Inspections of Bioequivalence Trials in India—hundreds of Generic Products pulled from the Market

Bioequivalence Trials under Scrutiny

In the last years, the U.S. Food and Drug Administration (FDA), the World Health Organization (WHO) and the European Medicines Agency (EMA) raised serious concerns related to the integrity of data provided by several Indian Contract Research Organizations (CROs) that conducted bioequivalence (BE) trials on behalf of sponsors. The authorities suspended hundreds of Marketing Authorizations for products that had been approved based on studies conducted by these CROs and where Marketing Authorization Holders (MAHs) were unable to provide pharmacokinetic (PK) data to confirm BE from reliable sources.

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Bioequivalence Trials

BE trials are conducted to determine if a generic medicinal product has the same bioavailability (BA) as a reference product. Two medicinal products containing the same active substances are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and the rate and extent of absorption into the blood after administration lie within acceptable predefined limits. The majority of BE trials follows a two-period, two-sequence, two-treatment, single-dose crossover trial design in healthy volunteers. In such trials, the parameters to be analysed are AUC (area under the concentration curve) and C_{max} (maximum observed concentration), and for these the 90 per cent confidence interval for the ratio of test and reference products should range within the acceptance interval of 80 per cent to 125 per cent. If these conditions are not met, BE between the products cannot be demonstrated and the trial is considered as failed.

EMA issued specific guidance for the conduct of BE trials [1][2][3]; in addition, general rules for the validation of analytical methods [4], the clinical trial conduct [5][6] as well as the analyses of the laboratory samples [7] apply. Likewise, FDA [8][9] and WHO [10] published relevant guidance documents in this area. Of course, guidelines issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) also apply for BE trials [11].

BE trials are expected to comply with regulatory requirements specified in Good Clinical Practice (GCP),

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Areas	GCP	GLP	GMP
Investigational Medicinal Products	X		X
Clinical Trial Conduct	X		
Analytical Method Validation		X	
Sample Handling and Analysis	X	X	
Reports	X Clinical Trial Report	X Bioanalytical Report	

Table 1: Regulatory Requirements in BE Trials.

Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) for the manufacturing of Investigational Medicinal Products (IMPs, test and reference) (see Table 1). The bioanalytical part of BE trials should be performed in accordance with the principles of GLP. However, as human bioanalytical studies fall outside the scope of GLP, the sites conducting the studies are not required to be monitored as part of a national GLP compliance programme.

Inspections of Bioequivalence Trials

Authorities inspect BE trials to assess compliance with applicable ethical and regulatory requirements to ensure that the results are valid and can be trusted [12][13][14]. For example, the FDA conducted more than one thousand (1,000) inspections of BE/BA trials between 2017 and 2021 (see Figure 1). Details on the outcome and observations made can be found in the FDA Bioresearch Monitoring (BIMO) 2021 Metrics Report [15].

During inspections of BE trials, the FDA, EMA as well as WHO's Prequalification Services Inspection Team (PQT) identified deficiencies in the conduct and analyses of such trials; several inspections provided results that were seriously worrying and led to the suspension of the Marketing Authorization of numerous medicinal products.

This article provides information on some of the published cases identified at several Indian CROs performing BE trials, the pattern of observations and the consequences of such serious non-compliance. The cases are presented in a pseudo-chronological sequence, based on the key inspection dates, whenever possible (see Table 2).

The selection of cases may appear arbitrary or even biased (as only CROs located in India are discussed) but it was guided by the accessibility of information from regulatory authorities. FDA, EMA and inspectorates located in European Union (EU) member states do not generally publish inspection reports but may issue updates regarding their investigations on their websites or in annual reports; some information can be requested via the US Freedom of Information Act (FOIA), for example.

Inspection reports issued by WHO's PQT are accessible on their website but only for three years following issuance and under the condition that the inspectee agrees to the publication. After that, only the inspection dates are listed with no information on the outcome of the inspection. Notices of Concern issued by WHO's PQT remain posted on the website until PQT is satisfied that the inspectee has effectively implemented an adequate and appropriate corrective and preventive action plan.

GVK Biosciences Private Limited, Hyderabad, India

On 6 May 2012, a whistleblower sent an e-mail to various regulatory authorities to inform about data manipulations at GVK Biosciences Private Limited (GVK Bio). The informant, an ex-GVK Bio employee, made specific allegations on how data had been fabricated to ensure that BE studies had the desired outcome. For example, PK samples

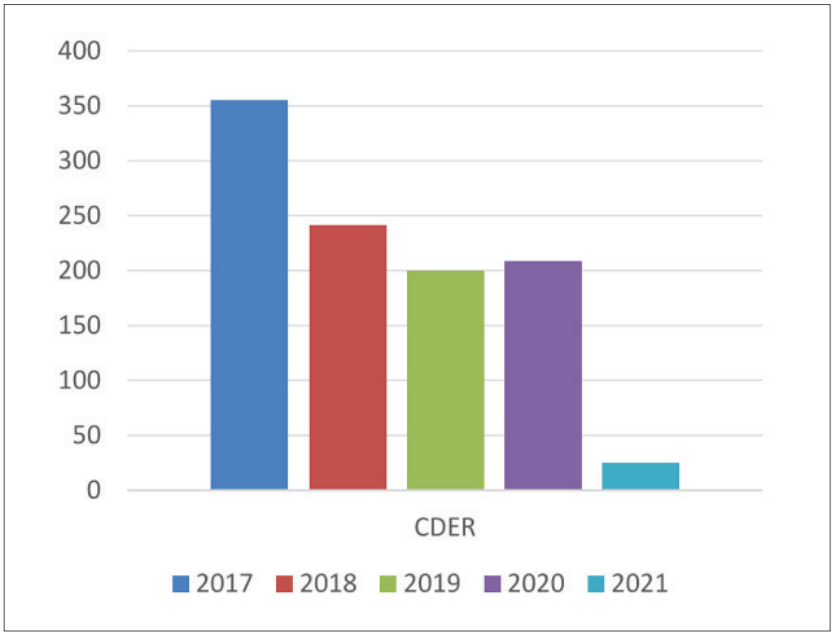

Figure 1: FDA BIMO BE/BA Inspections 2017–2021 [15].

CRO	Regulatory Inspections and Resulting Actions		
	WHO	FDA	EMA / EU Inspectorates
GVK Bio	25–29 June 2012[1]	25–29 June 2012[1]	25–29 June 2012[1] (FR + AT)
			19–23 May 2014 (FR)
			26 September 2014: EMA Referral
Quest Life Sciences	13–17 October 2014[2]	13–17 October 2014[2]	
		17 October 2014: Form 483	
	30 June 2015: Notice of Concern		
			February 2016 (UK)
		14–18 November 2016	
		18 November 2016: Form 483	
		26 February–2 March 2018	
		2 March 2018: Form 483	
Semler Research	12–16 July 2010		
	11–15 July 2011		
	25–28 March 2013		
		December 2013	
		September 2014	
	27–31 January 2015		
		29 September–9 October 2015	
		9 October 2015: Form 483	
	2–5 December 2015 (follow-up)		
			February 2016 (UK)
	12 April 2016: Notice of Concern		
			29 April 2016: EMA Referral
Alkem			9–12 March 2015 (DE + NL)
			24 March 2016: EMA Referral
Panexcell	24–27 July 2018		
			14–17 October 2019 (AT + DE)
		18–22 November 2019	
			28 February 2020: EMA Referral
	9 October 2020: Notice of Concern		
		15 September 2021: Untitled Letter	
Synchron			2005 (FR + NL)
			2009 (FR + DE)
	17 May 2010		
	11–15 June 2018		
		18–22 November 2019	
		15 September 2021: Untitled Letter	
			31 January 2022: EMA Referral

Table 2: Chronology of Events related to the CRO Inspections and Regulatory Actions taken.

[1] Joint inspection, triggered by whistleblower e-mail of 6 May 2012.

[2] It cannot be confirmed if this was a joint inspection by WHO and FDA, despite the identical inspection dates.

BOX 1: ANSM conclusions from the 2012 inspection at GVK Bio

"No documented evidence was found during the inspection to either support or dismiss the first allegation described in the anonymous e-mail received by various regulatory authorities. The manipulations described were found to be technically feasible. The results of the review of the data of trial […] are fully consistent with the information received and give them a strong credit. Information on sample substitution provided as part of this allegation is considered as highly credible in the case of trial […]. It is however noted that no similar pattern was seen when reviewing the data of seventeen other trials performed by GVK Bio and submitted to ANSM. Trial […] was not submitted to ANSM.

A recommendation will be made to assessors reviewing marketing authorisation applications dossiers containing data from trials conducted at GVK Bio to systematically check the data with the utmost vigilance for possible suspicious trends, patterns or similarities." * [16]

* Emphasis by the author

from trial participants were switched from period 1 and period 2 or replaced with samples from other trial participants (already analysed and with known results). These manipulations resulted in a final data set that confirmed that the generic and the reference products were bioequivalent – and the trial was considered a success.

To investigate these allegations, **FDA**, **WHO** and two European inspectorates, the French Agency on Medicinal Products (Agence Nationale de Sécurité du Médicament et des Produits de Santé – **ANSM**) and the Austrian Agency for Health and Food Safety (Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH – **AGES**), conducted a joint inspection at GVK Bio from 25 to 29 June 2012.

On 13 July 2013, ANSM issued a final inspection report [16] and included some interesting conclusions (see Box 1)—these are relevant in the discussion of subsequent case studies in this article. As the observations made by ANSM related to a BE study that was done for the US market, ANSM could not take this any further.

Following the joint inspection, FDA did not issue a Form 483 to GVK Bio. No information could be found from WHO or AGES related to this joint inspection.

From 19 to 23 May 2014, **ANSM** conducted another inspection at GVK Bio to assess a total of nine BE trials which were performed between 2008 and 2014. The inspectors were seriously concerned about the reliability of the electrocardiograms (ECGs), including the falsification of ECGs observed in all nine trials. The fact that the ECG manipulations were of systemic nature, took place during an extended period of time and involved a number of staff from the CRO casted doubts about the authenticity of all other clinical records in these trials.

The inspectors concluded in their final inspection report of 4 August 2014 [17] that GVK Bio's Quality Management System (QMS) was seriously flawed and that staff lacked understanding of the importance of data integrity. The nature of the deficiencies identified and the GCP non-compliance observed raised questions regarding the acceptability of the clinical part of all other BE trials performed by the company in support of Marketing Authorization Applications (MAAs).

EMA was notified on 4 August 2014 and a referral according to Article 31 of Directive 2001/83/EC was started in September 2014. GVK Bio was requested to provide further clarifications and affected MAHs were informed of the case. On 20 February 2015, EMA issued a list which included almost seven hundred (700) products for which the Marketing Authorizations were recommended for suspension from the EU market. Details on the chronology of events can be found on the EMA website [18].

On 1 June 2021, GVK Bio was rebranded to Aragon Life Sciences.

Quest Life Sciences Pvt Ltd, Chennai, India

From 13 to 17 October 2014, **WHO** inspected Quest Life Sciences Pvt Ltd (Quest Life Sciences) to the conduct of one BE study. Following the review of the inspectee's responses, the WHO issued a Notice of Concern [19] to the CRO in July 2015 which addressed the following critical observations:

- almost 70 per cent of the pre-study ECGs were duplicates of each other where the CRO changed trial participant details and dates, making it appear as if they were from each of the individual subjects when in fact they were not (one ECG was "recycled" for up to nine subjects);
- several trial-related forms were completed retrospectively (even during the inspection), were incomplete, or missing approval signatures;
- and the CRO installed Adobe Acrobat Editor® on computers in the Quality Assurance department which posed the risk of documents being amended without leaving a trace.

Concurrent with the WHO inspection, **FDA** inspected the CRO also from 13 to 17 October 2014 (it could not be determined if it was a joint inspection). The Form 483 issued listed observations related to the content of the informed consent form, failure to train or to document training of study personnel, storage of samples outside the specified temperature range, using wrong blood sample collection tubes, calibration issues related to a centrifuge, and insufficient shipment records for samples to a third-party laboratory. Another inspection followed from 14 to 18 November 2016, which also resulted in a

BOX 2: WHO conclusions from the 2015 inspections at Semler Research

"PQT is under the impression that these observations are an indicator of fraud, as they are consistent with interim statistical analysis followed by deliberate sample manipulation of remaining subject samples, when the point estimate at the interim analysis indicates the existence of product differences in terms of rate or extent of absorption, with the intention of bringing point estimates towards unity and thereby increasing the chances of proving bioequivalence. […]
Manipulation of at least five studies over an extended period of time indicates this is a common practice; WHO is of the impression that to execute this type of manipulation several staff members on various levels within the organisation have to be collaborating and coordinating. The issue is thus not confined to a single person operating outside of the quality management system. […]
The above problems observed at Semler and other problems described in the report, indicate the existence of a general or systematic deviation from commonly accepted quality standards, and cannot be ascribed to a single person or two working outside of the quality management system. On these grounds, PQT recommends an immediate stop for all submissions of dossiers relying in whole or in part on involvement from Semler […]." [21]

Form 483 highlighting deficiencies relating to source documentation, poor ECG copies with faded data to identify the subjects, failure to document which ECG machine was used and laboratory reports for all subjects included the wrong age. A third inspection followed from 26 February to 2 March 2018 and, again, resulted in a Form 483 which described three instances of non-compliance with the CRO's Standard Operating Procedures (SOPs) related to archiving of study documents and dispensing of IMPs.

In February 2016, the Medicines and Healthcare products Regulatory Agency (**MHRA**), United Kingdom, inspected Quest Life Sciences and observed several data integrity issues. As a result, MHRA suspended the Marketing Authorization of one product that had been approved based on BE data generated by Quest Life Sciences; four pending applications for Marketing Authorization that rely on studies conducted by Quest Life Sciences might be rejected. Unfortunately, no further information could be found [20].

Semler Research Center Private Limited, Bangalore, India

The **WHO** had conducted several inspections at Semler Research Center Private Limited (Semler Research), e.g., 12 to 16 July 2010, 11 to 15 July 2011 and 25 to 28 March 2013, according to information on WHO's website.

However, the inspections which WHO performed from 27 to 31 January 2015 and a follow-up from 2 and 5 December 2015 to assess GCP and GLP compliance of BE trials conducted by the CRO yielded surprising results. Both inspections resulted in critical and major deviations as documented in the inspection reports sent on 6 October 2015 and 11 February 2016.

On 19 April 2016, WHO sent a final Notice of Concern to Semler Research [21], which listed significant doubts regarding data integrity in that study samples were manipulated by replacing trial participant samples by samples from other subjects and where reference and test were swapped. Such manipulation pattern was observed for several studies reviewed during the WHO inspection. (And this was also the pattern which ANSM had previously identified in the joint inspection performed in 2012 at GVK Bio!) Core conclusions from WHO's final Notice of Concern are included in Box 2.

Between the two inspections which WHO performed at Semler Research, the **FDA** also inspected the CRO from 29 September to 9 October 2015 to review regulatory compliance of three BE trials. At the conclusion of the inspection, FDA issued a Form 483 [22] which listed seven observations, relating to substitution of plasma samples (two observations); failure to include all aqueous humor samples in the study report in one study; failure to retain and make available all study-related documents and bioanalytical raw data in study folders; insufficient protection of chromatography data so that laboratory analysts had the ability to delete, copy and rename such data; and insufficient protection against accidental loss of data generated in the bioanalytical laboratory by using portable thumb drives.

On 19 April 2016, FDA issued an Untitled Letter to Semler Research [23] that echoed the above observations and included a detailed assessment of the replacement of trial participants' plasma samples with those of different participants that had already been analysed. Concentration-time profiles for the participants for which samples were substituted showed almost identical concentration-time profiles for the pairs that were switched. Further analysis of BE endpoints identified that they differed significantly between the trial participants with substituted and non-substituted samples. (Now this pattern becomes already familiar!) The CRO was unable to explain this inconsistency in the PK data. Because of the manipulations, the studies met the BE criteria. FDA's conclusion is depicted in Box 3.

The day after FDA issued its Untitled Letter, sponsors of NDAs and ANDAs were notified that included data from Semler Research in their applications that clinical and bioan-

BOX 3: FDA conclusions from the 2015 inspection at Semler Research

"FDA found evidence documenting that you engaged in practices and processes that undermined the analytical methods used at your firm, which resulted in the submission of invalid study data to the FDA. As a result, FDA has significant concerns about the validity and reliability of bioequivalence and bioavailability data generated at your firm that is submitted to the FDA in support of Abbreviated New Drug Applications (ANDAs) or New Drug Applications (NDAs). […]
This substitution of samples undermines the reliability and validity of the analytical methods used at your firm and the study data produced by your firm." [23]

alytical studies conducted by the CRO were not acceptable as a result of data integrity concerns and need to be repeated.

It is Interesting to note that previous FDA inspections at the same site in December 2013 and September 2014 did not result in Form 483s.

EMA started a referral procedure on 29 April 2016 to review products for which studies had been conducted at the CRO after serious concerns were raised during FDA and WHO inspections at Semler Research. EMA did not opt to perform their own inspection at the CRO. On 21 July 2016, EMA recommended to suspend almost three hundred (300) drugs; products under evaluation for authorisation and which relied only on BE data from the CRO should not be authorised until BE is demonstrated using alternative PK data.

In their assessment report, EMA concluded: "Where the bioequivalence is not established, safety and efficacy cannot be extrapolated from the EU reference medicinal product to the generic medicinal product as the bioavailability of the active substance between the two medicinal products may differ. If the bioavailability of the generic product is higher than the bioavailability of the reference medicinal product, this may result in a higher than intended exposure of patients to the active substance, leading potentially to an increase in the incidence or severity of adverse effects. If the bioavailability of the generic product is lower than the bioavailability of the reference medicinal product, this may result in a lower than intended exposure to the active substance, leading potentially to a decrease in efficacy, a delay or even a lack of therapeutic effect. Therefore, for products either authorised or seeking a marketing authorisation based on data generated at Semler, bioequivalence is not established and benefit-risk balance cannot be considered positive, as the possibility of safety/tolerability or efficacy issues cannot be excluded." [24]

On 22 January 2018, following the scrutiny by several authorities that identified unacceptable practices at Semler Research, the CRO filed a legal complaint against FDA [25] seeking 50 million USD for damages (30 million USD for collapsed sales and 20 million USD for compensations asked by clients). The complaint document includes interesting details on the FDA inspection and suggested that the inspectors had a clear idea on what they were looking for by focusing the inspection on computer validation and BE/BA testing, including the review of access restrictions to data and hard drives. However, Semler Research was not successful with the claim against FDA and the court dismissed the case on 13 November 2018.

Alkem Laboratories Ltd, Taloja, India

From 9 to 12 March 2015, **EMA** performed a routine inspection, conducted by inspectors from the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte – **BfArM**) and from the Health Care Inspectorate (Inspectie Gezondheidszorg – **IGZ**) of the Dutch Ministry of Health, at Alkem Laboratories Ltd (Alkem) to assess three BE trials performed at the Taloja site. The inspection revealed misrepresentation of data in two different BE trials performed in 2013 and 2014. The findings were related to ECG data, e.g., an ECG printout that was used as source data for two different trial participants as well as other documentation and ECG assessment irregularities. They raised concerns regarding the overall adequacy of the QMS in place at the site, and thus questioned the reliability of the data of BE studies conducted between March 2013 and March 2015.

A referral was initiated on 24 March 2016. On 23 June 2016, EMA recommended that one drug should be suspended and two products currently under evaluation should not be authorised unless alternative data from other sources were provided. [26]

Panexcell Clinical Lab Private Limited, Navi Mumbai, India

From 24 to 27 July 2018, **WHO** performed a routine inspection at Panexcell Clinical Lab Private Limited (Panexcell) to assess two BE trials conducted by the company. According to the final inspection report, it was concluded that the studies were "conducted at an acceptable level of compliance with WHO GCP and GLP." Non-compliances were observed during the inspection but were not detailed in the published version of the inspection report; the report confirmed that these observations were satisfactorily addressed before the final report was issued. [27]

From 14 to 17 October 2019, the Austrian Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen – **BASG**) and the German **BfArM** performed

a joint inspection at Panexcell on request of **EMA** to review one BE trial. The inspection focused on the bioanalytical part and PK of the trial and the inspectors had doubts about the reliability of the BE study data, based on the critical observations which were made. Serious concerns were raised regarding the suitability of the CRO's QMS and the overall reliability of data generated by the company and submitted to support EU MAAs.

On 28 February 2020, the EMA started the referral procedure and assessed products that were on the EU market based on data generated by Panexcell. This resulted in suspension of six products from the EU market. All information on the referral procedure can be found on the EMA website [28]. See Box 4 for details regarding the critical observations noted at Panexcell during the inspection.

The EMA assessment report also referenced responses from some MAHs who had submitted Panexcell data and who claimed "that the data analysis techniques employed for fraud detection were unable to detect any clear anomalies in the data and that their investigations did not reveal any indications of fraud or misconduct" by the CRO and that "the observations made by the Austrian and German competent authorities in the 2019 joint inspection had not been observed in another inspection carried out at the same CRO by another EU Competent Authority" [28].

EMA countered: "Although it is acknowledged that audits or inspections carried out in the past at Panexcell Clinical Laboratories Priv. Ltd., India, may have had positive outcomes, the findings observed during the BfArM and BASG 2019 joint inspection are considered to reflect broader problems concerning corporate culture and quality management. These can affect all areas of trial conduct and are, because of their nature, either difficult to identify or not possible to detect during an inspection. Considering the nature, the severity and the extent of the joint inspection findings, any other inspection performed at the site would not provide enough reassurance since they may not have detected serious GCP violations, even if present." [28] One will be reminded of this statement later in the article.

From 18 to 22 November 2019, the **FDA** also inspected Panexcell and found significant instances of misconduct and violations of applicable regulations in seven BE trials. Following the inspection, the FDA analysed PK data in a number of other BE trials performed by Panexcell and found "similar and significant anomalous PK data trends" to those which they had seen during the inspection: "unexpected, non-physiologic PK data" in eleven studies. The FDA reviewed the responses provided by the CRO on 6 December 2019 and 12 April 2021. On 15 September 2021, the authority issues an Untitled Letter to the CRO [29], concluding that the company submitted falsified data to the FDA. None of the CRO's explanations to refute the FDA's observations were accepted by FDA.

On 16 September 2021, FDA informed the pharmaceutical industry of the outcome of the inspection and that data generated by Panexcell in support of NDAs and ANDAs were unacceptable because of data integrity concerns and studies must be repeated (see Box 5).

On 10 October 2020, **WHO** issued a Notice of Concern to Panexcell [30]. Based on EMA's initiation of the referral procedure, WHO reassessed the two BE trials which they had inspected in 2018 at Panexcell and came to the conclusion, following review of CRO's response, that Panexcell was unable to explain the following discrepancies in the trial data: In one study, random distribution of PK parameter ratios for […] were noted and trends/partial trends in group/subgroup were identified and random distribution of the data was not considered a reasonable probability; and failure to implement a robust QMS to exclude any possible data manipulation or misrepresentation of data. WHO also referenced the concerns raised during the EMA inspection and referral procedure.

Synchron Research Services Pvt. Ltd., Ahmedabad, India

WHO inspected Synchron Research Services Pvt. Ltd. (Synchron) on 17 May 2010 and from 11 to 15 June 2018. No information on the outcome of the in-

BOX 4: BASG, BfArM and EMA conclusions from the 2019 inspection at Panexcell

"The reported PK profiles […] of several subjects were found to be exceptionally similar. From the verification done during inspection it is apparent that study samples could not have been mixed-up accidentally. The similarities of the profiles are of such extent that they cannot be explained and there are serious doubts whether the reported concentrations of the subjects do actually originate from these. Moreover, the confidence interval, which was > 125 per cent after the samples of the first 32 subjects were analysed showed a downwards trend and appeared to be only within the acceptance limit after the affected subject samples were analysed.

In light of the nature, the seriousness and extent of the inspection findings identified during the joint BASG and BfArM inspection, the CHMP considers that the data generated at Panexcell Clinical Laboratories Priv. Ltd., do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product foreseen in Article 10 of Directive 2001/83/EC. Therefore, in the absence of demonstration of bioequivalence, the CHMP considers that the efficacy and safety of the medicinal products concerned cannot be established and hence the benefit-risk balance cannot be considered positive." [28]

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BOX 5: FDA conclusions from the 2019 inspection at Panexcell

"Subjects' PK study data appeared to separate into two distinct populations, with a change occurring after the midpoint of the study, which would not be expected based on normal subject physiologic variability across a subject population. Specifically, the test product peak drug concentration (C_{max}) appeared to be higher than the reference product in the first half of the subjects, but the opposite was true for the second half of the subjects. During FDA's inspection, we requested that you provide a bioequivalence assessment for each group independently, Subjects 1–12 and Subjects 13–24, and compare that assessment to the bioequivalence assessment of all study subjects. We also requested that you calculate C_{max} and AUC_{0-t} geometric mean ratios (GMRs) with their respective confidence intervals for the two study subject groups, to evaluate the overall trends in terms of the bioequivalence endpoint. The calculations resulting from your analysis […] indicated that the GMRs data for Subjects 1–12 were distinct from the data for Subjects 13–24. […] You failed to resolve FDA's concern regarding the validity of data for Study [x] given the presence of two distinct populations around the midpoint of the study, which would not be expected based on normal subject physiologic variability across a subject population. […]

Concentration profiles for several subject pairs were nearly identical, which is not expected based on normal physiological differences, and is indicative of sample substitution. During the inspection, we requested that you plot the concentration profiles for subject pairs that appeared to have nearly identical PK profiles […]. The resulting plots from your analysis showed significant overlap between those subject pairs. […]

For those [eleven] studies, FDA requested that you provide an explanation for the anomalous PK data identified; that is, that you explain the study data (1) showing multiple pairs of subjects with overlapping time-concentration profiles, (2) showing distinct groups of subjects where the T/R ratio for C_{max}, AUC_{0-t}, and $AUC_{0\rightarrow\infty}$ for most subjects in the subgroups is above or below 1, or (3) having both concerns. […]

FDA's concerns regarding study data generated by your firm remain; that is, Panexcell's study data are inconsistent with normal variation or distribution found in a healthy population, and are not expected by chance across the significant number of studies identified by FDA." [29]

spections is available on the website.

The **FDA** performed an inspection at Synchron on the exact same days as they did at Panexcell, i.e., from 18 to 22 November 2019. In fact, FDA investigated BE studies undertaken by Panexcell and Synchron in parallel and issued their conclusions in form of Untitled Letters to the CROs and informed the pharmaceutical industry also on the same dates. Five BE trials were reviewed during the inspection at Synchron and six more BE studies after the inspection: the observations echo the findings noticed during the Panexcell inspection. The same falsification pattern was identified with switching subject samples in the analysis and anomalous overlapping time-concentration profiles for several subject pairs. The Untitled Letter to Synchron is like a "déjà-vu" when compared with the Panexcell one. FDA raised the same serious concern regarding the reliability and validity of clinical and analytical data generated by Synchron and came to the same conclusion that data from Synchron in support of NDAs and ANDAs were unacceptable because of data integrity concerns and studies must be repeated. On 16 September 2021, FDA informed the pharmaceutical industry of the outcome of the inspection and that data generated by Synchron were inadequate. [31]

On 31 January 2022, **EMA** started the referral procedures for Synchron [32] which followed the FDA's conclusion after the inspection from 18 to 22 November 2019 that the CRO "was responsible for the creation of false data and that all their studies were therefore unacceptable". The notifications by Sweden, Finland, Denmark, the Netherlands, and Belgium referred to the FDA inspection findings. They also included information on two previous EU inspections conducted by France and the Netherlands in 2005 and France and Germany in 2009 at Synchron, both of which had identified data manipulations. While the data from the affected studies had been rejected following the 2005 and 2009 inspections, "these cases were treated as isolated non-compliance at that time." In the assessment report issued in May 2022, EMA concluded that the CRO's processes and procedures for the conduct of BE studies raised serious concerns about the QMS and the reliability of data from Synchron. Based on the doubts, the suspension of about one hundred (100) medicines on the EU market was recommended as no adequate BE data was available from other sources.

Discussion

In 2021, almost 90 per cent of prescriptions dispensed in the USA were generics but represented only 18 per cent of total drug spending; this number has increased consistently since 2005 when the percentage of generics was around 50 per cent. In Europe, the numbers are lower and about two-thirds of all dispensed drugs are generics, representing almost 30 per cent of pharmaceutical expenditures. These numbers illustrate the significant reliance of the medical sector on generic products in the USA and Europe and their

contribution to lowering the costs of healthcare.

The falsification and non-compliance observed in clinical data generated by Indian CROs resulted in hundreds of generic products being pulled from the market. This does not only affect the USA or Europe, but also many other countries around the world where generics are vital to ensure cost-effective access of patients to safe and effective drugs. Manipulating PK data so that generics without reliably confirmed BE reach the market is a risk for patients in that they may be exposed to over- or underdosing which might have a negative impact on their health and recovery.

In addition, such behavior erodes trust in medical treatments and in the pharmaceutical industry in general. The fact that the deficiencies described in this article were all identified in inspections of CROs located in India does not mean that these issues can be handled as an "Indian anomaly". In India alone, 80 BA/BE study centers and bioanalytical laboratories are registered with the Central Drugs Standard Control Organization as per 10 June 2021. The patterns and regulatory violations uncovered may also be visible in other BE trials that have not yet been scrutinised sufficiently, regardless of whether these were performed in India or elsewhere.

The falsification of PK data by switching samples remained undetected in routine audits or inspections, unless you know exactly what you are looking for and you can lay your hands on to data in the CRO's computer system while being on site. As noted in some references to inspections, non-compliance and manipulations were observed; however, they were considered as isolated events … until the pattern of fabrication and discrepancies unfolded in an in-depth investigation.

The author assumes that the majority of routine BE audits do not dig as deep as it would be necessary for such manipulations to be observed; reasons may be manyfold: time constraints during the audit, limited experience with auditing, with computerised systems, with the nature of BE studies and data analysis, etc. Also, the audit might be performed just before the samples are magically switched in the analysis. The fact that several regulatory inspections (and most likely even more audits) were performed at the Indian CROs before the fraud scheme was detected confirms that this remains unnoticed by applying routine approaches.

We need to be more vigilant and less trusting so that results that are "too good to be true" and look great at the first glance get a second (or third) look. Carefully reviewing the details in the inspection reports and the associated documents as well as related publications will help gain a deeper knowledge on how the CROs executed the switching of concentration profiles so that passing results for BE studies were achieved. The mechanism of fraud followed by some of the above CROs was also fully described in a publication that will provide insight about the processes how to analyse the data to determine if "the switch" was made [33].

And do not forget to periodically scan the regulatory landscape for updates in this area. In November 2020, WHO published a useful document on Frequent Deficiencies in Bioequivalence Study Protocols, for example [34].

Spreading the word and talking about the deficiencies noticed in BE trials will help, too. |

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