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Analysis of FDS's Risk Assessment Methodology at Pharmaceutical Manufacturing Site

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ABSTRACT

This research describes how the FDA has incorporated risk analysis methodology into its inspection of pharmaceutical manufacturers in the time period between 2004-2008. It analyzes the violations specified in FDA warning letters that are issued after site inspections of pharmaceutical facilities. The outcome of this analysis is to evaluate the FDA's performance to determine whether it has improved the overall inspection process and increased its quality assurance.

U.S.A. FOOD AND DRUG ADMINISTRATION

This paper outlines an initial investigation of the FDA's new risk methodology as it is applied to the manufacturing sector of the bio-pharmaceutical (BP) industry. The research reviewed FDA regulations concerning quality assurance, the corresponding procedural manuals, as well as, examining the violation warning letters issued by the FDA from 2004 to 2008. This research will serve as the basis for developing a more formal research proposal to study in-depth changes in the FDA as well as the BP industry.

In 2004, the FDA announced that its oversight of the BP industry would incorporate a risk-based methodology in its inspection of manufacturing processes. In the almost 5 years between the 2004 announcement and 2008, questions have arisen as to how this decision has impacted the FDA oversight process, in terms of manufacturing sites inspected, types of observations completed at each site, and outcomes of these inspections. Knowing this information is basic to understanding how risk methodology is incorporated into manufacturing site visits on one hand, and on the other how successful this new approach has been for the FDA (Adis, 2007). This study gathered data from site visits, categorized the number and type of annual manufacturing inspections, and examined the frequency and type of violations detailed in the warning letters issued to manufacturers. As far as evaluating the success of this new approach, the data looked at the FDA's performance and whether it has been more capable of finding violations in the inspection process, and better at providing directions and guidance to manufacturers during this time period.

Gathering this information is both a significant and complex task, considering the thousands of inspections that occur at diverse manufacturing facilities around the country. Yet this task has been made somewhat easier by the Freedom of Information Act which makes important data available to researchers and the BP community. The problem quickly becomes that of sorting through the vast amount of information available at the FDA web site, which details the full

operation of the Agency. Therefore, the researchers made the decision to focus on one particular subset within the BP industry – that of medical device manufacturers. Within this industry subset, the research then established benchmark indicators showing how the risk methodology has been incorporated into the FDA current Good Manufacturing Practices (cGMP). Specifically this paper reviews and analyzes how quality assurance and CAPA risk methodology (as detailed in FDA regulation 820.100) is incorporated within the FDA rubric of cGMP. CAPA is a critical component in measuring risk, since problem containment and remediation are intrinsic in determining the outcome (COSO, 2004).

The choice of focusing on one FDA cGMP sector – that of medical device manufacturing – enables a comparison to be made between similar manufacturing sites, while using the same FDA inspection methodologies. Therefore it becomes easier to judge how the FDA incorporates CAPA and quality assurance in its emphasis on manufacturing excellence. This research provides an initial cut at evaluating the risk methodology and providing measurement data to determine how and with what success the Agency performs its oversight function.

FDA'S CURRENT GOOD MANUFACTURING PRACTICES METHODOLOGY

The main objective of the FDA is to ensure public safety through establishing industrial quality standards, benchmarks and vigorous oversight. Its role is that of principal supervisory Agency, assuring that industry best practices are followed (GAMP, 2001) in the research, development and manufacturing life cycle of drugs, vaccines, other biological products, and medical devices. Its tasks are to inspect sites, examine products and processes, issue warning letters, and order recalls. The exceptionally low tolerance for variability or deviation in quality pharmaceutical products is built around its compliance guidelines (FDA, 2003a; FDA, 2004a).

The FDA has chosen to add to its best practice methodology a new risk-based paradigm for achieving its oversight objectives and managing its inspection tasks (de Neufville, 2004). This decision came from the fact that the FDA's own internal reviews made it clear that limited budgets, lack of staff and insufficient resources prevented it from meeting its goals of inspecting domestic BP facilities within a 2 or 4 year cycle, depending on type of products and processes used in the manufacturing. Coupled with this is the knowledge that the situation can only get worse as the number of BP research and production sites keeps increasing, while FDA resources remain relatively unchanged. The inevitable outcome is that the number of FDA visits and inspections would remain at approximately the same level, resulting in an increasing and untenable backlog. To resolve this situation the FDA chose a different methodology that orders and prioritizes inspection sites based on their associated risk (FDA, 2004b). This transition began in 2004-2005 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 tasks of choosing which manufacturing sites have the highest priority, how the site inspection process is carried out, and whether warning letters and recalls are necessary (FDA, 2008a). "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, in addition to normally scheduled inspections, the FDA now schedules site visits by prioritizing those manufacturing facilities that have a previous history of violations, or perform processes that have an inherent risk of system failure. The Agency includes CAPA requirements regarding the need for systems that monitor performance and can correct and remediate anomalies (ICH, 2005). The FDA inspectors' task is to ensure that these monitoring and remediation systems are in place. The FDA then has necessary feedback from the BP industry to update its quality assurance database concerning the frequency and severity of events associated with different production practices (FDA, 2008c). The FDA applies this risk methodology to filter and prioritize the data to focus on those that represent the greatest hazard. This is accomplished by using risk management statistics in combination with the industries best business practices. The FDA can then compare this information with its overall industry risk guidelines. On this basis, the FDA can build a performance history for each manufacturer and then schedule site visits and evaluations focusing on these key risk indicators (ICH, 2007).

WARNING LETTERS

The FDA uses the quality assurance and risk method regulations as the basis of facility inspections. The results of the site visit are recorded on Inspection Form 483. The next step is for the Agency's regional offices to examine the key performance indicators found in the 483 forms and issue warning letters (WLs) where there are violations and deficiencies. These warning letters, which are available online through the Freedom of Information Act (FOIA, 2008), provide a window for seeing into the cGMP and its risk methodology, for they summarize the inspection process for those firms that are in violation. A study of several years' worth of WLs can serve as a baseline in determining the Agency's overall oversight performance, by examining the WLs issued, and determining their scope and depth. In addition, a review of the WLs may be helpful in analyzing which factors the FDA wants to emphasize in its future inspections. These factors may be related to a particular risk issue, but can also indicate general FDA policies.

Table 1 offers an initial guide to the contents of a warning letter. It is an abbreviated composite based on the review of hundreds of WLs issued between 2004 and 2008. The outline uses FDA language and frequently quotes from the regulations, making it in many instances awkward to read. This also may be the result of a computer program called EIR Turbo which takes the contents of Form 483 and automatically produces the WL (EIR, 2008).

Table 1 has two columns. The first lists the topics frequently found in many cGMP WLs. The second column lists the corresponding 820 regulation that is being cited. For our research purposes the topics can be divided into two groups: CAPA (820.100) and those other 820 regulations that address quality assurance.

RESEARCH

The research examined the warning letters issued by the FDA in the time period 2003-2008 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 review hundreds of WLs that met the following criteria:

Table 1: Warning Letter Guide.

Warning Letter Topics	**cGMP for Medical Devices (CFR), Part 820**
Inadequate Response	Form FDA 483, List of Inspection Observations
Failure to ensure that an adequate and effective quality system exists throughout the organization	21 CFR § 820.20
Quality audits did not assure that the firm's quality system is in compliance	21 CFR § 820.22
Failure to adequately establish and maintain procedures for implementing CAPA. Incomplete documentation of CAPA activities	21 CFR § 820.100(a) 21 CFR §820.100(b)
Failure to adequately analyze quality data sources, or identifying existing and potential causes of nonconforming product or other quality problems	21 CFR § 820.100(a1).
Failure to adequately implement procedures for receiving, reviewing, and evaluating complaints	21 CFR § 820.198

- Issued in 2003-2008 time frame
- Subject was cGMP found in regulations 501(h) of the Act (21 U.S.C. §351(h))
- Included FDA regulations section 820, Quality System, and its subpart CAPA risk methodology, 820.100.

Table 2 shows the total number of inspections per year that the FDA performed at facilities that manufactured medical devices. In addition the table shows the total number of WLs that were issued based on violations at those sites. These data were was reviewed in conjugation with the FDA document 2008 FDA's Field Activities – Office of Regulatory Affairs (FDA, 2008b) and other congressional reports (Crosse, 2008). These reports to Congress contain very useful data including budgetary and staffing information and field activities. Using these resources, it was straightforward to determine the total number of field inspections per year, as well as those that triggered WLs. It should be noted that the field manual and inspection guidelines indicated that site visits were generally of two kinds. The first took place because it was a routinely scheduled inspection, or in some instances was a follow-up to ensure that a previous deficiency had been rectified. In this category few violations should be anticipated. The second type of visit was based on risk factors associated with certain pharmaceutical manufacturing processes, and plants with site violation histories.

Reviewing the data in the table several trends are noticeable. The first is the decrease in total number of inspections, moving from 1,736 in 2003 to 1,362 in 2007. This represents a drop of 374 site inspections, or 22% over 5 years. (The data for 2008 is not currently available, yet preliminary information from various reports seems to indicate that it will be in the range of 1,250.) This decrease of 22% is in keeping with FDA statements concerning their limited staff,

budget and resources that prevent the Agency from keeping up with the inspection of manufacturing sites.

Table 2: Inspections of Manufacturing Sites producing Medical Devices.

Year	(A) Total Inspections	(B) cGMP WLs	(C) Percent (B/A)
2003	1,736	95	5.5%
2004	1,631	121	7.4%
2005	1,471	127	8.6%
2006	1,501	142	9.5%
2007	1,362	136	10.0%
2008	n/a	162	n/a

The next column (B) focuses on inspections that resulted in WLs being issued for cGMP violations. During the time period 2003 to 2008, the WLs in this category increased from 95 to 162, or 71%. While the percentage seems significant, the actual numbers involved in the increase was only 67 WLs, not a very large amount. The last column shows the gradual shift towards increasing emphasis on cGMP as a subject for violation in the WLs over the 5 year time frame.
The research then further analyzed the same cGMP WL data to see how many emphasized quality assurance and CAPA regulations. This more granular analysis is important because it addresses whether the FDA is actually emphasizing the CAPA regulations which are fundamental to risk analysis. This task was done by searching the WLs for those that focused on Subchapter H--Medical Devices, Part 820 Quality System Regulation which also includes CAPA 820.100.

Table 3 shows the total number of cGMP warning letters that cite Part 820 and CAPA (820.100). The first column (A) of this table, cGMP WLs, is taken from Column B of Table 2. (It does not include the year 2003 since this was before the switch over to cGMP.)The next column (B) reviews those WLs to see if inspectors cited Part 820 Quality System Regulation violations. This column shows a decrease in Part 820 WLs, except for a small uptick in 2008 due to the large number of inspections that year. Column C shows that 820 quality assurance violations decreased from 98% to 56% of all cGMP WLs. So while there was an overall increase in the number of cGMP WLs during this period, there was a significant decrease in percentage of those that addressed 820 violations. This means that inspectors and their district offices focused on issues other than quality assurance and risk. These might include such factors as dirty premises, food lacking refrigeration, fire safety, and a myriad of other cGMP regulations outside of 820, such as pharmaceutical drug violations (21 Part 210, 211)

As mentioned earlier, CAPA (820.100) risk methodology is a subpart of the 820 quality systems regulations, and columns D-F highlight this relationship. Column D shows the actual decline in WLs that make specific references to CAPA violations (820.100). Column E shows this as a percentage decline of WLs that cite CAPA violations (D/A). Column F provides a different perspective, showing that a rather steady percentage (65-76%) of 820 warning letters focused on

820.100 CAPA during the time period. Those cGMP WL and 820 WL that did not reference CAPA, instead focused on other issues within the cGMP rubric, such as devices or services that were lacking pre-market approval, misbranded items, poor packing or storage, and the like.

Table 3: cGMP WLs and those that specifically cite Part 820 and CAPA (820.100).

Year	(A) cGMP WLs	(B) 820 WLs	(C) Percent (B/A)	(D) 820.100 WLs	(E) Percent (D/A)	(F) Percent (D/B)
2004	121	119	98%	91	77%	76%
2005	127	109	86%	72	57%	66%
2006	142	89	63%	58	41%	65%
2007	136	82	60%	55	40%	67%
2008	162	90	56%	62	38%	69%

Without belaboring the point, the WL data indicates that 820 and CAPA are not as dominant as one might expect, given the FDA statements over the years about its movement to a new risk based methodology. Based on data in this table, it is correct to say that 820 and CAPA are frequently used regulations but they have not in fact dramatically changed the actual number of cGMP WLs. In fact both Part 820 and CAPA show a generally decreasing influence on cGMP WLs.

EXAMINATION OF 820 AND CAPA 820.100

In further examining the role of CAPA within the 820 WLs, the research focused on 820.100 violations and calculated how frequently they were cited. This information gives an insight into the practical working of the FDA risk methodology as it applies to 820 quality assurance regulations.

As a first cut through the WL data, the research focused on two years, 2005 and 2008. The reason for this choice is straightforward. 2005 was the first full year that the new methodology was used by the Agency, while 2008 has the most current available data for the researchers to use. Only 2 years were chosen for multiple reasons. The first is to become familiar with the WL data and to work out a satisfactory method for reviewing and analyzing the data. The second is that it takes significant time to go through the several pages that make up each WL and categorize the salient features. Therefore this initial research served as a pilot study, testing the approach and the findings to determine if they needed further exploration.

Table 4 and Table 5 focus on how CAPA is incorporated into WLs for 2005 and 2008. Table 4 lists the full set of CAPA regulations (820.100) and the number of manufacturing sites that were in violation. For instance in 2008, CAPA violation 820.100a was cited in 40 out of the 62 WLs. By contrast in 2005, 820.100a was cited in 28 of the 72 WLs. This is followed by Table 5 which places the CAPA regulations in order of the most frequently cited regulations.

One of the most interesting findings in these 2 tables is the fact that some regulations are frequently referenced (820.100a, a1, a3, b) in both years, while others are rarely used

(820.100a5, a6, a7). Those that are frequently referenced make sense in that they call for reports, statistics, actions needed, and documentation. Of those that are infrequently cited, it is significant that management review (a7) has such a poor showing, since management is so intrinsic to CAPA activities.

Table 4: CAPA regulations cited in WLs for years 2005 and 2008.

CAPA	Description	2008 CASES n=62	2005 CASES n=72	% Change
820.100 a	CAPA General Procedures,	40 65%	28 40%	+25%
820.100 a1	CAPA Processes, Reports, Statistical Methods	16 26%	29 40%	-14%
820.100 a2	CAPA Investigations	8 13%	13 18%	-5%
820.100 a3	CAPA Identification of Action Needed	14 23%	21 29%	-6%
820.100 a4	CAPA Verification and Validation of Effectiveness	10 16%	17 24%	-8%
820.100 a5	CAPA Implementations and Modifications	9 15%	6 8%	+7%
820.100 a6	CAPA dissemination of information	4 6%	11 7%	-1%
820.100 a7	CAPA Management Review	2 3%	4 6%	-3%
820.100 b	CAPA Activities/Documentation	12 19%	24 33%	-14%

Table 5: Most Cited CAPA Regulations in 2005 and 2008.

Order	2008 820.100	(%) n=62	2005 820.100	(%) n=72
1	a	65%	a	40%
2	a1	26%	a1	40%
3	a3	23%	b	33%
4	b	19%	a3	29%
5	a4	16%	a4	24%

Both Tables 4 and 5 clearly show a general trend away from citing CAPA regulations in the WLs between 2005 and 2008. Within Table 4, seven of the nine regulations show a decreased usage between 2005 and 2008. Furthermore, five regulations show a decrease of more than 5 percentage points between these two years. The noteworthy exception is the increase in 2008 WLs that cite 820.100a which is CAPA general procedures. Table 5 shows a very large positive increase in 100a citations, going from 40 % in 2005 to 65% in 2008. Even more surprisingly,

additional research found that a large number of WLs only cited 820.100a violations and failed to specifically cite any other CAPA regulation (100a1-a7, b). In 2005, 25% of the WLs only referenced 100a to the exclusion of the other CAPA regulations, while in 2008 this increased to 39%.

It seems that the inspectors, in collaboration with their district offices, are using the 820.100a regulation as an indicator of general CAPA weakness, rather than detailing more specific violations CAPA regulations. It would be fair to say that this does not provide the level of guidance that one might expect from the FDA, nor does it match the Agency's stated emphasis on a new risk methodology.

ADDITIONAL 820 QUALITY REGULATIONS

So far the discussion has focused on just CAPA, one subpart of the 820 regulations. It is important now to broaden the analysis to the full set of 820 Quality Systems regulations, because in many instances there are overlapping relationships between corrective and preventative actions and the maintenance of quality.

Table 6: Part 820 Quality System Regulation.

820 Regulations Mentioned in WL	2008 n=62	2005 n=72
Subpart A--General Provisions	n/a	n/a
§ 820.1 - Scope.		
§ 820.3 - Definitions.		
§ 820.5 - Quality system.		
Subpart B--Quality System Requirements		
§ 820.20 - Management responsibility.	44%	51%
§ 820.22 - Quality audit.	40%	39%
§ 820.25 - Personnel.	24%	22%
Subpart C--Design Controls		
§ 820.30 - Design controls.	48%	53%
Subpart D--Document Controls		
§ 820.40 - Document controls.	21%	29%
Subpart E--Purchasing Controls		
§ 820.50 - Purchasing controls.	35%	33%
Subpart F--Identification and Traceability		
§ 820.60 - Identification.	<10%	<10%
§ 820.65 - Traceability.	<10%	<10%
Subpart G--Production and Process Controls	32%	39%
§ 820.70 - Production and process controls.	15%	17%
§ 820.72 - Measuring, and test equipment.	27%	33%
§ 820.75 - Process validation.		
Subpart H--Acceptance Activities		
§ 820.80 - Device Acceptance.	39%	51%

§ 820.86 - Acceptance status.	<10%	<10%
Subpart I--Nonconforming Product		
§ 820.90 - Nonconforming product.	24%	29%
Subpart J--Corrective and Preventive Action	n/a	n/a
§ 820.100 - Corrective and preventive action.		
Subpart K--Labeling and Packaging Control	<10%	<10%
§ 820.120 - Device labeling.	<10%	<10%
§ 820.130 - Device packaging.		
Subpart L--Handling, Storage, Distribution,	<10%	<10%
§ 820.140 - Handling.	<10%	<10%
§ 820.150 - Storage.	<10%	<10%
§ 820.160 - Distribution.	<10%	<10%
§ 820.170 - Installation.		
Subpart M--Records		
§ 820.180 - General requirements.	<10%	<10%
§ 820.181 - Device master record.	21%	22%
§ 820.184 - Device history record.	23%	36%
§ 820.186 - Quality system record.	<10%	<10%
§ 820.198 - Complaint files.	69%	61%
Subpart N--Servicing		
§ 820.200 - Servicing.	<10%	<10%
Subpart O--Statistical Techniques		
§ 820.250 - Statistical techniques.	<10%	<10%

Table 6 displays the complete set of 820 subparts that make up Quality Systems. In addition, this table shows the percentage of times each regulation was cited in the WLs issued in 2005 and 2008. In Subpart A (General Provisions) and Subpart J (CAPA) there are no percentages shown. The reason for the former is that all WLs cite Subpart A to generally describe the need for the WL. The reason for the latter is that this pilot study examined only WLs that cited 820.100; therefore it was not applicable to note the percentage, since by design it was 100%.

One of the interesting findings in Table 6 is the fact that some regulations are frequently cited in both years, while others are rarely. Those 820 regulations that are frequently referenced are complaint monitoring (198), design controls (30), management responsibility (20), quality audit (22), and product acceptance (80). However, some might find it strange that statistical techniques (250) was cited in less than 10 percent of the cases, since the inspections concern the determination of quality assurance. (The actual percentage in 2005 was 7% of the cases, decreasing to 5% in 2008).

Overall there seems to be a strong logical link between CAPA's regulations and the WLs' focus on quality issues such as complaints (198) and on Subpart B quality system requirements (20, 22,

25). This makes sense, since complaint tracking clearly links together with corrective measures, and quality systems with preventive measures.

One potential disparity is noted between CAPA management review (100a7) and management issues found in 820 Subpart B. CAPA management review (100a7) makes up only 3% of the 2008 WL cases, while Subpart B Management responsibility (20) is 44% of the 2008 WL cases. It seems that given the choice, the WLs prefer to bring up management issues in terms of quality requirements rather than CAPA.

Furthermore, in reviewing the general changes that took place between 2005 and 2008, Table 6 shows that ten of the fourteen regulations listed show a decrease. This means that these regulations were cited fewer times in 2008. Three out of the remaining four showed minor increases in usage. Only the complaint files regulation (198) shows a large increase, going from 61 % in 2005 to 69% in 2008. This is further elaborated in Table 7 which shows the most frequently cited 820 regulations between 2005 and 2008. This table shows a similarity in order ranking in the citations for the years 2005 and 2008, and again highlights the significance of 198 as the most often cited 820 regulation, the other being CAPA 100a (shown in Table 5).

Table 7: The most frequently cited 820 regulations between 2005 and 2008.

Order	2008 820	2008 (%)	2005 820	2005 (%)
1	198	69%	198	61%
2	30	48%	30	53%
3	20	44%	20	51%
4	22	40%	80	51%
5	80	39%	22	39%

After reviewing all the 820 regulations, it is clear that the trend in violations shown by the WLs is downward, with the few exceptions mentioned above, and this is captured in Table 8. Combining the results from this and the previous CAPA section, the two regulations that stand out in 2008 are 820.100a (general procedures) cited in 65% of the WL and 820.198 (complaint files) in 69%. The direction that the Agency seems to be frequently taking with 820 regulations is to cite general CAPA violations (100a), and then use the example of failures in maintaining adequate complaints procedures (198).

The Agency seems to be using complaints 820.198 as a proxy for overall quality on one hand and to support the more general CAPA 820.100a on the other. It is certainly a possibility that the Agency is focusing on this particular strongly related CAPA component as a way to build compliance.

Table 8: Changes of greater than 5% between 2005 and 2008 with 820.

820 Regulations	2008 n=62	2005 n=72	% Change
§ 820.20 - Management responsibility.	44%	51%	-7%
§ 820.30 - Design controls.	48%	53%	-5%
§ 820.40 - Document controls.	21%	29%	-8%
§ 820.70 - Production and process controls.	32%	39%	-7%
§ 820.75 - Process validation.	27%	33%	-6%
§ 820.80 - Device Acceptance.	39%	51%	-12%
§ 820.90 - Nonconforming product.	24%	29%	-5%
§ 820.184 - Device history record.	23%	36%	-13%
§ 820.198 - Complaint files.	69%	61%	+8%

DISCUSSION

It should be noted at the beginning of this discussion that the research methodology of analyzing WLs has its limitations, and provides only one perspective on FDA performance. Other avenues of research could be reviewing 483 observational inspection forms and written responses from the manufacturer, as well as data about product recalls, fines and penalties. These other factors are important, and may lead to a different understanding of the FDA inspection process. Clearly more depth could be gained with a detailed comparison of the findings in the WLs with the FDA inspection manuals and quality assurance guidelines (FDA, 2003b; FDA, 2003d; FDA, 2003e). Furthermore, future research could possibly examine the strong likelihood that the WLs are vetted by the FDA's legal staff to prevent lawsuits claiming a biased inspection process (Goldstein, 2008). Part of this WL vetting process 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 report writing inspection reports and WLs (EIR, 2008).

Similarly this research did not specifically review the WL data from the manufacturers perspective, though it did gain insight through previous research into the pharmaceutical industry (Macher & Nickerson, 2006; Adis, 2008). The manufacturers' response letters have not been not reviewed or analyzed, nor have the specific steps taken by manufacturers to comply with CAPA and 820 regulations. At this stage of the research there have been only preliminary discussions with manufacturers about quality assurance issues. 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, some preliminary conclusions can be drawn based on the data in this study. The results clearly show that the FDA is doing less cGMP inspections, is less focused on CAPA/quality assurance, and the work it does is of a more general nature. This seems to be independent of other research results that indicate dramatic improvements in manufacturing within the pharmaceutical industry in this period (Macher & Nickerson, 2006).

This research provides some basic insight into the FDA cGMP process through the study of WLs as an outcome of FDA regulations. It confirms several known trends within the FDA, and it establishes its own initial benchmarks:

- Fewer FDA inspections over the time period 2003-2008.
- While more cGMP WLs issued, a smaller percentage addressed 820 quality assurance.
- Similarly there was a downward trend in CAPA citation based WLs.
- CAPA WLs became less specific, focusing on the general provisions found in 100a
- Inspectors cited fewer 820 provisions, with an emphasis on complaints (198)

If the FDA is using the inspection process as a policy tool to wake up manufacturers to the need for quality systems, then there is some logic to the more general and less specific approach to the oversight process. But if the purpose of the inspections is FDA oversight, in a drive for quality assurance, then it is less successful. By not detailing the specific inspection violations, the FDA is not providing the necessary guidance to the industry. The CAPA risk methodology within the 820 quality assurance framework has the potential to focus on weaknesses within the manufacturers' production processes. With detailed WL information, manufacturers can be guided to building superior CAPA systems to correct and prevent system failures. Yet without rigorous inspections, it is likely that manufacturers will try to 'game the inspections' and meet quality and CAPA standards through building of complaints files and the like. This can only be avoided when the FDA invigorates its 820 inspections systems.

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