FDA investigators are continuing to uncover serious data integrity issues at facilities in India, including repeat citations – highlighting the challenges regulators face in getting companies to make changes in their quality culture.

Since the middle of 2013, seven Indian firms have received warning letters referencing the integrity of their records, procedures, and interactions with FDA investigators.

Those letters followed in the wake of an equal number of warnings issued from the beginning of 2012 to mid-2013 addressing integrity problems, three of which involved plants in India.

[Editor’s Note: For an in-depth analysis of the drug GMP warning letters issued by FDA from 2012 through mid-2013 that reference data integrity see IPQ August 22, 2013. The story focuses in particular on the issues that surfaced during that time frame at RPG, Fresenius Kabi, Wockhardt, and Ranbaxy. A listing of all 14 of the letters from 2012 through April 2014 that cite data integrity is provided below. The earlier IPQ coverage extended through the letter issued to Wockhardt in mid-July 2013. The Aarti Drugs letter in the listing was issued in late July 2013 and was not part of the earlier coverage.]

Large generic company Wockhardt, already on FDA’s data integrity watch list from a warning letter received at one of its plants in July, 2013, was delivered a second letter in November covering two other facilities that manufacture oral solid and injectable products.

Along with Wockhardt, four API manufacturers in India (Aarti Drugs, Posh Chemicals, Canton Labs and Smruthi Organics), one injectable firm (Agila Specialties) and one oral solid manufacturer (USV) also received letters that focused in part on integrity lapses.

In addition, data integrity issues were raised in 483s issued to Sun Pharma and Ranbaxy in December 2013 and January 2014, respectively. Both resulted in import alerts on products manufactured at the implicated facilities.

Problems were found at the Ranbaxy facility in spite of the company already being under a consent decree that was signed in 2012, arising from significant integrity issues uncovered at another two of its key India plants (ibid.). Sun announced in March that it was purchasing Ranbaxy from Daiichi Sankyo, and that fixing Ranbaxy’s compliance problems was a “top priority.” Sun’s own compliance problems were not referenced in the announcement.

In late April, an Indian court temporarily halted Sun’s $3.2 billion purchase of Ranbaxy Laboratories until it decides on a petition for a probe into alleged insider trading.
FDA Warning Not Heeded by Wockhardt

Wockhardt’s problems detailed in the July 2013 warning letter were based on a six-day inspection of its Biotech Park facility in Waluj, India the previous March (ibid.). The letter provides eye-opening insights into the integrity lapses and efforts to cover them up that FDA has been finding in India.

Two days after the July letter was issued, agency investigators began simultaneous inspections of two of the company’s other plants in India – a second facility located in Waluj, and one in Chikalthana. Similar and repeat observations during the inspections led to a second warning letter to the firm five months later in December, addressing the findings at both facilities.

Observations cited in the December letter that were the same as those noted in July included: ● performing “trial” sample analysis ● QC laboratory computer instruments on which lab personnel could delete raw data files, and ● operations personnel performing manufacturing steps without a batch record or a manufacturing form to document the results contemporaneously.

The repeat observations “indicate that your quality unit is not exercising its responsibilities and may not have the appropriate authority or ability to carry out its responsibilities,” according to the December letter. FDA was “particularly concerned” about the firm’s “inability to implement a robust and sustainable quality system.”
It “is apparent that Wockhardt is not implementing global and sustainable corrective actions,” the letter states. FDA “strongly” recommended that Wockhardt’s executive management “immediately undertake a comprehensive and global assessment” of its manufacturing operations “to ensure that your systems and processes, and ultimately, the drug products you manufacture, conform to FDA requirements for safety, efficacy, and quality.”

Using language identical to that in the July letter, the agency also “highly” recommended that Wockhardt “hire a third party auditor with experience in detecting data integrity problems to assist you with this evaluation and to assist with your overall compliance with CGMP.” The letter adds that it is the firm’s responsibility to ensure that data generated during operations is “accurate” and that the results reported are “a true representation” of the quality of its drug products.

In responding to the letter, FDA’s Office of Manufacturing and Product Quality (OMPQ) Director Steve Lynn asked Wockhardt to “provide a list of all the batches of drug products shipped to the U.S. market that relied upon missing, inaccurate, or unreliable test data.”

**Just prior to the December letter, FDA issued an import alert restricting entry into the US of human drug products manufactured at the two plants.**

After the letter was issued, a second import alert, described as “detention without physical examination” of veterinary drugs from the plants, was announced. While the company had reportedly sold its animal health division in 2009 to the French veterinary care company Vétoquinol, Wockhardt may have been manufacturing veterinary drugs on a contract basis in a way that was not apparent earlier to FDA.

**State FDA in India FDA Weighs In**

In late March, the Food and Drug Administration for the Indian state Maharashtra issued “show cause notices” to the Wockhardt plants that had received the FDA warning letters, according to the Indian newspaper *DNA*.

*DNA* was reportedly informed by a source from Wockhardt that Maharashtra FDA officials sought an explanation as to why GMPs are not being followed.

**The Indian news source reported that last December the Indian state agency instituted a three-member special investigation team (SIT) comprising drug inspectors from Ahmednagar, Solapur and Mumbai to inspect the three pharma plants.**

The inspection report, which was obtained by *DNA*, cited significant violations of GMPs and general sanitation expectations, including: ● biomedical waste dumped openly ● up to 114 rusted drums containing glycerine – used in making injections – lying unused for months ● a proliferation of insects and rodent excreta, and ● used gloves and medicine packs lying in the open.

An official from the inspecting team explained to *DNA* that empty trial tablet packs, which are produced to check packaging norms, were dumped in the open, and could have easily been stolen or illegally recycled for use with counterfeit medicines.
He also noted that 5,000 vials of agar gel, which is used as culture medium for injectable products, were lying in the open – presenting an ideal breeding ground for the uncontrolled growth of microorganisms, threatening contamination of the atmosphere.

State FDA commissioner Mahesh Zagade confirmed in late March in an interview with DNA that the “show cause notices” were issued and that Wockhardt has been asked to respond.

According to the DNA report, Zagade said that if drug inspectors find that the plants do not step up their compliance level, suspension or cancellation of manufacturing license may be initiated.

Since 40% of the medicines being produced in Indian plants are exported abroad, India needs to be wary of faulty practices to ensure its export market, he emphasized.

On April 22, Wockhardt announced a further suspension imposed by Indian regulators.

The firm said that the “State Drug Controller in Himachal Pradesh has suspended the manufacture, sale or distribution” of its fixed-dose combo drug made up of dicyclomine HCl 10 mg, tramadol HCl 50 mg and acetaminophen 325 mg. Wockhardt said the drug accounted for 3% of its sales last year and that is was appealing the suspension.

The suspension resulted from a tip to the Indian agency that some of the ingredients the company used to make the painkiller had been banned by the Indian government, Himachal Pradesh state drug regulator Navneet Marwah told Reuters.

He explained that the action was taken after receiving complaints from consumers, adding that his office has reported the problem to the federal authorities and that the ban would remain in place until action was taken at that level.

The suspension was revoked on April 26 after the federal agency investigated and said it found no problems with the products’ safety and efficacy, a state drug regulator told Reuters.

Ranbaxy Had Similar Issues

Data integrity issues reported by FDA in the Wockhardt warning letters were similar to those that led to the Ranbaxy consent decree in January 2012 (IPQ, January 30, 2012).

The decree stemmed from investigations by FDA beginning in 2008 that revealed numerous problems with Ranbaxy’s drug manufacturing and testing at facilities in both India and the US, and data integrity problems at its India operations, including backdating of tests and submitting test data for which no test samples existed (IPQ May/June 2009).

In May 2013, the firm pleaded guilty to three felony counts of violating federal drug safety laws and four of making false statements to FDA.
The issues at Ranbaxy continued to garner media attention as more information surfaced from former Ranbaxy employee whistleblower Dinesh Thakur, which outlined a culture of fraud and corruption (IPQ August 22, 2013).

In a statement released after the guilty plea was entered, Ranbaxy noted that the settlement involved “conduct that occurred several years ago.” Ironically, Ranbaxy CEO Arun Sawhney said in the statement that “today’s announcement marks the resolution of this past issue.”

**Ranbaxy’s Past Is Prologue**

An FDA inspection at a Ranbaxy plant just eight months after the guilty plea indicated that the company’s problems had not been resolved.

In January 2014, FDA inspectors visited a Ranbaxy facility in Toansa, in a rural area north of New Delhi, and found data integrity and GMP issues similar to those uncovered in the previous inspections of Ranbaxy sites that led to the warning letter and consent decree.

Investigators discovered workers running analytical tests repeatedly until they got the desired results, computer systems that allow deletion of raw data by operators, and back-dating of forms – including those specifically used to comply with the terms of the firm’s consent decree – according to the FDA 483 issued after the inspection.

In addition to the data integrity issues, the investigators also found GMP problems in the laboratory, including unusable equipment, open windows that could not be closed, flies “too numerous to count,” and a defective refrigerator containing a pool of water where working standard sample containers were stored.

Investigators emphasized that the same lab observations were previously noted and discussed with company management during an inspection close-out meeting in December 2012.

Shortly after the inspection, FDA placed an import alert on the APIs made at the Toansa plant. The agency had already restricted imports from three other Ranbaxy facilities in India, including those in Paonta Sahib, Dewas and Mohali, resulting from previous poor inspections.

Ranbaxy voluntarily suspended all shipments of APIs from Toansa and a second Indian plant in Dewas after the FDA ban, Ranbaxy’s parent company, Tokyo-based Daiichi Sankyo, said in a Feb. 25 statement. Ranbaxy is continuing to make finished products for non-U.S. markets using API inventory from Toansa and Dewas and from external sources.

In late March, Indian authorities withdrew the Toansa site’s “written confirmation” – effectively suspending the export of products, as the confirmation must accompany APIs shipped to foreign countries.

The announcement came only days after Indian-based Sun Pharma announced it would buy Ranbaxy in a $3.2 billion all-stock deal with Daiichi Sankyo. The combined entity will be the world’s fifth largest generics maker with $4.2 billion in revenue, with the U.S. accounting for $2.2 billion.
EMA said in early April that a team of inspectors from Germany, the U.K., Ireland, Switzerland, and Australia performed an “unannounced” inspection at the Toansa facility following the FDA import ban, and found issues similar to those found by FDA. EMA is planning an inspection of the Ranbaxy Dewas plant in June. The European agency said it will not permit any imports from the two facilities until it has confirmed that the problems have been fixed.

Both Ranbaxy and Sun recently announced product recalls, both for oral solid products.

In mid-March, Sun initiated a voluntary recall of nearly 3,000 bottles of metformin hydrochloride extended release tablets after a customer complained of the presence of some gabapentin tablets, a drug used to treat seizures, in a bottle.

In late April, Ranbaxy announced a Class II recall that it had begun in February of nearly 30,000 packs of an allergy-relief medicine containing loratadine and pseudoephedrine sulphate extended release tablets for packaging defects. The product was manufactured by the firm’s Ohm Labs plant in New Jersey, which is the company's only facility currently making generics for the U.S.

Imports Also Banned from Sun Pharma Plant

Ranbaxy’s purchaser Sun Pharma also found itself in regulatory trouble after a late-2013 FDA inspection, which resulted in an import alert in mid-March, 2014.

Notably, the same FDA investigators who inspected Ranbaxy in January had previously inspected Sun’s cephalosporin facility located at Karkhadi, Gujarat in India in November – Peter Baker and Dipesh Shah, both consumer safety officers based in FDA’s India office. The plant is one of 25 that Sun owns, and accounts for less than 1% of the company’s sales.

The form 483 issued by the investigators at the conclusion of the inspection was obtained by Economic Times of India (ET), which published many of the observations.

“Drug products failing to meet established specifications and quality control criteria are not rejected,” the 483 noted. Investigators “identified multiple torn/partially destroyed raw data CGMP manufacturing and quality records.”

Their review of the records, the 483 reports, “identified the practice of maintaining duplicate versions of cGMP raw data records. Undesirable data was found to be changed in the official versions in order to meet specifications.”

The 483 also reported observations of poor housekeeping and unsanitary conditions, characterizing the toilet facilities as in a state of “total disrepair.”

“The two urinals present in the washing and toilet facility provided for quality control laboratory male employees were found to drain directly onto the floor. Urine was found to be collected in and around an open drain. A strong smell of urine was observed throughout your firm’s quality control environment,” the 483 states.
Investigators also noted a garbage dump in the perimeter of the manufacturing area and various forms of infestation. “Buildings used in the manufacture, processing, packing or holding of drug products are not free of infestation by rodents, birds, insects and other vermin.”

Ironically, two years earlier, Sun Pharma had been asked by FDA to step in to fill a shortage when Johnson & Johnson was no longer able to supply its injectable cancer drug Doxil to the market due to compliance problems at its Doxil contractor, Bedford, Ohio-based Ben Venue.

Compliance problems uncovered during mid-2011 inspections by FDA and EMA at the Ben Venue facility resulted in the site halting manufacturing, and eventually led to critical shortages of the drug (IPQ November 29, 2011). Injectable Doxil is used in multiple treatment regimens, including treatment of ovarian cancer after failure of platinum-based chemotherapy. The drug is also indicated for use in AIDS-related Kaposi’s sarcoma and multiple myeloma.

In response to the shortage, FDA allowed the importation of Lipodox, an injectable Doxil substitute manufactured by Sun that had not been approved in the U.S. (IPQ Feb. 24, 2012). In 2013, FDA approved a generic version of Sun’s drug for the U.S. market that further helped ease the shortage.

Temporary importation of unapproved foreign drugs is considered in rare cases when there is a shortage of an approved drug that is critical to patients and the shortage cannot be resolved in a timely fashion with FDA-approved drugs.

In 2009, FDA ordered manufacturing to be halted at Sun’s Detroit-based unit after a string of recalls over manufacturing defects. Three years later, the FDA cleared the subsidiary to resume operations with two products.

Other Indian Firms Banned

In 2013, FDA banned about 20 plants in India from exporting drugs to the U.S. and warned several others.

The most recent import alert was placed on Canadian-based Apotex’ plant in Bangalore in early April, due to significant GMP deviations.

The alert covers the company’s drugs and antibiotics, with the exception of riluzole, used in the treatment of amyotrophic lateral sclerosis, commonly known as Lou Gehrig’s disease.

Apotex received a warning letter in early 2013 for issues discovered during an August 2012 inspection of its Richmond Hill, Ontario, Canada facility. The letter pointed to GMP concerns regarding: ● microbial control SOPs ● OOS investigations ● process validation ● laboratory records ● environmental monitoring, and ● CAPA.

An import alert was also placed on APIs coming from Canton Labs’ facility in Vadodara, India after its receipt of a warning letter at the end of February (IPQ April 17, 2014).
Topping the warning letter was the finding during an inspection a year earlier that Canton was reporting on its CoAs that batches were meeting microbial and metal impurities limits without actually doing the testing or having any supporting data.

**Data Integrity Warning Letters Examined**

At a PharmaLink conference in March in Cincinnati, Ohio, co-sponsored by FDA and Xavier University, National Expert Investigator Rebeca Rodriguez provided her perspective on the problems the agency is seeing with data integrity in the context of warning letters issued to foreign firms in 2013-2014 (see box below for Rodriguez’ complete remarks on this topic).

Although data integrity issues are more frequently discovered in certain countries, Rodriguez emphasized that FDA is not “targeting any particular country.”

The recurrence of warning letters citing data integrity problems to firms in particular countries may be reflective of a number of factors, she said, including: ● “regulatory maturity” ● experience of the investigator, and ● location of the firm within a country.

> **The regulatory maturity of both the country regulators and the inspected firms is an important factor, Rodriguez commented. She explained that regulatory maturity “comes from experience and knowledge of what things can happen.”**

“It is not that people don’t know or people are stupid – it is regulatory maturity. We learn from mistakes. And we learn from things that can happen and from risks that we didn’t see before.”

Regulatory maturity can also manifest itself in terms of the investigator performing the inspection, with more experienced investigators better able to uncover problems.

“I know for a fact,” the FDA expert said, “that some of the [agency] people involved in the data integrity warning letters are people who have a lot of experience, because they have worked with these systems themselves. They know the lab systems and how to work with them.”

> **Rodriguez also pointed to the geographical location of a firm as an important factor in being able to attract and retain the expertise it needs to become and remain compliant.**

“I have seen companies that have very knowledgeable people, but their area of expertise is maybe for the same processes, but for food establishments, not for drugs. I have seen people who mean well. They were knowledgeable of the processes, but they were not knowledgeable of the drug regulations.”

“It is not only the country, but even within a city,” the expert investigator commented. One company she is familiar with face problems in getting people with “the right expertise” due to its location outside of an area where people wanted to live. “They wanted to live near the nice city, not an hour away. I have seen this with some companies that are having trouble hiring the right expertise because their sites are not located where people want to be.”
FDA’S RODRIGUEZ ON DATA INTEGRITY IN FOREIGN WARNING LETTERS

I looked at warning letters that were issued to foreign and domestic firms in 2013 and 2014. I particularly looked at four warning letters that were issued to drug manufacturers – including one API manufacturer, and 13 foreign firms. Some of these warning letters were issued to multiple facilities of the same company. Some of these warning letters were also issued for OTC manufacturers, re-packers, re-labelers, contract labs, etc. But the bulk were mostly to API and finished drug product manufacturers.

When I was looking at those warning letters, what really stood were data integrity observations – data integrity issues with foreign establishments. I don’t know how familiar you are with the issues, but it has been in the news…

We are really not targeting any particular country. But the data integrity problems may reflect on several factors regarding regulatory maturity of the companies and the country…. There are a number of things that may be playing into this recurrence of warning letters to particular countries.

Part of those warning letters were also related to the integrity of data that is coming from computer systems, which is also part of data integrity. That was the point in showing warning letters relating computer systems to the integrity issues. And there also was a failure to review and investigate production and QC laboratory deviations. Those are the three things that stood out to me in those warning letters.

The data integrity issues were mostly related to HPLC processing methods – for example, people running multiple runs of the same samples and changing integration parameters until they got the results they expected or wanted. That is obviously not acceptable. That is basically testing into compliance. For whatever reason – I am not saying it was intentional, I am not going there – it was happening.

Another issue that was found during these inspections was the documentation trail of the computer systems, of the chromatographic systems, was disabled. The audit trail basically tells you every time someone performs a critical operation with a signature – that the system documents that step, and that that action was taken. That trail was disabled. They were changing data and changing parameters. Whatever the functions that the audit trail was supposed to follow were not being documented. The absence of that audit trail was enabling people to delete data and change operation parameters, integration parameters, and that kind of stuff. They used the same password and username. That is a clear no-no. But we still find these things. I, myself, have found companies that are still doing this.
Another issue that the investigators found was that the system did not protect the data. It was possible to access the system and make changes or deletions to the system. These are just similar iterations of the same issue – the failure to implement access controls to the system.

Excel spreadsheets were also mentioned. Calculations in the spreadsheets were not protected. People could make changes to the formulas that were in the spreadsheets. This is pretty much the same stuff. These are just some of the issues that were cited related to computer systems.

There were also less complex issues. Speaking of complexity or lack of complexity, in this particular case, people were using post-it notes or small pieces of paper to write stuff, and then they were transferring that to worksheets or formal documentation. That kind of practice lends itself to people documenting the data to meet whatever expectations they have. So that is completely unacceptable.

And also, people were performing multiple runs of the same samples, and calling them different names such as trials or demos, until they got the ones that were acceptable. Out-of-specification (OOS) results were ignored and not investigated – they were accepting only the good results.

I thought this one was really interesting. In this case, the reason for the continuous testing and re-testing was that the company was having API batches that failed. They were blending the bad batches with the good batches and they were running them again, so then they got a good result. The blending of a bad batch and a good batch is a GMP violation in itself. Then they covered that up in the re-testing practice.

In this particular case, the managers of the company claimed in their response to the 483 that they didn’t know why operators were doing that. Personally, I have a hard time believing that. I don’t have any stake in the company or that batch. I am not getting the money for that batch. So I don’t know how this practice was not being encouraged by management. I just really wonder when I see stuff like this.

Other issues that they found were that people were pre-documenting operations. If they were going to perform a step, they would fill in the data before they performed a step. So that was a little bit of foreseeing an event or something. This happened not only in lab operations, it was happening in manufacturing operations as well – they were not documenting operations as they were performed.

Those are the data integrity issues that were reported in multiple warning letters. And it was to one particular country. When I look at this, I wonder what the outcome of this is, because some of these firms were placed on import detention. Basically, they can’t sell product to the U.S., though in some cases the FDA had to allow some things into the U.S. for very specific reasons.

But what does a company do when their supplier of a critical API cannot supply because they have been placed on import detention? What does a U.S. manufacturer do about that? It is a huge problem. Could that U.S. manufacturer have prevented these problems to some extent by doing their homework and qualifying their supplier? That is a question. I am not concluding anything. These data integrity issues are not always easy to find. On the other hand, in these particular cases, they seemed to be pretty extensive practices. There were things that the investigators readily found.
Data Integrity Findings Impact Shareholder Value

Following Rodriguez to the podium at the Xavier/FDA conference in March, MHRA GMDP Inspections Group Manager Mark Birse provided an analysis of the impact of the data integrity observations on the market value of a firm.

Birse provided a case study that involved inspections conducted simultaneously by FDA and MHRA during which many of the data integrity deficiencies Rodriguez pointed out in her talk were uncovered. While neither mentioned the firm’s name, Wockhardt clearly fits the profile.

The UK official noted that the share price for the firm involved had quadrupled during 2012. However, as inspections revealed deficiencies that resulted in FDA import alerts and EU statements of non-compliance (SNC), the value of the company declined rapidly (see box below).

The three inspections conducted are represented in the figure by red circles. During first inspection, MHRA was “on site at exactly the same time as FDA,” Birse noted, and uncovered many of the same integrity issues.
The first stock price drop occurred when FDA issued an import alert, followed by a smaller drop after EU issued an SNC.

A second MHRA inspection of a different site coincided with the issuance of an FDA warning letter to the company that resulted from the first inspection. During the second inspection, the company issued a statement to the press that the inspection “was not going well,” Birse commented, at which point the stock price “hit rock bottom.”

After the stock drop, the firm issued another statement to the press “to try and put a positive spin on things,” at which point the price went up slightly. “But then in the EU we issued a statement of non-compliance for ‘site two’ and a statement of non-compliance for ‘site three,’ which we had inspected,” he explained.

“All in all, all of the good work that that company had previously been doing building up share prices for investors was just destroyed,” Birse said.

“Just imagine how much stock value was being lost during that time. Imagine if a small slice of that had been taken off and been spent on quality – actually doing the right thing. They would not be in this position now if they had really thought about it.”

**MHRA Data Integrity Expectations Outlined**

Birse went on to discuss his agency’s expectations for a company’s review of data integrity during its internal audits. The expectations were published on MHRA’s website in December (see box below).

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**MHRA Expectations for Data Integrity Self Auditing**

*The following expectations regarding self inspections by pharma firms were announced by the UK’s MHRA in December, 2013:*

- The MHRA is setting an expectation that pharmaceutical manufacturers, importers and contract laboratories, as part of their self-inspection program, must review the effectiveness of their governance systems to ensure data integrity and traceability.

- This aspect will be covered during inspections from the start of 2014, when reviewing the adequacy of self inspection programs in accordance with Chapter 9 of EU GMP.

- It is also expected that in addition to having their own governance systems, companies outsourcing activities should verify the adequacy of comparable systems at the contract acceptor.

- MHRA invites companies that identify data integrity issues to contact them by email at: GMPInspectorate@mhra.gsi.gov.uk
“We thought long and hard about what a company is going to do” if it finds data integrity problems, Birse commented. “Are they going to come to us? We do invite you to come and tell us if you find data integrity issues.”

He emphasized the double-edged sword nature of the endeavor. “If you find a data integrity issue, we want you to come and discuss it with us. Now it may be that it is so serious that we still end up having to take regulatory action. But at least we can sit down and have a sensible discussion.”

What the agency does not want to have happen is firms finding data integrity issues and “burying” them. “We really need to engage and have sensible discussions if you do find those issues so we can work through them together.”

**Detecting and Preventing Data Integrity Problems**

At an ICH Q7 training workshop cosponsored by PIC/S and PDA in February, 2014 in Bethesda, Maryland, FDA Division of International Drug Quality Director Carmelo Rosa reviewed aspects of data generation and traceability, the systems used to generate it, and the controls that should be in place to ensure its integrity.

He provided a list of eight questions firms should ask when examining data and the systems used to produce it *(see box below)*.

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**Keys to Prevent & Detect Data Integrity**

*At the ICH Q7 training workshop, FDA’s Rosa presented the following list of questions to ask when examining data and the systems used to assure its integrity:*

- Is the data reliable, trustworthy and verifiable?
- Was the data generated following GMPs?
- Is the data traceable and/or referenced to original raw data and reviewed by a reliable quality structure?
- Are the appropriate controls in place to ensure that all data is reported?
- How long in a process can an employee go w/o direct oversight?
- How do you know all the data is available?
- Do you have mechanisms to ensure the data is authentic, retrievable?
- Where critical data are being entered manually, is there an additional check on the accuracy of the entry? This can be done by a second operator or by the system itself.

“If the data is complete, if the data is trustworthy, if the data is reliable and consistent and accurate, then you have good data integrity,” he said. “That is what we expect from firms.”
On the other hand, a firm’s inability to detect and prevent poor data integrity practices “raises serious concerns about the lack of a quality system’s effectiveness and the decisions made using that data,” Rosa emphasized.

Regarding active pharmaceutical ingredient manufacturing operations, the agency director pointed out that production needs to have sufficient control to prevent unauthorized changes to data as clearly stated in Q7. There should be controls to prevent omissions in the data to avoid systems being turned off and data not captured. This is a problem area FDA is seeing “more and more.”

**Finding Integrity Problems is Difficult**

Rosa stressed that it can be difficult for FDA investigators and inspectors from other regulatory agencies to find data integrity problems. “You can’t just go into a facility and have data integrity just jump out at you.”

Investigators may only have four or five days to perform an inspection, and “finding the evidence of wrongdoing and documenting it is a very tough job,” he commented. “I have all the respect in the world for the investigators. I have been there. I have done many inspections. I have the highest respect for them because of the difficulties of identifying these types of problems.”

To be effective, investigators need to understand the systems they are evaluating and how to “look at the process from a different perspective.”

*Rosa declined to share how agency investigators are trained to find integrity lapses. “I am not going to tell you is our bag of tricks,” he said. “I can’t.”*

One reason he chose not to share the information is because “many firms are not using that information to get better at what they do. Unfortunately, some of them are using that information to cut corners and get more sophisticated” in how to hide data integrity issues.

Rosa commented that he sees all foreign GMP inspection reports, and has seen “how sophisticated some companies are becoming in deceiving and engaging in these types of bad practices.”

**Establish Audit Trails**

Rosa emphasized the importance of recording any changes made and of having an audit trail that traces back to original raw data.

He noted that the agency has seen “many” quality units in which an analytical or quality package is received, and those responsible for approving it “review it, sign off on it, but don’t spend time going into the system to see the audit trail. They don’t go into the system to see if there were failing results that were not reported. They don’t take the time to look at and challenge the data that they are reviewing. That, of course, is a gap in that operation.”

*Rosa pointed to the importance of the quality system reviewing data to help prevent and detect data integrity issues.*
“Is the reference to the raw data and the review done by a reliable quality structure?” he asked. “Why is this important? If you have wrongdoings on the floor, and you have a broken quality system, the rest doesn’t matter, because the quality system is broken. How can you rely on the quality system when they are aware of and are not actually responding or doing the right things to bring that operation under a state of compliance?”

All data must be reported, not just selective data that supports a desired outcome. Computer files that are “discarded or ignored” should be easily retrievable.

Also important for industry to consider, Rosa commented, is the length of time an employee can go unsupervised. “How much can an employee, an analyst or operator do on his own without being supervised or without somebody having direct oversight and challenging the operation?”

**Challenging Authority Problematic**

Rosa explained that there are countries and places where “it is almost seen as a sin to challenge an authority – to challenge higher level management.”

**He commented that some cultures instill a sense of respect for elders and people in positions of authority at a very young age, and breaking away from that is difficult.**

“When I look at my dad, I still bow my head,” he said. “That is the sense of respect that we had growing up for the people who had authority over us. And that is no different than what we see in some firms and some cultures – there is just such high respect for that authority that, God forbid, we try to tell them, ‘this is wrong, I can’t do it.’”

In such cultures, it is especially important “to make sure that the entire operation and culture understand the expectations of regulators, but also of what good GMPs mean.”

“Who? When? What? And how is the data collected? How is the data processed? Is the data reviewed and is the data reported? Who does it? When was it reported? What data are we looking at? And how is it reported? Just basic questions to keep in mind.”

**Capitol Hill Briefed on Problems in India**

“Searching for Safety,” an organization that tracks and reports on counterfeit and substandard medicines, sponsored a “briefing” in late February in a Congressional meeting room on “FDA, India and substandard drugs.”

About four dozen congressional staff, FDA, White House and State Department representatives attended the briefing, *Bloomberg* reported.

Presenters at the briefing and the topics they discussed were:

- Ranbaxy whistleblower Thakur outlined problems with substandard generic drugs and manufacturing processes in India, their causes, and what could be done to solve them (*see box below*).
Amir Attaran, a Professor of Law and Medicine at the University of Ottawa, discussed the risks of substandard and falsified medicines, especially those made in India. He cited “obsolete” Indian laws and a “lack of oversight” by India’s FDA as primary reasons for concern about the quality of drugs made there.

Harry Lever, a senior cardiologist at the Cleveland Clinic, discussed the problems resulting from his increasing encounters with inferior quality medicines and how clinical outcomes from generic medicines made abroad generally compare unfavorably with those made in the U.S. He presented anecdotal evidence showing that his patients taking the cardiac drug metoprolol succinate experienced adverse symptoms that “seemed to improve” when they were switched from an Indian-made version of the drug to a U.S.-made product.

Preston Mason, a member of the Cardiovascular Division at Brigham and Women’s Hospital and Harvard Medical School, presented his extensive research into poor quality atorvastatin (generic Lipitor), which he maintained shows that “generic Lipitor samples from overseas had elevated and alarming levels of impurities” compared to those produced in the U.S.

**Hamburg Proposes India Observing FDA Inspections**

A week before the late-February briefing, FDA Commissioner Margaret Hamburg traveled to India to meet with government officials on quality and other regulatory topics.

Hamburg’s visit included the signing of a “Statement of Intention” to clarify the points on which both countries will cooperate, such as: ● sharing of CGMP compliance and facility information, ● India investigators observing FDA inspections, and ● enhancing communication and public meeting collaboration.

Thakur, Attaran and American Enterprise Institute Adjunct Scholar Roger Bates, who organized the late-February briefing, commented on Indian agency officials observing FDA inspections in an op-ed piece in *Forbes* in late March.

Allowing the officials access to FDA inspection methods “may inadvertantly make it easier for Indian companies to cheat,” they wrote. Congress should impose “severe penalties in the form of trade barriers on any country that repeatedly exports poor quality medicine to America,” the authors suggested.

**RANBAXY WHISTLEBLOWER DINESH THAKUR ON PROBLEMS IN INDIA’S GENERIC DRUG INDUSTRY AND PROPOSED SOLUTIONS**

*The following is excerpted from a statement by Ranbaxy whistleblower Dinesh Thakur at a briefing on “FDA, India and Substandard Drugs,” held on Capitol Hill in late February 26, 2014. Thakur outlined the problems with substandard generic drugs and manufacturing processes in India, their causes, and what can be done to solve them.*
My name is Dinesh Thakur. I am the whistleblower in the case against Ranbaxy Laboratories, which was unsealed last May where the company pleaded guilty to seven counts of felony in a US court and agreed to pay $500 million in penalties. I am here today to speak about the risk we face as to public health with adulterated drugs resulting from a globalized supply chain and what we are asking the US Congress to do to address this risk….

We have made tremendous progress in our understanding and oversight of the global supply chain that provides life-saving medicines to patients in the US, [including through provisions in FDASIA, *(IPQ September 29, 2013)* and the “Drug Quality and Security Act” *(IPQ January 23, 2014)*.]

My case against Ranbaxy in India and what happened with heparin in China demonstrate that unscrupulous actors in the global supply chain take advantage of gaps in our regulation for financial gain. Economically driven adulteration has become a new category of fraud in the pharmaceutical industry….

While the U.S. FDA is making every effort to address this area of risk, based on my past experience, incentives need to be aligned for pharmaceutical companies located overseas to play by our rules….

In order for the efforts made by the FDA to produce the desired results, we need an able and willing partner in the overseas regulators. Unfortunately, their objectives are more aligned with promoting commercial interests of their industry than focusing on public health. I wish regulators overseas were as capable and competent as the US FDA; unfortunately, they are not. In fact, the Parliament of India has called the Indian regulator incompetent and corrupt.

As much as the FDA expands its footprint in countries like India and China, it cannot replace the role of a national regulator whose job ought to be to protect public health by guaranteeing good quality medicines for its people. Data confirm that one in five medicines that are manufactured and distributed in India are spurious. Recent news reports say that antibiotics administered intravenously to infants in the state of Kashmir did not have any active ingredient in it, leading to deaths of several hundred children.

Clearly, we need a competent and effective national regulator in countries which provide medicines for the US marketplace to work collaboratively with ours. The FDA can educate, but it cannot enforce local standards, which vary widely among countries that supply our medicines.

I am here today to ask you to consider three proposals that I think will help alleviate this problem to a large extent.

1. Incentivize the countries that supply our medicines to upgrade their skills, comply with our quality standards and improve public health for their own citizens. The US Congress will have to take a carrot and a stick approach. As much as it wants to educate and train foreign regulators, please also consider punitive action against repeat offenders.

2. Make the reporting of drug substitution (substituting a brand drug for a generic due to lack of effect) mandatory. We just do not have enough data to really understand what impact generic substitutions have on our public health. While lack of effect cases are reported to the FDA Medwatch, we need additional data to better understand whether the lack of effect was due to a generic substitution.
3. Make the pharmaceutical industry monitor its supply chain for economically driven adulteration, especially from sourcing ingredients to manufacturing the product. We need to complement the existing track and trace legislation to make sure that the other half of the supply chain is also monitored continuously for risks from global sourcing and manufacturing. After all, what good is it to track and trace a product that is adulterated in the first place?

There are, unfortunately, no quick fixes in the long road towards drug safety. However, if we work together and apply the right mix of force, incentives and education, I am confident we can foster a much safer and more dependable generic drug supply chain.

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