Annex II

Scientific conclusions

Scientific conclusions

The Federal Office for Safety in Health Care (BASG), Austria, and the Federal Institute of Drugs and Medical Devices (BfArM), Germany, performed a joint GCP inspection from 14 – 17 October 2019 at the contract research organisation (CRO) Panexcell Clinical Laboratories Priv. Ltd., located in Navi Mumbai 400 701, India. This inspection focussed on a bioequivalence trial performed by this CRO in 2018 and 2019 for the substance doxorubicin. The following critical observations were made during the inspection which cast serious doubts on the reliability of the data of this bioequivalence study:

- The reported PK profiles for free doxorubicin and doxorubicinol of several subjects were found to be exceptionally similar. From the verification done during inspection it was apparent that study samples could not have been mixed-up accidentally. The similarities of the profiles were of such extent that they could not be explained and there were serious doubts whether the reported concentrations of the subjects originated from these.
- During the inspection, study personnel intentionally documented the wrong room temperature in order to pretend that room temperature in the sample processing area was within the acceptance range.

The severity and the extent of the findings of the inspection of BASG and BfArM raise serious concerns relating to the suitability of the quality management system at Panexcell Clinical Laboratories Priv. Ltd. and about the overall reliability of the data generated by this CRO since the set-up of the site under the name Panexcell Clinical Laboratories Priv. Ltd., and submitted to support the marketing authorisation applications for medicinal products in the EU.

On 19 February 2020 Germany (BfArM) therefore triggered a referral under Article 31 of Directive 2001/83/EC and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of products which have been authorised in the EU on the basis of clinical trials performed at Panexcell Clinical Laboratories Priv. Ltd. since the set-up of the site under the name Panexcell Clinical Laboratories Priv. Ltd., or pending approval, and issue a recommendation as to whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

In applications for generic medicinal products under Article 10(1) of Directive 2001/83/EC, the concept of bioequivalence is fundamental. The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product.

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 of patients to the active substance, leading potentially to a decrease in efficacy, a delay or even a lack of therapeutic effect.

In view of the severity and the extent of the findings of the joint GCP inspection of BASG and BfArM at Panexcell Clinical Laboratories Priv. Ltd. casting serious concerns about the suitability of the quality management system at Panexcell Clinical Laboratories Priv. Ltd. and the overall reliability of the data generated by this CRO and submitted to support the marketing authorisation applications for medicinal

products in the EU, the data from all bioequivalence studies performed at Panexcell Clinical Laboratories Priv. Ltd. since the set-up of the site under the name Panexcell Clinical Laboratories Priv. Ltd. and submitted to the Competent Authorities to demonstrate bioequivalence of medicinal products with their originator are considered unreliable.

In the absence of reliable data demonstrating bioequivalence with an EU reference medicinal product, the benefit-risk balance of the products either authorised or seeking a marketing authorisation based only on data generated at Panexcell Clinical Laboratories Priv. Ltd. to demonstrate bioequivalence could not be considered positive, as the possibility of safety/tolerability or efficacy issues cannot be excluded.

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. Therefore, it is considered that these arguments do not demonstrate that the said studies can be relied upon. The CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have affected the said studies and is of the opinion that the studies cannot be relied upon to establish bioequivalence vis-à-vis the EU reference medicinal product.

Results of a bioequivalence study conducted in the US with the US reference product have been provided. According to Article 10 of Directive 2001/83/EC, the bioequivalence needs to be established vis-à-vis an EU reference medicinal product. Results from bioequivalence studies using non-EU reference medicinal products can therefore not be accepted for demonstrating said bioequivalence.

In the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal product, the requirements of Article 10 of Directive 2001/83/EC cannot be considered fulfilled, the efficacy and safety of the concerned medicinal products cannot be established and therefore, the benefit-risk balance cannot be considered positive. The CHMP therefore recommends the suspension of the marketing authorisations for all medicinal products concerned by this referral procedure.

For marketing authorisation applications included in this review, the CHMP considers that, for the reasons explain above, the applicants did not submit information which allows to establish bioequivalence to the EU reference medicinal product, and therefore the marketing authorisation applications do not currently fulfil the criteria for authorisation.

Grounds for CHMP opinion

Whereas,

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for marketing authorisations and marketing authorisation applications for medicinal products for which the clinical and/or bioanalytical parts of the bioequivalence studies were performed at Panexcell Clinical Laboratories Priv. Ltd., located in Navi Mumbai, India, since the set-up of the site under the name Panexcell Clinical Laboratories Priv. Ltd.;
- The CHMP reviewed available data and information provided by the MAHs/applicants, as well as information provided by Panexcell Clinical Laboratories Priv. Ltd.

- The CHMP considered that the alternative bioequivalence data or justifications submitted to support the marketing authorisations of iron sucrose or amoxicillin were insufficient to establish bioequivalence vis-à-vis the EU reference medicinal product. In addition, the CHMP considered that no new information was provided by Panexcell Clinical Laboratories Priv. Ltd. changed the conclusions drawn by the inspection teams;
- The CHMP concluded that the particulars supporting the marketing authorisation/marketing authorisation application are incorrect and that the benefit-risk balance is considered not favourable for all authorised medicinal products and marketing authorisation applications listed in Annex I.
- Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the CHMP concludes that:

    a. Marketing authorisations for medicinal products for which bioequivalence data or justification were not submitted or considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (Annex I) should be suspended, as the particulars supporting the marketing authorisations are incorrect and the benefit-risk balance of these marketing authorisations is considered not favourable pursuant to Article 116 of Directive 2001/83/EC.

    The condition for the lifting of the suspension of the marketing authorisations is set out in Annex III.

    b. Marketing authorisation applications for which bioequivalence data or justification were not submitted or considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (Annex I) do not satisfy the criteria for authorisation, as the particulars supporting the marketing authorisations are incorrect and the benefit-risk balance of these marketing authorisations is considered not favourable pursuant to Article 26 of Directive 2001/83/EC.