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McNeil Healthcare, Puerto Rico: FDA Case Study

Warren Adis
Iona College

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Warren Adis
Iona College, USA
wadis@iona.edu

ABSTRACT

The McNeil case study examines the FDA's quality assurance methodology through a detailed 12-year review of McNeil Consumer Healthcare, focusing on one of its major manufacturing facilities. It includes summaries from plant inspection reports, out-of-compliance findings, and warning letters for this period between 2000 and 2011. The results of this case study are then compared with a broader review of the FDA's performance within the same sector of Finished Bio-Pharmaceuticals (BP) over a similar period. This analysis provides a perspective on how the FDA incorporates its risk methodology in the overall inspection process and in particular in its quality systems practices.

Keywords: FDA, CAPA, cGMP, enforcement, warning letters, pharmaceuticals.

FOOD AND DRUG ADMINISTRATION CASE STUDY

The U.S. Food and Drug Administration (FDA) is the principal regulatory agency for the U.S. bio-pharmaceutical (BP) industry. In that role, it provides guidance, supervision and oversight. Together with the BP industry, the FDA has the task of ensuring that its products are safe, effective, and manufactured in accordance with "cGMP," the current Good Manufacturing Practice (U.S. Food and Drug Administration [FDA], 2004a).

This paper is a case study of McNeil Consumer Healthcare and one of its main manufacturing facilities at Las Piedras, Puerto Rico. During this 12-year period, 2000 to 2011, the FDA determined that this manufacturing facility had significant out of compliance problems. These findings are highlighted in plant inspection reports, Form 483 observational reports, and warning letters (WLs) as well as product recalls, and a court ordered consent decree. This material offers a valuable window on FDA activities and performance over a 12-year period at this site. Using data from this in-depth case study provides a first step in understanding FDA performance in terms of compliance, oversight, and governance (FDA, 2004a).

To determine whether the initial findings fit into a larger pattern of FDA practices, the results were then compared with other research that focuses on FDA performance using sector-wide data. The two principal academic investigations of the FDA's quality assurance (QA) that we are aware of are Adis' risk studies (2007; 2008) of the BP industry, and Marcher and Nickerson's (2006) review of quality systems. Both were sector evaluations, rather than a case study. Adis has also done some work with BP case studies (Adis, 2011).

The McNeil Las Piedras facility is noteworthy in that it posed significant compliance challenges to the FDA during the 12-year period. That facility, as well as the Ft. Washington manufacturing site, was subject to several FDA Field Alerts concerning failed manufacturing processes and several large-scale recalls of such popular product as Tylenol, Motrin, and Listerine.

McNeil's ongoing violations and the magnitude of the drug recalls have forced the FDA to post the 12-year history of inspections and out of compliance reports. With these reports, one can track and review FDA oversight and plant compliance (EIR, 2008). For the researcher, this opens the door to the site inspection process, and therefore quality assurance and risk prevention activities at Las Piedras. In addition, there are other public documents available: a judicial consent decree to mandate external monitoring, congressional transcripts of the FDA testimony concerning McNeil's recalls, and public statements from McNeil's management and their parent company Johnson and Johnson. Together, these documents fill in the narrative of activities during this timeframe of large-scale pharmaceutical recalls.

The FDA's supervisory agency, the Center for Drug Evaluation Research (CDER), is directly responsible for the Finished Pharmaceuticals sector, which includes over-the-counter drugs (U.S. Food and Drug Administration, Center for Drug Evaluation Research [CDER], 2007). It is a large agency with approximately 960 FTE field employees and an annual budget approximately $195 million. It performs hundreds of inspections and enforcement activities per year, just in the area of over the counter drugs. Consequently, this review of McNeil Las Piedras is in fact a very narrow investigation into CDER's quality assurance activities, presenting some initial evidence about CDER performance and its use of quality assurance techniques. To supplement these findings, the research then looked at CDER's activities and performance at inspection sites throughout the BP sector.

BACKGROUND: MCNEIL CONSUMER HEALTHCARE

McNeil, a subsidiary of Johnson and Johnson, had annual sales of U.S. $2.1 billion and 2600 employees in 2004. Its major manufacturing sites are Ft. Washington, Pennsylvania, which also is its headquarters, and Las Piedras. Both facilities manufacture, package and distribute a range of well-known over-the-counter drugs, including Tylenol and Motrin. Its manufacturing facilities produce finished pharmaceuticals and therefore must meet the FDA current good manufacturing practices (cGMP). These guidelines are the basis for quality systems and mandated industry best practice regulations (CDER, 2009).

Throughout this case study period, QA problems at Las Piedras and Ft. Washington caused the FDA to issue several field alerts and product recalls. For instance, in the 2008-2010 period the FDA in conjunction with McNeil recalled more than 100 million bottles of Motrin and Children's Tylenol from the distribution channel (FDA, 2011a). The Tylenol event is one of the largest recalls of child medication in FDA history.

These recalls were a further catalyst for additional FDA EIR inspections of Las Piedras. The resulting EIRs reported significant quality-control problems at the plant, and specifically noted

metallic particles in the children's medications. These violations triggered the recall of an additional 136 million bottles of pediatric medications, and curtailed production at the plant.

During this same period, McNeil faced additional recalls of over-the-counter products. These included Benadryl, Motrin, adult Tylenol and Zyrtec, which were produced at both the Las Piedras and the Ft. Washington sites. These multiple recalls were the result of the chemical breakdown of a protective coating on wooden transport pallets causing a moldy odor. This was transferred and absorbed into the drug containers and their contents.

Recalls are not taken lightly by the consumer, manufacturer or the FDA. The FDA defines recalls as a flagrant QA violation. It occurs when the agency determines that there is a reasonable probability that the use of, or exposure to a violative product will cause serious adverse health consequences or death. McNeil's recalls during this timeframe were mainly Class I, the most serious category.

After 12 years of recalls and out of compliance findings, the FDA took legal action against McNeil, and obtained a Consent Decree of Permanent Injunction (*United States v. McNeil-PPC, Inc., Cruz & Erdemir*, 2011). The Decree alleged that McNeil and certain corporate officers were responsible for cGMP violations in the life-cycle production of drugs. This specifically includes the manufacturing, processing, packing, labeling, holding, and distributing of their drug products. The Decree names the McNeil Corporation of New Jersey, and key defendants such as the VP of Operations and the VP of Quality Control. The decree permanently restrained and enjoined McNeil to curtail activities at Las Piedras and Ft. Washington until cGMPs were certified as restored. McNeil consented to the decree without admitting or denying the allegations, yet immediately closed the Ft. Washington facility. Part of the decree forced McNeil to hire outside cGMP consultants to make QA recommendations to remedy violations at their facilities.

The magnitude of the recalls and the popularity of the drugs involved led to a U.S. Congressional investigation of the FDA-McNeil situation. The congressional committee's purview included McNeil's quality controls as well as the FDA's supervisory oversight (FDA, 2010). It is likely that this investigation contributed to the FDA's release of the previously withheld McNeil site inspections reports. These released documents have provided a way to probe inside the quality assurance activities at both the FDA and McNeil for the last 12 years.

CURRENT GOOD MANUFACTURING PRACTICE

As the responsible supervisory agency to the BP industry, the FDA mandates quality systems (GAMP, 2001) in all manufacturing stages of drugs, vaccines, and other biological products. Its regulatory tasks are to inspect facilities to ensure that industrial standards are maintained, guaranteeing purity, potency, and quality for biological products. The range of activities include testing, examining production and quality control log books, and such enforcement actions as issuing warning letters for serious infractions, followed by ordering recalls. The regulatory guidelines (FDA, 2003b; FDA, 2004a) adhere to manufacturing best practices, with deviations in pharmaceutical products and processes triggering regulatory action.

As the BP industry continues to add more research and production sites, there is a parallel increase in the FDA's regulatory responsibilities. Yet it is well known that the Agency resources have been constrained by a flat budget and few staff increases over the past several years. Furthermore, this situation is exacerbated by the need for more trained information system staff to meet the computer driven QA methodologies. These insufficiencies make it difficult for the Agency to meet adequately its stated goals of inspecting domestic BP facilities on a regular basis. In fact, the Agency cannot meet its mandated two-year inspection cycle now, or its four-year cycle for more complex products and processes. This outcome has caused both a backlog for site inspections on the one hand, and, on the other, more partial inspections.

To address this resource bottleneck, the FDA adds to its industrial best practices inspections a QA methodology that 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 chooses manufacturing facilities with the highest risk priority, pinpoints the focus for the site inspection, and determines if 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." The Agency believes that this methodology makes "the best use of its limited surveillance and enforcement resources while maximizing the impact of those resources on the public health" (FDA, 2004a, p. 3).

More specifically, this research paper analyzes the role of risk management as detailed in the cGMP regulations. Central to this methodology are the concepts of corrective and preventative actions (CAPA). Best practices, combined with CAPA, are the basis for problem prevention, containment, and remediation. Consequently, they are intrinsic for both BP manufacturing and FDA inspecting (Committee of Sponsoring Organizations of the Treadway Commission, 2004). CAPA is an integral component for monitoring system performance, record keeping, and quality assurance (ICH, 2005a; ICH, 2005b; FDA, 2003a).

Based on CAPA, the FDA performs priority inspections for those manufacturing sites that have a previous history of production problems, or processes that have an inherently higher risk of system failure (FDA, 2008b). Each site inspection adds to the manufacturer's performance history, focusing on the following risk management statistics (ICH, 2008):

- Overall compliance history of the company and facility
- Results of the company's quality risk management activities
- Complexity of the manufacturing process
- Complexity of the product
- Therapeutic importance of the product
- Number and significance of quality defects (e.g. recalls)

The McNeil inspection documents that were published online permitted the researchers to track and evaluate the effectiveness of the FDA's implementation of CAPA.

RESEARCH METHODOLOGY

The researchers examined the McNeil Las Piedras documents, focusing especially on cGMP and CAPA issues. The research evaluated FDA performance by noting the frequency and depth of the site inspections, QA violations cited, and the cGMP guidance given by the FDA. This was then contrasted against actual field alerts, recalls and plant closings. In the mind of the researchers, the fundamental questions were whether the FDA had provided sufficient CAPA oversight, and whether more oversight would have eliminated these negative outcomes.

Using published documents and the Freedom of Information Act, the research was able to review FDA activity that met the following criteria:

- Took place at the McNeil Las Piedras facility during 2000-2011 period.
- Specifically addressed cGMP Practice for Finished Pharmaceuticals, found in regulations 501(h) of the Act (21 U.S.C. §351(h)) (FDA, 2008b).
- Included QA and CAPA risk methodology as mentioned directly or indirectly in FDA regulation Part 211.

Table 1 is a review of major FDA activities that take place at BP facilities, and is a helpful guide in understanding the direction of this research. The first column lists the common name used by the FDA, followed by a brief definition (FDA, 2008b). For the most part they are self-explanatory, though the more important ones, such as warning letters (WLs), will be further developed as the paper proceeds.

One should note that referenced activities in Table 1 are in logical order of growing importance. Category 1 contains CAPA activities to correct and prevent production problems. For instance, the EIR report firstly documents the inspection. The next row is the observation Form 483 stating that objectionable conditions were found during the inspection. The last entry in this category is the warning letters (WLs) for violations of regulatory significance, which also establish that prior notice was given before judicial action.

This grouping is followed in the table by Category 2, another class of CAPA activities that focusses on alerting the distribution chain concerning problems of non-conforming batches of drugs. This is done when the manufacturer, in collaboration with the FDA, issues field alerts, and if necessary recalls products (FDA, 2011 b).

Category 3 lists the most serious CDER enforcement activities: consent decrees to halt manufacturing with full plant closure. When the FDA realizes that their normal CAPA activities (483s, WLs) have failed to eliminate production hazards, they turn to the courts for legal action such as obtaining an injunction to temporarily stop production, or to close manufacturing operations. These enforcement actions are sometimes bypassed when the manufacturer voluntarily closes the plant to attempt to avoid the negative publicity of an FDA closure.

Category 1	**FDA Corrective and Preventive Activities**
EIR	Establishment Inspection Report: The EIR documents the inspection. FDA guidelines establish a 2-4 year manufacturing inspection cycle, plus additional inspections based on risk evaluation.
483	FDA Form 483: A summary of objectionable conditions listed in the EIR or related documents which are cited to support specific regulatory recommendations. These become the basis for WLs.
WL	Warning Letters are issued only for violations of regulatory significance. Significant violations are those that may lead to enforcement action if not promptly and adequately corrected. WLs are the agency's principal means of achieving prompt voluntary compliance and establishing prior legal notice.
Category 2	**FDA and Manufacturer CAPA Remediation Activities**
Field Alert	A manufacturer is required to file a Field Alert when an anomaly occurs in the manufacturing, viz., testing, processing, packing, labeling, storage, or distribution of a licensed biological. In particular those anomalies in which the safety, purity, or potency of a distributed product may negatively impact the public health. Certain Field Alerts may escalate to recalls of distributed products.
Recall	Recalls are actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority. A recall means there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences.
Category 3	**FDA Enforcement**
Consent Decree	Consent Decree of Permanent Injunction. An agreement by a defendant to an action to discontinue all activities viewed by the government as being illegal. This agreement occurs with the consent of both parties to the action and has court approval but stops short of a definitive judicial determination.
Plant Closing	An example is the voluntary plant closing by McNeil and Johnson and Johnson's management, prior to the issuance of the Consent Decree.
Category 4	**Congressional Investigative Activities**
Congressional Investigation	Congressional Committee on Oversight and Government Reform hearing on FDA oversight of McNeil.

Table 1: Review of Major FDA Activities.

The last category is U.S. congressional investigation. This is initiated only when the magnitude of recalls are significant. In this instance, Congress chose to review the FDA-McNeil business interactions.

Of all the items listed in Table 1, the researchers were particularly interested in how the CDER uses Warning Letters (WLs), since they are one of the stronger enforcement mechanisms. By formally establishing prior notice, the WL has the ability to both warn and guide manufacturers to correct significant regulatory violations. As the FDA states, "Warning Letter is the agency's

principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act (the Act)" (FDA, 2012b, 4-1-1 - Warning Letter Procedure, para. 2).

Here is a general summary of the CDER criteria for issuing WLs:
1. The violation reflects a history of repeated violations
2. There is a violation of cGMP in terms of manufacturing, ingredients, dosage, quality systems and oversight
3. The product contains illegal pesticide residues
4. The product shows short contents, subpotency, or superpotency

The WLs are a critical enforcement tool for addressing significant manufacturing QA failures. The WLs, together with the other McNeil related documents, present an in-depth look at the interactions between the FDA and McNeil during this 12-year period under study.

ANALYSIS

In 2010, the FDA obtained a court ordered injunction against McNeil and several of its manufacturing sites. While in the initial phases of court proceedings, McNeil voluntarily closed its Ft. Washington plant. In the following year, a congressional investigation began into the interactions between the FDA and McNeil. Its initial focus was on their latest recalls, but expanded into other areas over time.

Similar to the congressional investigation, this research probes and analyzes the FDA-Las Piedras interactions. The first step is to summarize the FDA-Las Piedras activity from 2000 to 2011 (see Table 2). The data in the table ranges from EIR Inspections to recalls and from consent decree to congressional investigation. In this way, the data represents a time chart showing the interlocking CDER activity and Las Piedras QA problems.

Table 2 shows that CDER addressed the QA issues with nine inspections, rather than the three or four that is typical for a well-functioning plant over a similar period. The inspections were detailed enough to generate eight 483 reports of objectionable conditions. Frequently, the CDER inspectors determined cGMP areas of QA and CAPA were the root cause of these manufacturing problems. It would be easy to claim that CDER did its job with guidance and ever-stricter oversight. Moreover, in reading these EIR reports, particularly in the 10-year period 2000-2009, some could loosely conclude that McNeil addressed, remedied or at least minimized any previously stated problem. This could be demonstrated by several years with either no inspections or inspections with no 483 reports of objectionable conditions. However, this preliminary interpretation may prove fallible when highlighting the serious QA failures from 2010 to 2011.

The basis of QA and CAPA methodologies are sustainable manufacturing practices, or what is referred to as "industrial strength" systems (Booch, 1994). The essential feature of an industrial strength system is 'day-in day-out' quality and reliability in all aspects of manufacturing. Problems with quality rarely materialize out of the blue, but are the result of failures over time. So it is a concern that the 483s, field alerts, and recalls are repeated over the 11 year period with

significant FDA intervention only occurring in the last two years. This has put paid the notion of sustainable manufacturing at Las Piedras and ever-stricter CDER oversight.

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
Category 1—CAPA Activities													
EIRs		1	1			2	1		1		3		9
483s		1	1			2			1		3		8
WLs											1		1
Category 2—CAPA Remediation													
Field Alerts						1		1		1			3
Recalls						1				3	2		6
Category 3—Enforcement													
Consent Decree												1	1
Plant Closing													
Category4—Investigative													
Congress Investigation											1		1
Totals	0	2	2	0	0	6	1	1	2	4	10	1	

Table 2: Summary of CDER McNeil Activity Las Piedras.

With this in mind, the researchers reviewed the CDER McNeil data more granularly. One can note that there was a general increase in CDER activity when there was a field alert/recall. Yet in the period directly preceding the field alert/recall, there was a lull in activity, as if there were no potential problems. For instance, there were no inspections in 2003-2004, prior to problems in 2005. Then while there was an inspection in 2006, no 483s were generated; yet in 2007 there was a field alert. The study period ends in 2011 with a serious systemic breakdown that culminated in an FDA initiated court injunction to close the Ft. Washington plant, and place Las Piedras under mandated cGMP supervision. It is all the years before the court injunction that are of particular concern.

Several questions can be raised:

- If QA and CAPA problems were adequately addressed, why did they return so vehemently?
- Were there weaknesses in the FDA oversight mechanism?
- Did the manufacturer's solutions actually meet the FDA cGMP standard?

These questions can be summarized by querying whether the FDA oversight was proportional to McNeil's QA and CAPA failures.

Table 2 provides some answers. There were 5 years when there were no inspections, interspersed with 7 years with inspections. In the years with inspections, there was only 1 year that the inspections did not yield a 483 for objectionable conditions. In fact, in the nine inspections total from 2000 to 2011, there were eight 483s generated.

This runs counter to CDER best practices and cGMP methodology, which specifically calls for increased focused activity based on the risk detailed in EIRs and 483s. This is even more troublesome in light of the product recalls in 2005 and 2009-2010.

Then even more strikingly, CDER issued only one warning letter at the end of the 12-year time period. As discussed earlier, a WL is one of the FDA's principal enforcement tools used to establish prior notice before stringent enforcement or penalties are invoked. Without due diligence on the part of the FDA and McNeil, the manufacturing problems can persist, and therefore the risks to the public would remain. By contrast, the data shows that only at the very end did CDER become proactive and exercise due diligence, required by its own cGMP methodology.

Another way to look at the same data is by comparing FDA EIRs for each year. As mentioned earlier, in 2004 the FDA established the new cGMP standards emphasizing quality and CAPA activities. Therefore, from 2004, the EIRs should uniformly reference the same cGMP standards, and this would help clarify the degree to which CDER followed its own oversight methodology.

Table 3 presents a summary from the FDA reports of 2005-2006, and compares this with the reports of 2010. It also includes a summary from the Consent Decree of 2011. The FDA language has been modified for the sake of clarity. The table uses standard CDER categories: quality systems, packaging, laboratory, and facility and equipment systems. The recurrent theme in these documents is that McNeil had substandard QA throughout its operations.

CDER determined that McNeil's quality control unit was not integrated with plant operations, and consequently failed to supervise, audit, and provide the necessary support. The quality control unit failed to thoroughly review and document any unexplained discrepancy. More specifically, investigations did not always include appropriate QA documentation, nor were they timely or complete. This failure was repeated throughout the report categories and throughout the timeframe.

Does this possibly mean that after the detailed 2005-6 findings, McNeil dramatically improved operations at Las Piedras; then unfortunately in the later period McNeil slipped and made an equally dramatic reversion to the old inferior standards? Or, more realistically, were CDER efforts at coaxing and providing "soft" guidance, in fact, unsuccessful? Similarly, did certain interim inspections tend to be pro forma and unfocussed as shown by the EIR conducted in April 2006 in which no 483s were issued in spite of a field alert and recall in 2005 of children's Tylenol Tablets?

The answers cannot be found in one case study, particularly since the EIRs and the 483s were filled with much redacted material. Yet QA experts understand that sustainable QA cannot show continual swings between poor quality, dramatic improvements and then reversals. (de Neufville, 2004). The Consent Decree is useful in that it provides some of the missing information.

Major Quality Assurance Functional Areas	CDER 2005-6	CDER 2010	Decree 2011
Quality Systems			
a. Failure to review thoroughly any unexplained discrepancy. Specifically, investigations did not always include appropriate QA documentation, nor were they always timely or complete.	✓	✓	✓
b. Unexplained discrepancy did not extend to other drug products that may have been associated with the specific failure or discrepancy.	✓	✓	✓
c. Responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.	✓	✓	✓
d. No written procedures for review of complaints, returned drug products, and conducting investigations.	✓	✓	✓
Packaging System			
e. Strict control is not exercised over labeling drugs.	✓	✓	✓
f. Labeling and packaging materials are not representatively sampled and examined.	✓	✓	✓
g. Quality Control unit did not review and approve procedures for packaging and reprocessing.	✓	✓	✓
Laboratory			
h. Batch production and control records do not include all necessary information.	✓	✓	✓
i. Laboratory records do not include necessary information: description of the sample received for testing, its source or location, the quantity and date of the sample.	✓	✓	✓
j. Quality control unit does not review or approve changes to equipment specifications or procedure.	✓	✓	✓
Facilities and Equipment System			
k. Written procedures are not established and followed for the cleaning and maintenance of equipment used in the manufacture, processing, packing or holding of drugs.	✓	✓	✓
l. Representative samples are not taken of each lot shipment for testing or examination.	✓	✓	✓

Table 3: QA Problems between 2005 and 2011.

The decree states that McNeil has the legal obligation to

- Hire a cGMP expert to eliminate its deficiencies in manufacturing.
- Develop a comprehensive, written quality assurance and quality control program that ensures continuous compliance. Johnson & Johnson, the parent company, is obligated to coordinate and support these tasks.
- Assure continuous compliance with the cGMP federal regulations relating to the safety, identity, strength, quality, and purity of drugs
- Have a Quality Control Unit at its facilities that is adequately qualified, trained and staffed to evaluate cGMP compliance, to prevent and promptly correct future deviations

CDER was fully tested over the 12-year period. It faced an obstinate McNeil, who were unable or unwilling to work towards achieving continuous compliance. Even the introduction of the new risk based cGMP methodology in 2004 failed to improve the overall safety of the plant, or strengthen the QA functions. Similarly, CDER gives the impression that it was unable or unwilling to increase its oversight. Since CDER did not issue a WL until 2010, it would be

hard to conclude that CDERs level of oversight was appropriate to the QA failures and dangers posed by Las Piedras. Only in 2010-2011 did CDER enforcement match the obduracy of McNeil.

DISCUSSION

This research case study focused on one manufacturing site, among the thousands of facilities that produce finished pharmaceuticals. While it is an in-depth analysis of McNeil-CDER interactions over a 12- year period, it lacks the breadth of a wider study. Consequently, the findings by their very nature are limited at this stage, yet for the following reasons are important:

- This is one of the few times the FDA has published EIRs and 483s showing their activity
- These EIRS and 483s reference the same site, with the same problems for 12 years
- The McNeil facility produces popular non-prescription drugs: Motrin and Tylenol
- McNeil has had recalls of millions of units over a 12-year period
- Johnson and Johnson, the parent company, which has a well-established reputation for quality, is indirectly involved in the McNeil failure.

Extrapolation based on one case study is problematic, though it is still fair to ponder how CDER could fail to follow its own cGMP guidelines in addressing McNeil's QA violations. Likewise, one may be taken aback in contemplating McNeil's flagrant disregard of best practices.

As stated earlier, CDER issued only one single WL after multiple years of 483s and recalls. This lack of WLs hampered CDER's oversight, because it failed to establish prior legal notice (Goldstein, 2008). This made future enforcement activities more difficult since CDER did not follow its own procedures.

It did not take long before there was a parallel research question. The researchers wanted to know if the absence of WLs was unique to the CDER—Las Piedras interaction or was this part of a larger pattern in the BP sector for finished pharmaceuticals. To address this issue, the researchers investigated the CDER-BP industry and reviewed the frequency in which CDER issued cGMP WLs. Table 4 shows the number of cGMP WLs that meet the relevant QA cGMP criterion for the period 2003-2011.

The principal source documents for the table are the 2012 FDA's Field Activities—Office of Regulatory Affairs (CDER, 2012) and other congressional budget reports (FDA, 2012a). These reports contain FDA budgetary and staffing information with its field activities. From these documents, it was straightforward to calculate the total number of CDER field inspections per year, as well as those that triggered WLs.

Table 4 displays the total of yearly CDER inspections of finished pharmaceuticals facilities and the WLs issued for QA Part 211 violations from 2003 to 2011. The number of inspections ranged from 983 to1,365, while the resulting WLs ranged from 13 to 48. This obviously shows a disparity between the large number of inspections and the smaller number of WLs. The ratio

shown as a percentage (Column C) emphasizes the fact that the percentage of WLs vary from between 1% and 4% of the yearly inspections. The introduction of cGMP risk methodology in 2004 does not seem to have any particular impact.

If the purpose of CDER's cGMP methodology is to focus its limited resources on risk prone manufacturers, then there is a noticeable break between the theory and practice. McNeil's Las Piedras is a real world example of missing inspections, 483s, and WLs. This break occurred in spite of the objectionable conditions, field alerts and recalls.

Year	(A) Total Inspections	(B) Part 211 WLs	(C) Percent (B/A)
2003	1,149	35	3.0%
2004	1,232	26	2.1%
2005	1,365	14	1.0%
2006	1,222	20	1.6%
2007	1,073	13	1.2%
2008	972	29	3.0%
2009	983	26	2.6%
2010	1,174	48	4.0%
2011	915*	38	4.2%*
* FDA estimate			

Table 4: FDA Inspections (Part 211) and Corresponding WLs for the Finished Pharmaceutical Sector.

A more extensive research agenda may in fact point to a different understanding of the weakness in the FDA inspection process. For instance, an expanded agenda could address CDER's:

- Actual enforcement policy
- Experience and training inspectors have with CAPA and risk methodologies
- Experience with enterprise resource planning (ERP) systems
- Policies on product recalls, fines and penalties
- History with manufacturers' litigation against the FDA

The researchers' goal is to continue building other case studies to see if they in fact replicate the patterns shown in the Las Piedras research. Using future case studies and broad sector analysis, the researchers plan to continue to investigate CDER's performance and how its limited staff and resources impact efficiency.

CONCLUSION

This case study highlights 12 years of CDER-McNeil Las Piedras business dealings. During this period the FDA was hampered by budgetary and resource problems. This may have resulted in a period when there were missed or incomplete cGMP inspections and unissued WLs. Unfortunately, this was also a period when McNeil failed to follow best practices, which resulted in massive recalls of popular products. Then when everything seemed to be on a downward trajectory, the inertia at the FDA disappeared and its enforcement actions at Las Piedras were clear and strong, issuing a court injunction mandating cGMP and best practices.

So depending on circumstances, CDER is an organization weighed by its constraints, or a proactive focused organization.

In summary, the inconclusive CDER activities at Las Piedras from 2000 to 2009 are as follows:
- Inconsistent EIR inspections, in spite of field alerts and recalls
- Ineffective 483 reports that failed to remedy conditions
- Failure to issue cGMP WLs when facing persistent and significant QA problems

The more focused CDER enforcement (2010-2011) included:
- Frequent and rigorous inspections
- Detailed 483s documenting objectionable conditions
- Warning Letter establishing judicial prior notice
- Recalls on products
- Judicial action through Consent Decree
- Court ordered cGMP compliance

It seems clear that CDER site inspections and 483s are a necessary first step, but by themselves, they are not sufficient. WLs become an essential enforcement activity when faced with the manufacturer's failure to respond to guidance, WLs are public documents in which the media exposes the manufacturer's flagrant quality control violations. Equally important, they are the basis for legal action. CDER's failure to issue necessary WLs endangers the public and can quite rightly be the subject of a congressional investigation.

The basis of cGMP and CAPA methodologies is the ability to escalate enforcement. The failures in this case study may be the result of CDER's constraints. Yet it may also stem from negligence and incompetence on the part of CDER. In either case, it needs to be further investigated and addressed. Through additional case studies, the researchers plan to look deeper into those quality issues that have dogged McNeil, and should have been addressed more seriously by CDER.

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