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Drug Regulatory Scrutiny & the Pharmaceutical Industry

Summary of Market Predictions

- The pharmaceutical industry is facing increased scrutiny by regulatory authorities globally, and in particular the FDA, which is establishing progressively higher standards of safety and quality
- Both big pharma and small companies are still failing in terms of cGMP compliance, and the number of drug recalls, market withdrawals and safety alerts reported over the last three years indicates that while many instances of noncompliance are inadvertent, some are deliberate
- As analytical technologies improve it is likely that the number of violations detected will increase further
- Increasingly stringent requirements and regulatory authority vigilance will prevent some smaller companies from entering the US market, ultimately reducing competition over coming years
- Industry must effect a cultural change in attitude, and implement processes both vertically and horizontally, enterprise wide, to keep up with a changing regulatory landscape and meet requirements
- Some collaboration and cooperation among drug regulatory authorities will help to cut development costs and reduce duplication, but large-scale integration of the global regulatory landscape is unlikely to be comprehensive over the next five years
- While the responsibility for willfully contravening regulations, for example by selling unapproved drugs, must lie solely with the industry, the regulator should take some responsibility for issues such as inadvertent cGMP deviations, and help advise and guide the industry to ensure it can meet manufacturing and drug quality and safety standards
- The regulator will need to become more transparent, and effect dialogue with the industry to teach, encourage and monitor best practice, and help address issues as its requirements become ever more exacting

The pharmaceutical industry is facing increased scrutiny by drug regulatory authorities across the world. Perhaps most notable of these is the US FDA, which requires the highest standards of drug safety and quality, and which employs rigorous investigative techniques and skills that are formidable from the perspective of any company. The adoption of progressively higher standards of safety and quality has led to a greater focus on data integrity and cGMP compliance, but the pharmaceutical industry's lack of awareness and inadequate appreciation of these continually evolving standards has resulted in many companies failing to meet requirements. Given that the US is the single largest market for medicines and its regulatory authority is considered a benchmark, this article focuses on FDA data as the foundation for analysis, and suggests action plans for improving compliance.

How Many, and For What?

An analysis of warning letters issued over the last 42-month period (January 2010 to June 2013) by the Office of Manufacturing and Product Quality provides some useful insights into the changing profile of regulatory inspection and oversight.

Table 1

Warning Letters by Office of Manufacturing & Product Quality, US FDA

No	Issue	2010	2011	2012	2013*	Total
A	**Active Pharmaceutical Ingredients (APIs)**					
1	Mfg facility inspection	2	8	5	1	16
2	Deviations from cGMP	5				5
3	Change notification	-	1			1
	Total APIs	**7**	**9**	**5**	**1**	**22**
B	**Finished Pharmaceuticals (Formulations)**					
1	Mfg facility inspection	2				2
2	Violations of cGMP	5	10	16	12[(a)]	43
	Total Formulations	**7**	**10**	**16**	**12**	**45**
	Total API + Formulations	**14**	**19**	**21**	**13**	**67**

Source: www.fda.gov (a) Includes API Mfg Facility Inspection of one Unit

* To 30 June Only

Table 1 shows that during the last 3.5 years warning letters relating to APIs, which largely concern manufacturing facility inspection, have decreased, whereas those relating to formulations have increased. It is evident from these figures that the detection of cGMP violations at formulation units is growing alarmingly. A further analysis of this data shows that 66 companies received a warning letter during the 42-month period, with one company, Apotex, receiving two. Prominent names among those on the receiving end of warning letters highlight both innovators and generics companies, including Boehringer Ingelheim, Hospira, Merck KGaA, Novartis, Novo Nordisk, Sanofi Aventis, SmithKline Beecham, Teva and Wyeth Lederle. Indian companies, which account for 40% of DMFs to date and 37% of ANDAs in 2012, accounted for 12% of the warning letters.

A similar analysis of warning letters issued by the Office of Drug Security, Integrity and Recalls during the same period (Table 2) provides another useful insight, and suggests that internet marketing is still eluding regulatory oversight.

Table 2

Warning Letters by Office of Drug Security, Integrity & Recalls, US FDA

No	Issue	2010	2011	2012	2013*	Total
1	Internet Marketing of Unapproved and Misbranded Drugs	-	2	6	-	8

Source: www.fda.gov

* Up to 30 June Only

The study also examined Drug Recalls, Market Withdrawals & Safety Alerts during the 42-month period, as shown in Table 3.

Table 3

Drug Recalls, Market Withdrawals & Safety Alerts by Reason, US FDA

No	Reason/Problem	2010	2011	2012	2013*	Total	% of Total
1	Undeclared ingredient; including sildenafil, acetaminophen, dexamethasone, diclofenac, etc.	17	14	8	9	48	27.0
2	Visible particulates; including fungal microbial contaminants, precipitation/crystallization, brass particulates, etc.	0	12	15	11	38	21.3
3	Unapproved drugs	1	2	7	4	14	7.9
4	Sterility	0	0	4	10	14	7.9
5	Deviations in fill volume, Size/Thickness of Tabs, variations in tablet strength, etc.	0	3	7	1	11	6.2
6	Packaging error; including mislabeled/incorrectly labeled bottles, and bottles containing wrong drugs, etc.	0	6	3	1	10	5.6
7	Quality control and manufacturing processes, insufficiencies in the development of the manufacturing process or non-compliance with drug manufacturing requirements	1	1	0	1	3	1.7
8	Equipment cleaning, leading to product containing trace amounts of other drugs	0	1	0	1	2	1.1
9	Others; including contamination, odour, impurity, leaking container, difficulty in using measure dosing system, etc.	0	18	13	7	38	21.3
	Total	**19**	**57**	**57**	**45**	**178**	**100.0**

Source: www.fda.gov

* Up to 30 June 2013

Further analysis of Drug Recalls, Market Withdrawals & Safety Alerts, by company, is presented in Table 4 below:

Table 4

Drug Recalls, Market Withdrawals & Safety Alerts by Company, US FDA

No	Frequency	2010	2011	2012	2013*	Total	% of Total
1	1 Time	17	24	30	25	96	80
2	2 Times	1	4	3	6	14	12
3	3 Times		2	1	1	4	3
4	4 Times	1		1		2	2
5	5 Times		1			1	1
6	> 5 Times		2	1		3	2
	Total	**19**	**33**	**36**	**32**	**120**	**100**

Not Learning from Mistakes

The 178 incidents reported in Table 3 relate to 120 companies. Ninety six of these were the subject of just one drug recall, market withdrawal or safety alert but, as shown in Table 4, another 24 companies were caught out more than once, and five of them more than five times. These include American Regent (13 instances), Hospira (10) and Bedford (6). Three major Indian companies, Glenmark, Sun and Ranbaxy, were among those companies that each had one violation.

The number of firms named through FDA drug recalls, withdrawals, or safety alerts almost doubled from 19 in 2010, to 36 in 2012, and there have been 32 in just the first six months of 2013. This rise is indicative of FDA's wider reach and drive to identify issues of violation. Well-recognized companies including Apotex, Bausch & Lomb, Bayer, BMS, Cephalon, Genentech, Gilead, GSK, Greenstone, J&J, Mylan, Sandoz, Smith & Nephew, Teva, Watson and West Coast, have all been cited by FDA. Again, this list indicates both innovator and generic companies.

An increasing number of companies are attracted to and have a presence in the US market, but this means the numbers of inspections and defaults are also rising. However, what may be of greater concern, both to the drug regulators and the public health administrators, is that the list of defaulters contains established companies. Also of concern is the types of default that are on the rise. Violations of cGMP may be related to packaging errors, equipment cleaning and sterility issues, but more than one-third of reported incidents relate to "undeclared ingredients" and "unapproved drugs". This suggests a willful attempt to bypass regulatory oversight, and in these cases the responsibility rests squarely with the pharmaceutical industry. It is noteworthy that these incidents declined somewhat between 2010 and 2012, but have risen again during the first half of 2013.

A third major concern relates to the rapid increase in the detection of foreign particles in drugs. A common problem, this isn't a deliberate violation, but needs to be addressed, with the help of guidance from the regulators and experts. Many other issues could be similarly resolved, but it will require a change in how the role of drug inspectors is perceived: less as a forensic auditor, and more as a guide, to help ensure the common goal of ensuring safe, effective and quality medicines.

Attempts to Beat the System

So, if some of the major global companies haven't been able to keep pace with the frequent regulatory changes that govern drug quality and cGMP, there is no reason to believe that new entrants to the US market will be any better placed to overcome these challenges. From what the last few years' of data show, some of the smaller and relatively lesser known companies seem to be indulging in willful default, and it is likely that a large number of new companies that are attracted to the US market could perceive this as an opportunity, which will result in further attempts at deliberate default.

Technology will play a key role in making sure that an increasing number of violations, whether deliberate or not, are identified, for example, by enabling the more accurate detection of foreign substances in manufactured products. The upshot is that we may hear more of alerts, recalls and market withdrawals, unless the industry adopts a new culture and plays an active part in reducing such incidents.

Cultural Change And Communication

A number of questions are raised, however. Which are the areas that will present the greatest future regulatory risks and lead to the largest numbers of warnings, and how can we stop or minimize them as new companies rush into the US market without adequate preparation? The growing trend towards zero tolerance will necessitate changes in attitude and culture across an organization. The industry needs to become more introspective and look for ways to overcome these issues. Leave it up to the regulator, and the solution may involve scaling up the penalty for willful default. Companies from all geographies must embrace these changes, both horizontally and vertically, enterprise wide. It is a slow process that will require patience and perseverance, as many organisations pay attention to

manufacturing, but devote little effort to prepare the people for change.

Regulatory authorities and companies will also need to make more effort to communicate the rationale of the prescribed processes that are put in place. Expecting compliance without understanding is futile. The mitigation of risks requires much better appreciation of the drug safety rules and a clearer understanding of the processes.

Barriers to Market Entry

We also need to consider the types of regulatory changes that may take place, and their effects on the market. Current outcomes and practises indicate that the majority of warnings will stem from the North (US, Europe and China). Some of the past changes are already perceived as being directed towards raising technical barriers to competition from the low cost, efficient producers, and the regulators and technical experts constituting the International Conference on Harmonization (ICH) may continue to strive for perfection at the risk of ignoring the cost-benefit analysis. This could delay entry of follow-on biologics, and may lead to some marginal players giving up the US market, which will ultimately reduce competition.

Another point to consider is the need for and likelihood of increased regulatory integration, and the consequences of it not happening. Most companies, irrespective of their size, sector (originator or generic) and domicile would like to see greater integration of regulatory processes to reduce delays and the associated costs of approval. However, while some cooperation between drug regulators in different markets is likely over the next few years, complete integration is unlikely in the near future. Some regulators may not be willing to give up their authority, and a push towards integration could also be met by barriers of sovereignty. It is thus likely that the industry will have to continue to have to negotiate regulatory delays and the cost of duplication.

Take all these points into consideration, and it's also likely that during the next five years, the regulatory landscape will push up the price of medicines as companies face ever-increasing costs of compliance, and these costs will price new companies out of US market, effectively reducing competition.

What's the Solution?

So what's the solution? Can independent auditors resolve all these issues? What should the FDA do? Independent auditors can only expose technical deficiencies and help overcome them every time they find them. The solution will have to come from within industry, through a change in culture and attitude. The regulator will play a role, through its willingness to share responsibility with the companies for issues such as cGMP-related failures, and the implementation of processes that could address causative issues. Rather than just policing the industry, the regulator will need to consider itself partly accountable for failures, and shift its role from one of purely inspection, to one of training.