GVK Bio and India's drug quality problem

Safe Medicines Coalition Working Paper

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In July 2015, India deferred talks on the India-EU Investment and Trade Agreement after the EU banned 700 generic drugs that were tested at Hyderabad-based GVK Biosciences (GVK Bio). The Indian government said it was "disappointed and concerned by the action."[1]

India exported $15.4 billion worth of pharmaceutical products in 2014, with Europe accounting for $3 billion, or approximately 20% of that total. Out of the $3 billion in European imports, generic medicines constituted approximately $1 billion, with drug ingredients accounting for the rest, according to Pharmexcil. As one of the largest export industries for India, even the partial loss of this trade could have a large imact on the Indian economy, arguably an important reason for the Indian government response.

However, the response was disproportionate and, given the evidence we will present, wrong. But Indian media and government, prone to see conspiracies against national interests, followed a policy that resonates within India.. To understand why, some brief background is required.

Background

Over the past fifty years India and the west have had a strained relationship over medicines. From 1970 to 2005 the Indian Government did not support product patents. In 2005, the Indian Government shifted policy and agreed to intellectual property agreements through the World Trade Organization. The Indian Government has allowed patent rights, but enforcement has been sporadic, creating tensions with the west. Indian pharmaceutical manufacturers have been able to offer products at substantially reduced prices, and therefore have underbid western manufacturers resulting in increasing market share in in most emerging markets. Indian manufacturers' increase in market share has furthered tensions, especially in light of difficult to prove claims of quality problems resulting from cutting corners in the manufacturing process. Western nations have occasionally unfairly blocked Indian products from transiting through European ports, but have been limited in their critiques of Indian drug quality, partly because they source so many of their ingredients and even final products from India.

As a result tensions are on the rise, and distrust between all parties continue to plague Indian pharmaceuticals. Yet western institutions seem capable of properly regulating the

[1] http://economictimes.indiatimes.com/articleshow/49809872.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst

industry and regulators following protocol and politicians are largely staying out of the debate. Within India this is apparently not the case. The hand of the commerce ministry and the Indian pharma industry is everywhere. Every criticism of Indian products, whether by foreign analysts, academics, physicians lawyers, regulators or health experts is viewed in India as a coordinated attack on its industry, that requires a coordinated defense from the various arms of the Indian government – acting as though it were the public relations arm of the industry. And the GVK Bio issue is perhaps the most important.

GVK BIO – A Convoluted Indian Story

In the summer of 2015 the European Medical Agency (EMA) withdrew approval of over 700 drugs, which had been licensed on the basis of the bioequivalence/bioavailability data from studies conducted by clinical research organization GVK Bio, which has since been renamed as Clinogent. The EMA cited the results of an inspection by ANSM (L'Agence nationale de sécurité du médicament), the French regulator as the reason for its decision to withdraw the approvals. Amongst other shortcomings documented in its final inspection report dated 21 July, 2014 the French regulator ANSM alleged that it had found that electrocardiograms had been falsified in nine different clinical trials which it inspected during May, 2014. The falsification was found to be systematic and was conducted by at least 10 individuals in the facility over a period of 5 years from 2008 to 2013. Since the individuals in question showed a lack of training, awareness and understanding of good clinical practices (GCP) like data integrity, the EMA found it necessary to question all clinical trials conducted at that facility.

In normal circumstances, the Government of India doesn't interfere (publicly at least) in regulatory action taken by a foreign regulatory body. But this time around, it got involved in the matter from the outset and gradually escalated the matter. First, the Indian Government threatened to retaliate against the EU by initiating legal proceedings at the WTO in response to the EMA decision to withdraw the approvals. In July of 2015, the government escalated the issue by cancelling talks with the EU over a Free Trade Agreement (FTA), which had been under negotiation for the past seven years. At face value this appears to be a rather drastic step and was harshly criticized by the retired Commerce Secretary Rahul Khullar. The repeated point made in the Indian media by representatives of the Indian pharmaceutical industry and the Government was that the EU had been highly disproportional and arbitrary in its decision to withdraw approvals and that the discrepancies in question were not very serious. This is a very atypical response and calls into question whether the government bureaucracy is being unduly influenced by the industry. While the Indian Government, notably the commerce ministry, routinely supports industry behind the scenes, such a blatant public display from government is unusual. But then India's Government has not conducted a root-cause analysis of the problems plaguing the industry and addressing them systematically, all it has done is increased the budget of the regulator, and parroted Indian industry talking points. If proof is required that this does

not fix the problem, at least 39 manufacturing plants in India have been cited for violations of cCGMP by the USFDA in the past three years.

On October 9, 2015 a new angle emerged to this controversy when *The Hindu,* a national newspaper, published a front page story, headlined "A love story that cost GVK its international reputation". The reporter, Vidya Krishnan, alleged in her piece that a former employee of GVK Bio turned whistleblower after GVK Bio dismissed him because he had eloped with a fellow employee, despite being married and having two children. According to the story, the parents of the girl approached the police, who then released the whistleblower's emails to the international regulators after searching his laptop. We have established after a review of the documents and based on our own research that this story is entirely baseless.

Without commenting on the merit of the whistleblower's allegation*, The Hindu* story proceeded to link the entire story of EMA's withdrawal of approvals with the issue of EU pharma companies complaining about India's intellectual property (IP) policies. This is the line of argument that the Indian pharmaceutical industry, through its lobbying arm, the Indian Pharmaceutical Alliance (IPA) has been selling for quite some time now. The underlying insinuation was that the withdrawal of approvals of 700 drugs based on a jilted man's email was nothing but an excuse to target India over its IP policy. The seed of doubt planted by Ms. Krishnan was then fanned by D.G. Shah, the Secretary General of the IPA who was quoted as saying that the ban had no basis because of weak evidence and that there was reason to suspect the EMA's actual intentions behind the ban. The IPA, it should be noted has been vehemently opposed to the India-EU FTA because Europe wants India to accept "data exclusivity", a form of IP protection, as part of the FTA. In other words, the IPA has had every reason to torpedo the talks.

A representative of the IPA has called the action of the French Inspector (and therefore the French regulator) not competent; a theme that has been repeated by the Minister of Commerce to justify pulling out of the Free Trade Agreement talks. It is important to note that the integrity and the competence of the ANSM inspector, Olivier Le Blaye, is beyond reproach. Mr. Le Blaye was the one who had uncovered similar fraudulent behavior at Vimta Labs back in 2003, which was the genesis of the investigation at Ranbaxy Laboratories.It is increasingly clear that this episode has been co-opted by the IPA to scuttle the FTA talks with the EU. The IPA's reaction to the piece in *The Hindu* clearly shows how it is selectively using this episode to further its agenda.

Dinesh Thakur was one of the recipients of the email messages that the whistleblower sent to a long list of people, both within the regulatory agencies, in the media and others asking for help. The whistleblower's email messages are very verbose and his style of writing laborious, which led many of the recipients of his messages to initially conclude that he was a disgruntled employee. However, Mr Thakur's team independently triangulated some of

the whistleblower's allegations with other information they had available and reconstructed the following sequence of events.

There are multiple storylines, which are separated below into issues and sub-issues, along with accompanying questions that are pertinent to raise within the respective geographies.

I. <u>Discrepancies & Errors in *The Hindu* story</u>

The day after the story in *The Hindu,* GVK Bio published a press release, subsequently published *in The Hindu,* stating that the employee was not dismissed but that he resigned of his own volition. It also stated that the person in question was not a whistleblower but a disgruntled employee and that the inspection triggered by his disclosures did not lead to any inspections at GVK Bio. *The Hindu* never published an apology, retraction or a clarification along with a rejoinder thereby leaving in doubt the actual facts or the sources for its piece (which we suspect is the IPA through its representative, D G Shah).

As per the whistleblower's emails, he voluntarily resigned from the company in a letter dated September 14, 2011 **(Annexure P-1)** seeking to be relieved of his duties on that very day. However, GVK Bio appears to have let him go only on October 17, 2011. **(Annexure P-2).** The letters seem to indicate an amicable separation between the whistleblower and GVK Bio. In fact GVK Bio kept him employed for an entire month despite him wanting to be relieved on the very date he submitted his resignation letter. Thus the assertion in *The Hindu* that he was fired was clearly incorrect. Once this fact is removed, the question that presents itself is how did GVK Bio discover the identity of the whistleblower when the emails in question were sent by him only in May, 2012, after he resigned from being an employee in with GVK Bio? Both emails, the first one to the regulators and the second one to the management of GVK Bio were both sent from an anonymous email ID.

The answer to the above question can be found in the preliminary report of ANSM after it participated in the joint inspection of GVK Bio's facilities, along with USFDA, WHO and other regulatory authorities in EU, in response to the emails from the whistleblower. In its report, ANSM notes that the management at GVK Bio had told them in the initial meeting that after they received the whistleblower's email, they had suspected who the whistleblower was because his name showed up in the "properties" of the PDF document.

GVK Bio then filed multiple police complaints. Apparently the IP address of the email account used to send the email was procured from Google and it was discovered that the emails had been sent from a cyber café (a public place where people can buy internet access). The location of this cyber café was then co-related with the location of the whistleblower's mobile phone, which was located by using the mobile towers. It is not clear whether GVK Bio managed to do this this on their own, or whether the police were involved in getting these details. It is highly unlikely that GVK Bio could get access to this level of data

without support of the local police. The legality of these actions is a storyline that needs to be pursued separately.

The ANSM report also notes that the whistleblower had reportedly left on good terms; but after his resignation he had eloped with a fellow employee, after which his wife filed a police complaint against him. According to GVK Bio, the whistleblower was under the impression that the company had instigated his wife to file the said complaint and sought to take revenge against GVK Bio by sending out alleged defamatory emails to regulators and customers of GVK Bio.

This account by GVK Bio to ANSM was contradicted by a police complaint it had filed on June 8, 2012 where it had named the whistleblower but had never made any allegations regarding an "elopement". Instead, it had stated that the complaint was the result of personal enmity between the whistleblower and the head of the bioanalytics division in its organization. The whistleblower provided copy of this complaint to the Hyderabad police dated June 8, 2012. **(Annexure A-2)** *The Hindu's* story is therefore highly doubtful and it casts doubt over the intentions of the reporter's source(s). Was an attempt made to defame the whistleblower (and by whom) or was it a case of the reporter's source trying to spin the story to make it look like the EU's actions had been based on a frivolous non-issue and thus demand the suspensions of the FTA talks? And who would benefit from such an action but the IPA?

On the unanswered question in *The Hindu* story – did the whistleblower's complaint actually lead to the suspension of the 700 approvals by the EMA? From the information that we have so far, the first inspection launched on the basis of the whistleblower's allegation did lead to an adverse inspection report by ANSM. The details of that report are discussed below in the next section of this report. However, the EMA action to withdraw the approvals of 700 drugs is the result of a second inspection.

The report from the first inspection by itself did not lead to the withdrawal, but an advisory to European regulators to exercise utmost diligence while accepting data from clinical trials conducted at GVK Bio. The reason perhapsthat ANSM could not recommend concrete action was because of the fact that the evidence substantiated by ANSM during its inspection of GVK Bio facilities pertained to clinical trials conducted for submission to the USFDA, and not for submissions to the EU. There was a second inspection by ANSM in May, 2014 which discovered the fabricated ECGs which eventually led to the withdrawal of the approvals. The fact is that ANSM discovered large scale discrepancies in the second consecutive audit of GVK Bio, which led to the decision of the EMA to withdraw 700 approvals. *The Hindu* story fails to explain the fact that there were two inspections and the discrepancies had been noted in both inspections.

II. <u>Events regarding the first inspection of GVK Bio in 2012</u>

The first email the whistleblower sent was on May 6, 2012 anonymously to regulators at the USFDA, ANSM (France), MHRA (UK), WHO, Inspectie voor de Gezondheidszorg (Dutch), Saglik (Turkish). **(Annexure R-1)** The document contained a PDF attachment, outlining the main allegations by the whistleblower, who alleged that the Head of Bioanalytical at GVK Bio, V. Chandrashekhar was forcing his subordinates to manipulate test results to ensure that the bioequivalence studies being conducted on generic drugs were successful (meaning the generic drugs were found bioequivalent to their innovator counterparts).

Before explaining the main allegations in the attached PDF document, it is first necessary to understand the importance of bioequivalence testing and the chequered history of such trials in India. Bioequivalence studies are an essential pre-requisite for generic manufacturers seeking to enter a market after the patent has expired or lapsed for the innovator drug. Unlike the innovator, who is required to conduct comprehensive and extensive clinical trials on patients to establish the safety and efficacy of a new chemical entities, the follow-on generics only have to prove that the generic formulation manufactured by them are bioequivalent to the innovator drug. This means that the generic manufacturer has to establish that its drug has the same bioavailability (dissolves at the same rate) and has the same effect on the human physiology as the innovator's drug. Such trials are almost always conducted on healthy human patients and cost only a fraction of the actual clinical trials conducted by the innovator pharma companies.

In order to win regulatory approvals in global markets, it is often desirable for generic pharmaceutical companies to have the bioequivalence studies conducted by independent Clinical Research Organization (CROs). In a way, the CROs are the pharmaceutical equivalent of a financial ratings organization. India has a booming CRO industry because of an abundance of affordable scientific talent and also the presence of a robust generic pharmaceutical industry. However, the reputation of Indian CROs has been tarred by a massive scandal at Vimta Labs back in 2004 when inspectors from the World Health Organization (WHO), during a routine inspection discovered that the CRO was fabricating data for several bioequivalence studies. Most of the drugs were ARVs being manufactured by Ranbaxy and were being sold in Africa. When this information was brought to the attention of the Ranbaxy management by Dinesh Thakur and Dr. Rajinder Kumar, the then President of R&D, the management at Ranbaxy refused to act. Dr. Kumar resigned because he wouldn't become party to manufacturing substandard drugs and the company made Mr Thakur's employment untenable after Dr Kumar left. Mr. Thakur resigned from his post soon thereafter. He then worked closely with the USFDA Office of Criminal Investigations for over two years helping them establish the nature and the extent of the fraud that the company was involved in. Based on the information he had provided to the USFDA, the US Department of Justice prosecuted Ranbaxy in a US Federal Court. In May 2013, the company pled guilty to seven counts of criminal felony and paid $500 million in fines and penalties to the US government. To the best of his knowledge, there was no action taken against Vimta.

Pharmaceutical companies have one of two reasons to fabricate data. The first is possibly time constraints. Since bioequivalence trials take time and the generic manufacturer maybe looking for a quick entry into a particular market (especially the US market where First to File often results in a windfall), the CRO may simply fabricate data to show that the generic version of the drug was bioequivalent. This fabrication is done by simply using patient data from different trials and substituting it for the current study.

The second reason for fabrication of data is usually because the generic is in fact not bioequivalent due to errors in synthesizing the active ingredient and its formulation. A bioequivalence study is supposed to catch exactly these flaws but CROs sometimes fudge their results either due to pressure from the sponsor or because of internal pressures from management. In the present case, the GVK whistleblower alleged that his manager was receiving bribes from the sponsors to ensure that the data from the studies conducted in his lab resulted in their drugs being bioequivalent to the innovator drug. This is not an uncommon phenomenon. This was documented extensively during the USFDA's investigation of the wrongdoing at Ranbaxy. The continued failure of the Indian industry to recognize the importance of "data integrity" has been the root cause of many of the problems that it faces with foreign regulators.

It is important to note that the current Chairman and part-owner of GVK Bio, D. S. Brar, was the CEO of Ranbaxy during the time that many of the fraudulent activities that the company pled guilty to in the US took place.

(A) The main allegations made by the whistleblower & the results of the first ANSM inspection

In the PDF document attached to his email, attached herewith as **Annexure R-2,** the whistleblower alleged that data was being fabricated and manipulated by GVK Bio over a period of 5 years. In addition he alleged a violation of Good Laboratory Practices (GLPs) and the code of ethics necessary to ensure integrity of the data for such CROs. The four main allegations are summarized below:

Allegation 1

i. Manipulation of bioequivalence data in Clinical Trial 145-08 (Felodipine) for Wockhardt's submission to USFDA: This particular trial was conducted to validate the bioequivalence of Felodipine formulated by Wockhardt. Felodipine is a drug used to treat hypertension.

   In 2008, the same year that GVK Bio conducted this particular study for Wockhardt, a healthy young man died while being a subject in a clinical study for Felodipine. It is not clear whether this study was sponsored by Wockhardt. The DCGI (Indian

regulator) announced an investigation but the investigation report hasn't been made public, which is typical of the way it operates.

In his email, the whistleblower alleges that the bioequivalence trial for Wockhardt was on the verge of failure until V. Chandrashekhar, the Head of the Bioanalytical Team at GVK Bio, intervened to manipulate the data. Apparently Chandrashekar had reviewed the data at an intermediate stage for approximately 70 out of 80 patients in the study and determined that the study would fail. On making such a determination, he replaced the data from 14 subjects enrolled in this study with data from other trial subjects who had provided better clinical data. In specific, the concentration profiles of specific patients were replaced. A concentration profile is a graphical description of the rate and speed of dissolution of a particular drug in a subject's bloodstream. This data is crucial to establishing the bioavailability of the drug. If the generic does not exhibit the same bioavailability as the innovator, there can be serious consequences for patients who are being administered the drug, particularly in the case of a drug being used to treat hypertension.

The whistleblower provides specific information regarding the subjects whose profiles were replaced and also provides the subject identifiers whose profiles were used to replace the unfavourable concentration profiles. He additionaly provides details on how paperwork had been fabricated since other protocols had to be violated to carry out these substitutions.

In its final inspection report, ANSM the French regulator, concluded that on the basis of its investigation of GVK Bio's systems, that these allegations were very credible. The USFDA, which was a part of the same inspection allegedly granted approval to Wockhardt's drug just a few months after the inspections of GVK Bio. As per the whistleblower's account, the USFDA had audited this particular trial in March 2011 and had not detected the anomalies.

Question to raise in the US: What was the basis of USFDA's approval of this drug application from Wockhardt, knowing that the French regulator had raised concerns about the validity and integrity of the data from this study? We do not have access to this report by the USFDA as it is currently not in the public domain.

ii. Manipulation of bioequivalence data in Clinical Trial 586-09 (Rasagiline) for Orchid Pharma submission to USFDA: Rasagiline was initially developed as a treatment for Parkinson's disease. In this particular case, the whistleblower has alleged that Orchid Pharma, the sponsor for the trial, was pursuing a first-to-file opportunity in the United States. Orchid appears to have not received approval because Teva, which

owned the patent for that drug, had sued Orchid Pharma and other companies. Orchid Pharma settled the lawsuit after an American court upheld the patent in a different lawsuit.

The main allegation made by the whistleblower, was that of the two separate trials conducted for this drug, one failed and the other was manipulated to ensure that the generic formulation could prove its bioequivalence. Unfortunately, he does not provide details to pin-point how the fabrication was done in the previous case.

This allegation was studied primarily by the USFDA whose final report is not in the public domain. ANSM also analysed some of the data but came to only an inconclusive finding.

iii. Manipulation of bioequivalence data in Clinical trial 046-08 (Ebastine & Carebastine) for Microlabs submissions to EU: The whistleblower alleged that data from this trial was submitted to the EU and that data fabrication in this case was similar to that carried out in Clinical Trial 145-08 discussed above. In this case, the whistleblower provided details of the substitutions made by GVK Bio. This allegation was never examined by the EU because the data was apparently never submitted to any regulator.

Allegation 2

In this allegation, the whistleblower alleges that the 17 Liquid chromatography–mass spectrometry systems (LCMS), which are used to analyse samples, were regularly manipulated to achieve pre-determined results. The whistleblower alleged that such manipulation could be detected by studying the audit trail on the system.

In its preliminary report, ANSM noted that due to deficiencies in the software on at least two of the LCMS systems, proper audit trail was not maintained for certain studies conducted before November 13, 2008. A corrective software patch which had been released by the software developer in 2008 to fix this deficiency had not been installed by GVK Bio till March 2009. The ANSM flagged this issue as a major deficiency in its inspection findings. This problem was specific to certain LCMS systems and not all of them. This is typical. Most Indian companies maintain two sets of instruments. The first set is off-the-grid, as it were. These instruments are used to determine which parameters needed to be tweaked in order to make the study “pass”. Once those parameters are established, the samples are now run on the “official” instruments with tweaked parameters which will result in the desired outcome. Due to lack of an audit trail, which is often by design, it was difficult for ANSM to provide a conclusive opinion on this point. Some of the other allegations with regard to record keeping were investigated and ANSM did not find any particular manipulations of data.

Allegation 3

The whistleblower alleged that if trials didn't meet batch acceptance criteria, the records were deleted entirely from one particular software system and replaced with accurate results. This, according to him, was in violation of GLP. ANSM didn't investigate this allegation in detail as the particular system was used for very few trials and it appears that ANSM had limited time during its inspections.

Allegation 4

The whistleblower had alleged that the head of the ethics committee was related to the head of the bioanalytics at GVK Bio and that this was a conflict of interest in violation of GCP and ICH guidelines. GVK accepted that the relationship was questionable, but rebutted the assumption that this was a violation of clinical norms.

Other findings

The ANSM also acknowledged that during the course of its investigation, it detected major lapses in the Standard Operating Procedure (SOP) followed by GVK Bio to keep the randomization lists protected from unauthorized access; thereby allowing personnel responsible for the clinical trial to access the lists. This resulted in compromising the requirement of blinded trials because personnel conducting the trials are forbidden from accessing the patient list. Such a lapse could possibly compromise an entire trial.

The USFDA was party to the same inspection conducted by ANSM. Its inspectors reviewed the same set of data. **The USFDA never released the final result of its inspection despite the fact that trial 145-08 was submitted to it for approval.**

QUESTION: Why did the US FDA not release its inspection report of GVK Bio's facilities in 2008? We do not have access to this report by the USFDA as it is currently not in the public domain.

(B) The Second ANSM inspection report led to the suspension of 700 approvals

In 2014, ANSM detected "falsified electrocardiograms (ECGs) in the documentation of two bioequivalence trials" conducted at GVK Bio and submitted to ANSM by companies seeking marketing authorisation. As a result, ANSM decided to conduct another investigation at GVK Bio to determine whether the falsified ECGs in the two trials were isolated incidents or whether these falsifications were part of a systemic problem.

On the basis of the investigation conducted from May 19 to May 24 of 2014 at the facilities of GVK Bio, in Hyderabad, ANSM prepared a 122 page preliminary report. The report concluded that the falsification of ECGs was a systemic problem since all 9 clinical trials inspected by the ANSM inspectors had revealed such falsifications. A summary of the main allegations is provided below:

1. ECGs were being recorded with instruments. These instuments allowed users to change the subject information and time of ECGs recorded on each instrument without leaving any audit trail. Usually all equipment used in such studies should leave an audit trail so that any changes or manipulations are recorded for post facto examinations. Indian CROs and companies are notorious for not following this rule. The ECG machines maintained by GVK Bio allowed it to take ECGs for one patient and then print out the same ECG with the subject numbers of different patients. This is the starting point of the fabrications.

2. Of the 9 clinical trials examined by ANSM, fabrications were detected in ECGs in all trials. Most of the fabrications followed a similar pattern described above i.e. recording the ECG of one patient and then using that same ECG for different patients by changing the subject numbers on the printout of each ECG. For example, the ECGs recorded for subject 38 in one of the trials were recorded for up to 5 different individuals. It was found that ECGs of periods 1 and 4 were actually recorded from subjects 27, 46, 45 and 78. ANSM is categorical that these discrepancies could not have been due to mistakes.

3. The ECGs recorded were very faint because of poor equipment.

4. The trial protocol was amended at the last minute to record more ECGs for each patient. However, permission for this amendment was not taken from the Ethics Committee and more importantly the patients were not asked for this consent since the initial consent forms that they had signed did not mention the additional ECGs.

In its conclusions ANSM states that although ECGs are not pivotal in proving bioequivalence, the scale of fabrication led to concerns regarding the lack of training of GVK Bio's staff with GCP practices. Separate from the ANSM report, it's important to note that ECG records are important to assess the health of patients especially in a facility like GVK Bio where a healthy patient died during a felodipine study in 2008.

GVK Bio was given a chance to comment on the findings contained in the preliminary report and after consideration of GVK Bio's defence, ANSM prepared a final report which confirmed most of the findings contained in the preliminary report.

The Final Report of ANSM led to various countries in EU to initiate suspension of product approvals before the EMA and the EC announced suspensions of 700 product approvals across EU.

III. The USFDA's unexplained divergence from the EMA's action

One of the lesser commented aspects of this story is the fact that the USFDA has not yet announced any action against GVK Bio, despite EMA finding enough evidence to take the unprecedented step of withdrawing approvals for 700 drugs that were approved on the basis of clinical studies at GVK Bio. According to media outlets, which have sought a

comment from the USFDA, the agency spokesperson has stated that although about 40 US applications were based on data from GVK Bio, no action was being taken as its inspectors did not find any systemic issues during their inspection of GVK Bio in September, 2014 after the second inspection by ANSM. According to other sources, there is no clarity whether some of the products withdrawn in the EU are being sold in the US on the basis of data generated by the EU.

The above reports are clearly unaware of the USFDA's previous inspection of GVK Bio in 2012. As explained above, the ANSM in its final inspection report had confirmed that the allegation of data manipulation in trial 145-08 for Felodipine manufactured by Wockhardt was in fact **"highly credible". (Annexure A-10)** In addition, a young healthy patient died in a Felodipine trial conducted by GVK Bio in 2008 – the same year in which 145-08 was conducted. There were two other factors the EMA flagged as serious, some were violations of GLP, such as the lack of proper protection of randomization lists and the lack of audit trail for some computers used in the analysis of the data for these biostudies. Given that the USFDA had reportedly audited this study in 2011, questions should be asked on how that audit missed these issues raised by ANSM. It is also important to ask the USFDA whether it actually approved Wockhardt's ANDA for Felodipine on August 15, 2012 just a month after it had conducted the inspection of GVK Bio. **(Annexure – A5).** What were the reasons for the USFDA to accord approval of this particular drug when the data was suspect? Was the underlying data properly examined by the USFDA?

There is also a need to investigate the USFDA's treatment of the whistleblower. According to the whistleblower's emails, the FDA inspector leading the inspection of GVK Bio in 2012 had interviewed him. During the course of the interview, the FDA inspector apparently spent most of his time querying the whistleblower on his personal life rather than asking for information that would aid the investigation into the allegations GVK Bio. This sounds highly unprofesional. More importantly, how would a USFDA inspector know of this whistleblower's personal situation. The preliminary ANSM report indicates that GVK Bio briefed all the regulators about its point of view of the situation with the whistleblower. Is that a reasonable expectation from a USFDA inspector in terms of his/her behaviour?

According to the whistleblower, both the inspection team and the FDA ombudsman declined to inform him or share with him the final report of their inspection and instead asked him to request for the information under the Freedom of Information Act. While this is the standard practice in the US, the FDA should have made an exception in this case because not only was the whistleblower out of a job and being prosecuted by GVK Bio, he actually required that report as a part of his defence in court. On the other hand ANSM readily shared redacted copies of its reports with the whistleblower. **(Annexure A-12)** At one point the whistleblower was pleading for the reports since GVK Bio had initiated criminal proceedings against the whistleblower and he required the FDA inspection report to defend himself in Indian courts. Copies of the communications with the USFDA can be

accessed at **Annexures A8, A9 & A11**. A full account of the investigation process as narrated by the whistleblower can be found at **Annexure Q-1**.

India focussed issues:

IV. The DCGI's approach and investigation of GVK Bio over the last few years

In 2008, after two deaths at GVK Bio during clinical studies, including that of a healthy 22 year old volunteer during a trial of felodipine, the DCGI ordered an investigation into GVK Bio and several other CROs which had reportedly violated GLPs. At the time, anonymous investigators were quoted as saying that there were widespread violations in the CROs that they had investigated, including and not limited to, GVK Bio. Apparently CROs were constantly ignoring SOPs and violating ethical norms in recruitment of patients. There has since been no publicly available information regarding the results of the investigation. GVK Bio has always denied any wrongdoing, although its statement did point towards ethical lapses in the conduct of its trials.

It is an accepted international convention for international regulators to inform the DCGI of any regulatory investigation within India. There is however no publicly available information in the press whether the DCGI was informed of such an investigation. In April, 2013, the DCGI renewed permission for GVK Bio to run a bioequivalence/bioavailability centre. **(Annexure A7)** After the withdrawal of the 700 approvals announced by EMA in earlier this year in January, 2015 the DCGI announced an investigation into GVK Bio and according to media reports gave it a clean chit recently. However, the report from this investigation is not publicly available and intriguingly the central government announced that it was setting up a six member expert panel to study the issue once again. The legality of this expert panel is questionable since CROs are required to register with the DCGI.

It should be noted that the DCGI as an institution, and more so the current DCGI, has a poor reputation for investigating or prosecuting pharmaceutical companies suspected of breaking the law. Even after Ranbaxy pled guilty in the USA and the Central Government ordered the DCGI to investigate the issue two years ago, no investigation was actually carried out by the DCGI. When Pan Drugs, another generic manufacturer based in India, publicly said that it was "diverting batches of failed drugs from the US market to India", the DCGI did not even take notice. Apparently the health regulator in India finds it acceptable to allow its citizens to consume drugs that were rejected from a foreign market.

In the present case, the DCGI has been quoted *in The Hindu* report as saying, "We do not know why the whistle-blower — if that was his intention — did not approach the Indian regulators first. Having said that, one must understand that there is a bigger game being played out here. I have repeatedly stated that multinational pharmaceutical companies constantly use incidents like this to bring disrepute to Indian generic drug makers". The blaming of all regulatory issues in India on a conspiracy by foreign pharmaceutical

companies is a standard line of argument taken by the Indian government every time the industry is faced with adverse reports from western regulators. This statement of the DCGI in the present case begs the question of whether the aim of his probe into GVK Bio was to investigate the truth or defend the image of the industry. Mr. Thakur has asked this question several times in the recent past.

- http://www.thehindubusinessline.com/opinion/columns/beware-of-made-in-india-medicine/article7531267.ece
- http://thewire.in/2015/09/14/why-the-commerce-ministry-should-not-act-as-spokesperson-for-indian-pharma-10741/
- http://www.newslaundry.com/2015/10/07/the-drugs-dont-work-indian-reporters-need-to-ask-regulators-tough-questions-on-substandard-medicines/

The latter seems more likely because the DCGI and the Ministry of Commerce, which has no expertise in drug regulation, have been handling the issue together as a matter of trade and commerce and not a matter of public health. Statements reported in the press from the Commerce Minister are focussed more on discrediting the ANSM report, than getting to the bottom of the problems at GVK Bio. This approach by the DCGI isn't surprising, since the Parliamentary Standing Committee on Health & Family Welfare had noted long ago "that most of the ills besetting the system of drugs regulation in India are mainly due to the skewed priorities and perceptions of CDSCO. For decades together it has been according primacy to the propagation and facilitation of the drugs industry, due to which, unfortunately, the interest of the biggest stakeholder i.e. the consumer has never been ensured". It appears that little has changed since the report.

V. GVK Bio's hounding of the whistleblower (Based on the whistleblower's allegations – we haven't been able to independently verify his allegations)

The last, but perhaps equally important component, of this story, is the manner in which GVK Bio hounded the whistleblower with criminal prosecutions and threats to his career. For context, it must be explained that GVK Bio is a part of the GVK, a conglomerate founded by GVK Reddy with interests in Energy, Resources, Airports, Transportation, Hospitality and Life Sciences.

Since the first email sent by the whistleblower in 2012, the whistleblower has alleged that GVK Bio filed a total of 3 criminal complaints against him. The first was filed in June, 2012 under S. 66A of the Information Technology Act, 2000 and the whistleblower was arrested in April 8, 2013 but released on the same day on bail. The second complaint which was allegedly a criminal defamation complaint filed under S. 499 of the Indian Penal Code (IPC) on July 30, 2014. Such complaints are typically private complaints and are prosecuted by the complainant. The third complaint was filed on January 11, 2015 under S. 66A of the IT Act, 2000 along with various provisions of the IPC (presumable for fraud, criminal breach of trust, etc.). Under this third complaint, the whistleblower was reportedly arrested and

remanded to custody from January 13 to 27 when he was finally given bail. S. 66A of the IT Act, 2000 was struck down by the Supreme Court in 2015 for being unconstitutionally vague. The remaining charges presumably survive.

While there is certainly no doubt that the whistleblower breached his contractual obligation to confidentiality, the manner in which GVK Bio has used the criminal system to try and gag him is unethical, especially when it appears that all of his allegations were in fact true and in the long run, presumably saved lives. That one of India's best known conglomerates would behave like the schoolyard bully speaks rather poorly of corporate ethics in India.

Question: UN Office on Drugs and Crime had commissioned the development of a prosecution framework for organizations while wilfully indulging in fraudulent activities. Prof. Amir Attaran was tasked with drafting the said framework and its associated regulation. Unfortunately, this process was scuttled by nations and interested parties who did not want this regulation to be created. This line of inquiry should include a perspective from Prof. Attaran to understand why.

VI. The future of overseas CRO regulation & whistleblower protection

The fact that so little has changed with the regulation of CROs since the Vimta scandal in 2004 indicates that Western regulators have not learnt their lessons. Since bioequivalence studies form the backbone of public confidence in generic drugs, it is time that Western regulators stepped up to the challenge posed by unscrupulous actors in the CRO industry. One of the problems faced by these CROs is that it is incredibly difficult to detect data manipulations without the help of information supplied by whistleblowers. However, instead of encouraging whistleblowers, the actions of the USFDA appears to be aimed at discouraging future whistleblowers. In this instance, can the Indian whistleblower with limited resources and who was facing a criminal prosecution, apply for an inspection report (which was triggered by his complaints) under the Freedom of Information Act? Could the USFDA be more insensitive? The USFDA should therefore be required (through Congressional action) to revamp the manner in which it handles future whistleblowers.

The other issue pertains to the manner in which the investigation is conducted by regulators. In this case, the whistleblower has alleged that a lot of manipulations were deleted without maintaining an audit trial on the computers. This allegation has been raised repeatedly in the Indian context. Regulators therefore should adapt their investigative skills and if required send the computer systems for a forensic audit. In order to seize evidence such as this, it may be required to treat investigations into CROs as criminal investigations. The regulatory framework for seizure of such equipment at an international location doesn't exist. This means that investigators should not be required to give prior notice to CROs. Surprise visits, need to be the standard protocol followed while inspecting these CROs. It defies logic to give prior notice to a CRO to investigate whether it has already destroyed crucial evidence that it was required to preserve under the law.

We suggest news media might want to investigate the subject and provide some themes below:

US:

1. Why did the US FDA approve Wockhardt's Felodipine despite knowledge (from their joint participation) from the inspection at GVK Bio along with ANSM where the French Inspectorate found the whistleblower's allegations about fraud "credible"?
2. Why were the US FDA inspectors unable to identify the problems with audit trail on the LCMS machines and compromised randomization lists?
3. How effective is the PIC/s organization? Did the FDA know of the ANSM inspection report?
4. How does the US FDA initiate criminal proceedings against a foreign entity, especially for search and seizure?

India:

1. How did GVK Bio get access to call logs, mobile location records etc?
2. What is the nature and role of IPA in driving the Commerce Ministry's agenda?
3. What protections, if any, does the law provide for whistleblowers in the private sector?