"

The upfront costs could be minimized by using third-party vendors for submission assembly. However these submissions are designed to be life-cycle events, not one-time events, this becomes a difficult business strategy because you are outsourcing routine work. Business would lose control of the ability to timely submit information and be reliant on third-party vendors for indefinite time periods.

- "What additional costs are associated with implementing a particular format or standard for an electronic premarket submission?"

Document management systems that create an XML-based eCTD submission are usually all-inclusive and wouldn't require additional costs beyond what has been outlined. Making a submission in a linked-PDF format (as our existing CBER DMF has been filed) removes all upfront costs as it uses standard desktop authoring software. While this format removes costs, there are potential issues with using it as a life-cycle document, as it is still manually developed and will likely have errors as amendments are made. CDER and other global regulatory agencies have either stopped or never allowed these types of submissions.

- "What would be the costs associated with providing an all-paper electronic submission compared to an all-electronic submission?"

An all-electronic submission is likely less expensive than an all-paper submission once a system is in place. Developing the system will require substantial upfront capital and resource commitment prior to submitting the first all-electronic submission. Subsequent submissions and life-cycle management will not require binding/copying/delivery costs.

- "Are there parts of a product application that are more costly to convert to an electronic format than others?"

The change to Structured Product Labeling (SPL) is more costly because this currently needs to be outsourced. As document management systems evolve, most are including SPL support. Once SPL can be generated in-house and documentation systems are in place, cost will not be an issue.

3. Time

- "How much time would be required for preparation to submit the entire application in an electronic format; or a portion by an entity providing services related to an application?"

In our experience creating a hyperlinked-PDF submission, it took about 120 hours of preparation beyond what was required for a paper submission. This would likely be

significantly reduced once a document management system was in place that would automate many of the processes by using the XML eCTD backbone. This is assuming the up-front labor to install and train on a new system is completed. This time would be greatly reduced by outsourcing this work, but at a cost of loss of internal control of our document life-cycle.

- "How long would it take you to prepare and submit an application electronically under the current format accepted by FDA for voluntary submissions?"

It would likely take us 80-100 hours beyond a standard paper submission to convert additional DMFs in CBER to a hyperlink-PDF based submission, based on our experiences on the first one. This format is only accepted by CBER, as CDER has stopped accepting this format.

- "How much time would you need to make a smooth transition to a new electronic submission?"

It would likely take 4-6 months after the purchase of a document management system to begin the process, and 1-2 months to submission. Initiation of the process is a business decision that will be up to management to devote capital and human resources to the project. This could be a process of months to years.

- "How would your estimated time differ for various product types or applications?"

For both our DMFs and our existing BLA applications, all documents are already available as word-processed electronic documents. Converting them to electronic submission documents should not take large differences in time.

4. Implementation

- "Should we consider an incremental phase-in implementation strategy for an all-electronic submission environment? If so, what should the strategy include? What is the order of priorities for phasing in implementation?"

An incremental process has advantages and disadvantages. The incremental process should likely be a phase-in of submission types, rather than sections of documents. The SPL requirement has already started the requirement that at least a portion of the submission be electronic. Expanding this to include clinical or CMC section and not other sections will likely cause confusion, especially over the life-cycle of the product when eventually the application would be all electronic. Making new NDAs/BLAs electronic, followed by new INDs, followed by existing INDs, followed by other existing approved applications would provide time for existing documentation to be made electronic.

- "What steps can we take to minimize the cost or other burdens of transitioning to an all-electronic submission environment?"

The FDA would likely have little influence over the cost that third-party software development firms charge for existing software packages. If alternatives were made available at lower cost, that would decrease the financial burden on sponsors.

- "What additional standards or revisions to current electronic standards would be helpful to make electronic submissions work?"

Much of the existing standards are written by IT technical personnel, and not for an audience that is largely non-IT. Much of it deals with the specific format of the XML files, which is useful to the software development vendors, but not to end users. A basic overview of the standards may be needed. Also, there is existing guidance for INDs, NDAs, and BLAs (which conform well with the structure of the eCTD), but there is little guidance for Drug Master Files, Adverse Event Reporting, and other document types that need to be filed. Specifically, we have noticed that sending Letters of Authorization to a Drug Master File increase the submission number, effectively being another submission. If this is the case, these would also have to be updated electronically and not summarized at the next annual report.

- "Are the tools and formats currently available for FDA electronic submissions adequate? If not, why? What is needed?"

The XML tools appear to be adequate, but cost can make them difficult to obtain.

- "Are there other submission mechanisms more suitable and beneficial than what is currently available?"

The eCTD system is recognized as the new standard, so other mechanisms would lack this uniformity.

- "Are there factors for harmonization with other government entities, the private sector, or foreign regulatory authorities that could reduce costs or increase the benefits of electronic submissions?"

Software packages/vendors should be reviewed and/or rated by the agency, or third-party reviewers, that their systems do comply with existing FDA and ICH guidance. This would allow sponsors to make knowledgeable purchases of systems with a known history of meeting FDA expectations.

- "Would issuing guidance be useful in helping with the transition? If so, what topics would you like addressed?"

Additional detailed guidance, specifically written for the non-IT audience, is always appreciated. Two guidances that we would like addressed are: 1) conversion of

existing paper document applications to an electronic system; and 2) FDA expectations for sequence numbering.

B. Third Party Entities

- "What are your general viewpoints on a third party entity or entities providing services related to such an electronic platform?"

A third-party entity is acceptable as long as it is a behind-the-scenes activity developing/running the platform. Applicants should not have to go through a third-party to communicate with the FDA. FDA is already using a third party for the Electronic Submission Gateway for the technical aspects of the system, but the communication is still with FDA. Data should also not be available to the third-party, as confidentiality issues related to clinical outcomes should only be reviewed by FDA.

- "What are your views on the establishment of a public-private partnership to initiate formation of an electronic platform?"

This would generally be acceptable. FDA shouldn't have to focus on IT development issues of the platform when it should focus on usability issues and make sure the system functions. Development should also include sponsors of different sizes. Large pharmaceutical companies tend to dictate based on their systems, rather than focusing on the needs of small business/academic/governmental sponsors.

- "How do you envision the business process modeling and nature of the third party entity or entities?"

The third-party should be contracted by the FDA. FDA should make sure that CBER and CDER (and other centers) are all involved in development and standardization between centers (like what has occurred with the Electronic Submission Gateway). Different systems between CDER and CBER should not be allowed.

- "What are the necessary attributes and characteristics of the third party entity or entities?"

The third-party entity should not have a vested-interest in the pharmaceutical industry and should not be relying on applicants for payment. The third party should be utilized by the FDA as a contracted entity. The FDA should verify the systems is open enough that if a change in vendors is required or, if different vendors are used for development and ongoing maintenance, that continuity is maintained.

- "What services could the third party entity or entities provide?"

Examples need to be provided by FDA for evaluation. Development of a database/document control platform, and ongoing maintenance of the system, would be an acceptable service. If the FDA is considering a system where third-party entities would develop software to assist companies in complying with electronic submission

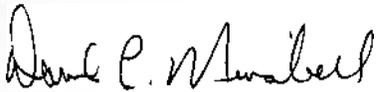
requirements, this could be seen as mandating a specific system for applicants and would likely be unacceptable.

- o "What collaborative efforts by FDA with a third party entity would be beneficial to establishing services?"

The development of a unified document system between centers would allow access to all document types. This system should allow applicants to view their existing submission numbering to maintain continuity between future amendment/supplement numbers. Collaboration should rely on the third-party to bring state-of-the-art IT system functionality to the FDA's user requirements.

Thank you for the opportunity to comment on this docket.

Sincerely,



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