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FDA’s Quality Systems Methodology at Pharmaceutical Manufacturing Sites

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ABSTRACT

This research details the FDA’s quality systems methodology used in its inspection of biopharmaceutical manufacturers in the time period between 2003 and 2009. It analyzes the violations specified in FDA site inspection warning letters, reviewing their frequency and specificity. This analysis is an exploration into FDA activity in this sector, focusing particularly on finished pharmaceuticals, and serves as an initial evaluation of the FDA’s performance. In addition, the study pays particular attention to whether the FDA’s risk methodology has enhanced the overall inspection process and increased its quality assurance.

U.S.A. FOOD AND DRUG ADMINISTRATION (FDA)

This paper is the result of an ongoing examination of the FDA’s new risk methodology, as it is applied to the manufacturing sector of the bio-pharmaceutical (BP) industry. It specifically addresses the manufacturing facilities that produce finished pharmaceuticals, including drugs for humans. As a basis for this study, the researchers continue to review FDA regulations and procedural manuals that relate to inspections and quality systems (QS), as well as examining violation warning letters issued to BP facilities from 2003 to 2009.

The FDA is continually seeking to improve its oversight of the BP industry, and in 2004 it announced that it would incorporate a risk-based methodology in its inspection of manufacturing processes. The data generated since this announcement up until 2009, provides sufficient information to analyze whether this decision has improved the FDA oversight process. To judge this new approach, the researchers evaluated the FDA data as to whether more inspections have been made, more violations found, and better guidance provided during this time period. The researchers gathered data from site inspections, grouped them into categories showing the number and type of annual manufacturing inspections, and then examined the type of violations and their frequency, as detailed in the warning letters (WLs) issued to manufacturers.

This task of gathering and analyzing data from thousands of inspections that occur at diverse manufacturing facilities around the country is significant and complex. However, the Freedom of Information Act of 2008 (FDA, 2008d) has released much important data concerning site visits. This then becomes a database problem of collecting, sorting and extracting information from the multiple folders found at the FDA web site. Consequently, the researchers made the decision to focus on one particular subset within the BP industry—that of drugs and biological products. Choosing this FDA sector allows a comparison to be made between similar manufacturing sites,
while using the same FDA inspection methodology. Thus it becomes easier to understand how the FDA performs its quality assurance inspections, and how well the agency performs its oversight function (Alavi & Leidner, 2001).

More specifically this paper reviews and analyzes how quality assurance systems and risk methodology (as detailed in FDA regulations Part 210 and Part 211 - Current Good Manufacturing Practice (cGMP) for Finished Pharmaceuticals) is incorporated within the FDA oversight rubric. Within Parts 210 and 211, the study focuses particularly on the concepts of corrective and preventative action (CAPA) to assure sustainable compliance. CAPA is a critical component in measuring risk, since problem prevention, containment, and remediation are intrinsic in determining the outcome (COSO, 2004).

The FDA is a large, complex, and sophisticated agency, and therefore this research can be only an initial investigation into its CAPA activities in one sector. By reviewing the timeframe 2003-2009, the research is establishing some baselines for performance, and for judging CAPA activities. This is an area that is not widely explored, other than by the Center for Drug Evaluation Research (CDER), a part of the United States Department of Health and Human Services, Food and Drug Administration (FDA) papers and congressional reports. Some additional information about QS and risk are usually found on pharmaceutical consulting sites. In the first instance, the information is a general overview and more informative than evaluative. In the latter instance, the information presented is often proprietary and seemingly aimed at generating client assignments. The two principal academic investigations of FDA and CAPA that we are aware of are Adis (2007, 2008) in his review of risk control systems, and Macher and Nickersons (2006) review of QS.

**FDA’S CURRENT GOOD MANUFACTURING PRACTICES METHODOLOGY**

The FDA’s principal objective is ensuring public safety through establishing industrial quality standards, guidance, and oversight. It functions as the responsible supervisory agency, mandating quality systems (GAMP, 2001) in all aspects of the manufacturing life cycle of drugs, vaccines, and other biological products. Its oversight tasks are to inspect facilities, examine biological products and manufacturing processes, issue warning letters, and take enforcement action, such as ordering recalls. The compliance guidelines (FDA, 2003a; FDA, 2004a) establish an exceptionally low tolerance for variability or deviation in all pharmaceutical products.

The FDA uses a best practice methodology as its criteria for performance. It has now added to this a new risk-based paradigm for performing its inspections and accomplishing its oversight tasks (de Neufville, 2004). Before this date, the FDA’s own internal reviews made it clear that there were problems in meeting its objectives. It realized that its limited budget, lack of qualified staff and inadequate resources prevented it from meeting its goals of inspecting domestic BP facilities within a 2 year cycle, or a 4 year cycle for more complex products and processes. It also became clear that the number of BP research and production sites would continue to grow, while the FDA resources would remain relatively unchanged. This would create an increasing and untenable backlog, as the FDA failed to keep up with its site visits and inspections. To meet this oversight bottleneck, the FDA chose to supplement its industrial best practices with a quality
assurance methodology that orders and prioritizes BP sites based on their associated risk (FDA, 2004b). This transition began in 2004, when the agency adopted this new risk-based methodology, outlined in part by the Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century (FDA, 2004a).

This methodology guides the oversight process by choosing which manufacturing facilities have the highest risk priority, determining the focus for the site inspection, and whether warning letters and recalls are necessary (FDA, 2008b). “The model is based on a risk-ranking and filtering method that is well-recognized, objective, and rigorously systematic. This approach should help the Agency make the best use of its limited surveillance and enforcement resources, while maximizing the impact of those resources on the public health” (FDA, 2004a).

Therefore, to the FDA’s normal inspection schedule there have been added priority site visits for those manufacturing facilities that have a previous history of warning letters, or perform processes that have an inherently higher risk of system failure. CAPA requirements are often integrated within the regulations, as the inspections emphasize systems to monitor performance, and correct and remediate anomalies (ICH, 2005). During the site visit, inspectors determine whether these monitoring and remediation systems are in place. Then during the course of the year, the FDA updates its quality assurance database, adding its findings about the frequency and severity of nonconforming production practices (FDA, 2008a). By applying this risk methodology, the FDA filters and prioritizes the data to focus on those that represent the greatest hazard. This is done by using the industries best business practices combined with risk management statistics. In this way, the FDA builds a performance history for each manufacturer and then schedules site visits and evaluations focusing on these key risk indicators (ICH, 2007):

- Overall compliance status and history of the company or facility
- Results of the company’s quality risk management activities
- Complexity of the manufacturing process
- Complexity of the product and its therapeutic significance
- Number and significance of quality defects (e.g., recalls)
- Results of previous audits/inspections

QUALITY SYSTEMS CAPA AND HUMAN DRUGS

This study focuses on inspections of facilities that produce human drugs, and asks how the FDA has incorporated regulations that achieve quality systems (QS) and CAPA outcomes. This is particularly important since QS and CAPA are critical components in FDA oversight and are the basis for an effective risk methodology.

The category “human drugs” falls within the domain of the Center for Drug Evaluation Research (CDER). Its tasks are to “evaluate the findings of inspections that examine the conditions and practices in plants where drugs are manufactured, packed, tested and stored…. We identify, evaluate and analyze inspection findings for trends in deficiencies. We publish guidance to assist drug manufacturers and distributors in gaining a better understanding of our regulations…. We determine which manufacturers are acceptable to supply active pharmaceutical ingredients or finished drug products to the U.S. market.” (CDER, 2007).
The CDER monitors its functional areas using specific guidelines. For human drugs, it bases its enforcement on Part 210 - cGMP in Manufacturing, Processing, Packing, or Holding of Drugs, and Part 211 - cGMP for Finished Pharmaceuticals.

Part 210 is a general series of regulations defining cGMP facilities/processes and human drug characteristics. The enforcement goals and inspection objectives are defined in Part 211. In those regulations it spells out staffing requirements, production controls, and necessary reports. It should be noted that Part 211 does not directly address quality systems or CAPA, as do other regulations, most notably 820.100 (Corrective and Preventive Action) within the FDA sector for manufacturing medical devices (Crosse, 2008). The researchers initially found this surprising, given the risk emphasis found in cGMP. Consequently, it became important to find out how CDER implements its Part 211 and whether it achieves the same effect as using CAPA methodology to assure oversight.

This is how CDER’s addresses this issue: “Nonetheless, FDA recognizes that each set of regulations is somewhat different because each is tailored to the characteristics of the types of products for which they were designed…. Typically, these express/specific requirements are related to the unique characteristics of a drug, device, or biological product. For example:

- Corrective and preventive action (CAPA): The QS regulation has detailed CAPA requirements (21 CFR 820.100), while CAPA principles are more generally identified in the CGMP regulation as part of Production Record Review (21 CFR 211.192).” (CDER, 2010).

As the CDER statement points out, CAPA requirements are spelled out in regulation 211.192, Production Record Review. Yet since this research is an initial review of CDER, the researchers made the decision to review all the regulations that made up Part 211, with a special focus on regulation 211.192. This was done to get an overview of the interplay between the regulations, and to see how other 211 regulations contribute to the tasks of CAPA data management and quality system analysis. The next section reviews the methodology for analyzing the how CDER uses its regulations.

**METHODOLOGY**

The researchers examined the warning letters that specifically dealt with cGMP, quality assurance and CAPA. As mentioned in the previous section, the research looked into the WLs to determine to what degree CAPA was integrated into cGMP inspection methodology. Using the Freedom of Information Act, the research was able to reviews WLs that met the following criteria:

- Issued in 2003-2009 time frame
- Subject was cGMP found in regulations 501(h) of the Act (21 U.S.C. §351(h))
- Included FDA regulations Part 210 and Part 211, cGMP Practice for Finished Pharmaceuticals
- QS and CAPA risk methodology as mentioned directly or indirectly in Part 211

This can be visually captured in Figure 1, which illustrates the granular focus of the research.
Figure 1. Granular Analysis of Warning Letters.

Total Inspections > WL > cGMP violations > Quality Assurance 211 > Subparts A–K >

Several important examples:
- Subpart B—Organization and Personnel
- Subpart F—Production and Process Controls
- Subpart I—Laboratory Controls
- Subpart J—Records and Reports

Much of this information can be sourced from the FDA’s Field Activities – Office of Regulatory Affairs (FDA, 2008c) and other similar reports to Congress (CDER, 2011). These congressional reports provide useful data on budgets and staffing, as well as field activities. By collating data from these reports, it was straightforward to determine the total number of site inspections per year, as well as those that triggered WLs. Information derived from the CDER field manuals and inspection guidelines showed that generally there were two kinds of field visits. The first were regularly scheduled inspections, or in certain instances re-visits to ascertain that a previous violation had been satisfactorily resolved. The second type were risk based, determined by the pharmaceutical manufacturing processes used, the type of biological products produced, and the site violation history of the plant. Or in FDA language, site selection is based on using a model that provides a risk score for each facility, which is a function of four component risk factors – Product, Process, Facility, and Knowledge.

The first step then becomes calculating the total number of cGMP Part 211 based site inspections. This information is found in Table 1, column A (CDER, 2011). Reviewing Table 1, several things become evident. There is no obvious improvement in CDER performance after the 2004–2005 implementation of the new risk methodology. Rather the data suggests a general decrease in the number of inspections over the last five years (column A), falling from 1365 to 983. This represents 382 fewer site inspections, or 28% over 5 years. This decrease of 28% is in keeping with FDA problems of limited staff, budget, and resources that prevent the agency from keeping up with the inspection of manufacturing sites. However, CDER estimates that in 2010 and 2011 its goal will be in the range of 993 inspections, a modest improvement.

Table 1: FDA Domestic Human Drug Site Inspections (Part 211) and Corresponding WLs.

<table>
<thead>
<tr>
<th>Year</th>
<th>(A) Total Inspections</th>
<th>(B) Part 211 WLs</th>
<th>(C) Percent (B/A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>1,149</td>
<td>35</td>
<td>3.0%</td>
</tr>
<tr>
<td>2004</td>
<td>1,232</td>
<td>26</td>
<td>2.1%</td>
</tr>
<tr>
<td>2005</td>
<td>1,365</td>
<td>14</td>
<td>1.0%</td>
</tr>
<tr>
<td>2006</td>
<td>1,222</td>
<td>20</td>
<td>1.6%</td>
</tr>
<tr>
<td>2007</td>
<td>1,073</td>
<td>13</td>
<td>1.2%</td>
</tr>
<tr>
<td>2008</td>
<td>972</td>
<td>29</td>
<td>3.0%</td>
</tr>
<tr>
<td>2009</td>
<td>983</td>
<td>26</td>
<td>2.6%</td>
</tr>
</tbody>
</table>
The next column (B) focuses on inspections that resulted in WLs being issued for Part 211 violations. During the time period 2003 to 2009, the WLs in this category ranged from 13 to 35. Neither the number of WLs nor their percentages seem particularly significant, given the large number of inspections. Column C highlights the lack of any particular impact from using cGMP risk methodology, with the WLs staying within 1% to 3% of the yearly inspections, regardless of methodology.

Furthermore, the paucity of WLs put paid to the notion that the FDA is concentrating on the most risk prone manufacturers. At least so far, it could be argued that the cGMP new emphasis on risk has not increased the number of inspections performed by staff, nor caused more WLs to be issued. In fact one could argue that the opposite exists, with few inspections, and few sites with violations.

The research then further analyzed the same cGMP WLs to see how many emphasized quality assurance and CAPA related regulations. This more granular analysis is important because it addresses whether the FDA is actually emphasizing the CAPA related regulations which are fundamental to risk analysis. This task was done by searching and categorizing the contents of each of the Part 211 WLs. Table 2 begins this process by showing the 211 Subparts cited in the WLs, and displaying the total count over the 5 year period (2005-2009) after the risk methodology formally became part of the inspection process.

Subpart A provides a general statement of the role of the regulations, which are found on all WLs, and are therefore not applicable. The remaining Subparts (B-K) are displayed, with the count of the number of times the field inspectors cited them during this period (column A), as well as their yearly average (column B). Particularly noteworthy is Subpart J, Records and Reports, for its high 5 year count of 176 citations, and its average count of 35.2 per year. The 176 citations represent 29% of all 604 citations for that five year period (column C). Furthermore when the researchers reviewed raw data for the last two years, they found that in 2008, Subpart J had 57 citations, while in 2009 it had 45. This finding points to the fact that Subpart J continues to be an increasingly important regulation.

Table 2: Part 211 Subparts A-K Citations within WLs (2005-2009).

<table>
<thead>
<tr>
<th>Part 211 Regulations, Subpart</th>
<th>(A) 5-Year Count</th>
<th>(B) Yearly Average</th>
<th>(C) (A/Total) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. General Provisions</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Organization and Personnel</td>
<td>60</td>
<td>12.0</td>
<td>10%</td>
</tr>
<tr>
<td>C. Buildings and Facilities</td>
<td>34</td>
<td>6.8</td>
<td>6%</td>
</tr>
<tr>
<td>D. Equipment</td>
<td>60</td>
<td>12.0</td>
<td>10%</td>
</tr>
<tr>
<td>E. Control of Components and Drug Product Containers and Closures</td>
<td>39</td>
<td>7.8</td>
<td>6%</td>
</tr>
<tr>
<td>F. Production and Process Controls</td>
<td>85</td>
<td>17.0</td>
<td>14%</td>
</tr>
<tr>
<td>G. Packaging and Labeling Control</td>
<td>29</td>
<td>5.8</td>
<td>5%</td>
</tr>
<tr>
<td>H. Holding and Distribution</td>
<td>5</td>
<td>1.0</td>
<td>1%</td>
</tr>
<tr>
<td>I. Laboratory Controls</td>
<td>115</td>
<td>23.0</td>
<td>19%</td>
</tr>
<tr>
<td>J. Records and Reports</td>
<td>176</td>
<td>35.2</td>
<td>29%</td>
</tr>
<tr>
<td>K. Returned and Salvaged Drug Products</td>
<td>1</td>
<td>0.2</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Total 5-Year Count of Citations</strong></td>
<td><strong>604</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In summary, those Subparts (B, D, F, I, J) that address quality assurance are the most frequently cited regulations over the time period 2005-2009. They make up in total 82% percent of all recorded citations. This makes sense since the FDA seems to be looking for the BP staff and their systems to collect, record, and report quality assurance data on the site.

Table 3 takes a more granular look at specific Subpart B-K regulations, reporting on those that were cited more frequently. In keeping with the overall paucity of WLs per year, only regulations that were cited a minimum of 5 times per year were displayed. As Table 3 shows, there were only 9 regulations out of the 58 (B-K) that met this criterion. All had QA and data reporting components which are necessary for quality systems and CAPA. As an example, take 211.22 - Responsibilities of quality control unit. By emphasizing this regulation, CDER is fostering a well-managed quality environment. The remaining 8 regulations also focus on testing, logging, and procedures.

One of the research themes was to understand on how CDER uses Subpart J 211.192, the enforcement of corrective and preventative activities. This is important since it is the cornerstone for building QS CAPA systems. This regulation is noteworthy with an average of 12 citations per year; with the yearly data showing that during the last 2 years there have been an increased number of citations. In 2008, for 211.192 there were 21 violations, and 2009 there were 16 violations. Certainly an improvement, but given the overall low numbers not overwhelming. Similar to comments made earlier about the paucity of WLs, Table 3 has few citations. As a matter of fact of the 58 regulations from Subpart B-K, 33 were cited on average less than once over the last 5 years. This unexpected result leads to the assumption that the FDA only focuses on certain priority QS and CAPA activities, as listed in Table 3. These nine regulations are cited a total of 334 times over this five year period. This represents 55% of the 604 citations that were found in the Part 211 WLs.

This is a targeted rather than a broad comprehensive approach. It may very well be that passing or failing is based principally on meeting the criteria posed by these nine regulations. Again, this is in keeping with the limited resources available to CDER.

**Table 3: Frequently Used Part 211 Regulations within WLs (2005-2009).**

<table>
<thead>
<tr>
<th>211 Subpart</th>
<th>Regulations</th>
<th>(A) 5-Year Count</th>
<th>(B) Yearly Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>211.22 - Responsibilities of quality control unit.</td>
<td>48</td>
<td>9.6</td>
</tr>
<tr>
<td>D</td>
<td>211.67 - Equipment cleaning and maintenance.</td>
<td>34</td>
<td>6.8</td>
</tr>
<tr>
<td>F</td>
<td>211.100 - Written production procedures; deviations.</td>
<td>34</td>
<td>6.8</td>
</tr>
<tr>
<td>F</td>
<td>211.113 - Control of microbiological contamination.</td>
<td>28</td>
<td>5.6</td>
</tr>
<tr>
<td>I</td>
<td>211.160 - General lab requirements.</td>
<td>43</td>
<td>8.6</td>
</tr>
<tr>
<td>I</td>
<td>211.165 - Lab testing and release for distribution.</td>
<td>31</td>
<td>6.2</td>
</tr>
<tr>
<td>I</td>
<td>211.166 - Lab stability testing.</td>
<td>31</td>
<td>6.2</td>
</tr>
<tr>
<td>J</td>
<td>211.188 - Batch production records.</td>
<td>25</td>
<td>5.0</td>
</tr>
<tr>
<td>J</td>
<td>211.192 - Production record review.</td>
<td>60</td>
<td>12.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>334</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

This research, focusing on finished pharmaceuticals in the BP sector, is just one of many avenues that can shed more light on the FDA’s risk based approach. Other areas could include

- the raw data found on the CDER site inspection form (FDA 483) used by the examiner
- the manufacturer’s written responses to the WL
- data specifically about product recalls, fines and penalties

A broader research agenda may point to a different understanding of the FDA inspection process. Furthermore, a detailed comparison of the findings in the WLs with the FDA inspection manuals and quality assurance guidelines (FDA, 2003b; FDA, 2008e; FDA, 2008f) would add greater depth. In addition there is some evidence that WLs are vetted by the FDA’s legal staff to prevent lawsuits claiming a biased inspection process (Goldstein, 2008). Part of this possible FDA vetting as well as the sameness in style, format, expressions, and perhaps even content, may be the result of the EIR Turbo computer software that the FDA has used since 2002 to automate the process of writing inspection reports and WLs (Betterchem, 2008).

While this research did not formally address the WL data from the manufacturers perspective, it did have the advantage of reviewing previous BP and FDA studies (Macher & Nickerson 2006; Adis, 2007, 2008). At this stage of the research there have been only preliminary discussions with the BP industry concerning quality assurance issues and their use of manufacturing execution systems software. Expanding the research to include manufacturers makes sense, and will be explored in future studies now that this work has established some baselines.

These limitations were kept in mind during this study and will in part be addressed as this research continues to probe the issues of quality and risk found in the FDA methodologies. Yet it seems fair to say that these initial findings can serve as a benchmark for understanding how the FDA is responding in terms of policy and direction to their internal problem of limited resources and staff, and the complexity of mandatory oversight.

CONCLUSION

However, in spite of these research limitations, findings drawn from this study provide some basic insights into the FDA CDER oversight activity. The findings also confirm the budgetary and resource problems faced by the FDA, and the inability of the risk methodology to significantly change the downward trend in inspections and WLs. The data clearly show that the FDA is doing less cGMP inspections in this sector over the last 5 years. While the WLs do focus on QS CAPA issues, most of the citations are of a general nature, using few of the regulations within each of the Subparts.

In summary, the findings show

- Fewer FDA inspections over the time period 2005-9
- Correspondingly, few cGMP WLs were issued
• Even when WLs were issued, they were narrowly focused on a few Subparts (B, D, F, I, J)
• While these Subparts dealt with QS CAPA, relatively few regulations were actually used
• Overall, few 211 regulations were cited in the WLs

These findings may be the result of manufacturers adopting manufacturing execution systems software (MES), such as SAP R/3 and Trackwise. The increased use of these automation and monitoring systems contribute to dramatic improvements in BP manufacturing, and meet many of the reporting requirements mandated by CDER regulations. Table 4 displays some of SAP’s MES software used in BP manufacturing for the monitoring, control and reporting of the manufacturing process. SAP software was chosen as it is the largest supplier of software to the BP industry.

Table 4: SAP R/3 Software for the BP Industry.

<table>
<thead>
<tr>
<th>SAP Enterprise Sub Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supply Chain Management System (SCMS)</td>
</tr>
<tr>
<td>Supplier Relationship Management (SRM)</td>
</tr>
<tr>
<td>Customer Relationship Management (CRM)</td>
</tr>
<tr>
<td>Materials Management (MM)</td>
</tr>
<tr>
<td>Quality Management (QM)</td>
</tr>
<tr>
<td>Corrective and Preventive Actions (QM-CAPA)</td>
</tr>
<tr>
<td>Laboratory Information Management System (LIMS)</td>
</tr>
<tr>
<td>Advanced Planner and Optimizer (APO)</td>
</tr>
<tr>
<td>Plant Maintenance (PM)</td>
</tr>
<tr>
<td>Environmental Health &amp; Product Safety (EH&amp;S)</td>
</tr>
</tbody>
</table>

The FDA may very well be using the inspection process as a policy tool to move the manufacturers to the need for MES quality systems. If so, there is some logic to the paucity of WLs and the less detailed approach to the oversight process. Through the adoption of MES, manufacturers would be more likely to obtain a ‘necessary and sufficient’ standard for passing inspections. They would meet both best practices as well as the reporting component necessary for the risk methodology. This premise will be tested in further research. However, if one of the purposes of the FDA inspections is direct QS CAPA oversight, then MES software alone will be insufficient.

By failing to detail the specific inspection violations, the FDA is not providing the necessary guidance to the industry. The QS CAPA risk methodology within the 211 quality assurance framework has the potential to both provide guidance and detail weaknesses within the manufacturers’ production processes. With detailed WL information, manufacturers can be better guided in implementing superior QS CAPA systems to correct and prevent system failures. Even with those that have adopted MES software, the inspections can still address the production issues of staffing and training, monitoring frequency, batch controls and reporting. Certainly that is a realistic expectation for the FDA.
REFERENCES


