Annex II

Scientific conclusions

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Between 29 September 2015 and 9 October 2015, the United States Food and Drug Administration (FDA) performed a Good Clinical Practice (GCP) inspection at the bioanalytical facility Semler Research Centre Private Ltd, 75A, 15th Cross, 1st Phase, J.P. Nagar, Bangalore – 560 078 India.

The inspection found significant instances of misconduct, including the substitution and manipulation of study subject samples. The findings reported during this inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) generated at the site. Therefore the FDA concluded that clinical and bioanalytical studies conducted by Semler Research Private Limited in Bangalore, India are not acceptable as a result of data integrity concerns[1].

The World Health Organisation (WHO) also inspected the same bioanalytical facility and the Semler clinical facility located at PA Arcade #21,22,23 Kodigehali Main Road, Sahakaranagar Post, Bangalore 560 092, Karnataka, India between 27 and 31 January 2015, and performed a follow-up inspection between 2 and 5 December 2015 to verify compliance with GLP and GCP. The inspections revealed critical and major deviations which led to the publishing of a WHO notice of concern[2]. The WHO concluded that the findings 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, the WHO pre-qualification team (PQT) recommended an immediate stop to all submissions of dossiers relying in whole or in part on involvement from Semler until the underlying issues have been verified to have been adequately resolved.

The findings of the FDA and WHO inspections raise serious concerns relating to the suitability of the quality management system at these sites and, consequently, the reliability of data submitted in applications for marketing authorisations submitted in European Union (EU) Member States.

In view of the findings described above and the necessity to protect public health in the EU, the United Kingdom, Germany, Spain, the Netherlands and Denmark considered that it is in the interest of the Union to refer the matter to the CHMP and request that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these sites and also that of pending marketing authorisation applications (MAA).

The CHMP was requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

Overall summary of the scientific evaluation

The findings of the FDA and WHO inspections raise serious concerns relating to the suitability of the quality management system in place at the Semler JP Nagar and Sakar Nagar sites. Data from all bioequivalence studies performed at Semler Research Private Limited in Bangalore India and submitted to the Competent Authorities to demonstrate bioequivalence of medicinal products with their originator is considered unreliable. Therefore, for those products bioequivalence is not established.

For a medicinal product with a marketing authorisation or marketing authorisation application under Article 10(1) of Directive 2001/83/EC as amended, bioequivalence is crucial for the conclusion that efficacy and safety are similar to that of the reference 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

[1] http://www.fda.gov/Drugs/DrugSafety/ucm495778.htm
[2] http://apps.who.int/prequal/info_applicants/NOC/2016/NOC_Semler12April2016.pdf

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.

In their own investigation and analysis of the studies concerned by the FDA inspection, and also in their investigation for similar anomalies or patterns in other studies, Semler found no conclusive evidence of inappropriate data manipulation, substitution or dilution. A number of corrective and preventive actions (CAPA) are proposed or have already been already implemented to address the findings of the FDA and WHO inspections.

Nevertheless, any CAPAs implemented after the FDA and WHO inspections cannot retrospectively correct the quality system failures observed during these two inspections. Therefore, bioequivalence of the products concerned by this procedure has to be established using alternative data.

For those products for which no alternative data is available to establish bioequivalence to an EU reference medicinal product, the main arguments put forward by the MAHs/applicants were as follows:

- Reanalysis and audits of data for specific studies did not point to any irregularity. In view of the failures of the quality management system in place at the sites, results and controls of data integrity of individual studies by MAHs cannot make the bioequivalence studies performed at Semler Research Center acceptable as basis for a marketing authorisation.
- In some cases, MAHs pointed out that only certain parts of the study had been conducted at Semler, with the remaining tasks conducted at a different site. This does not change the fact that any data generated at Semler is considered unreliable and therefore cannot be used to demonstrate bioequivalence.
- Pharmacovigilance data on specific products included in this procedure have not indicated any problems which could be attributed to non-bioequivalence, such as reduced efficacy or worsened safety and tolerability. However, pharmacovigilance activities may lack the ability to detect a signal with regard to efficacy or safety and tolerability, therefore CHMP is of the opinion that the absence of any pharmacovigilance signal does not offer sufficient reassurance to conclude on a positive benefit-risk balance in the absence of the demonstration of bioequivalence with the EU reference medicinal product.
- In some cases it was pointed out that products containing certain active substances could be eligible for biowaiver. However, no formal request was submitted and the detailed information necessary to assess the appropriateness of a biowaiver was not made available by the MAHs/applicants.
- For some products, results from bioequivalence data using non-EU Reference Medicinal Products may be available. Under Article 10(1) of Directive 2001/83/EC, these data are not acceptable to support a positive benefit-risk balance for the concerned products and cannot substitute the requirement to demonstrate bioequivalence between test product and a suitable EU reference product.

Alternative data were submitted to demonstrate the bioequivalence of abacavir/lamivudine-containing medicinal products to an EU reference medicinal product. Having assessed the alternative data, the CHMP recommends the maintenance of the marketing authorisations for abacavir/lamivudine-containing medicinal products (annex IA) and concludes that, with regards to marketing authorisation applications for abacavir/lamivudine-containing medicinal products, bioequivalence has been demonstrated vis-à-vis the EU reference medicinal product using alternative data.

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, hence the benefit-risk balance cannot be considered positive. The CHMP therefore recommends the suspension of the marketing authorisations for all remaining medicinal products concerned by this referral procedure (annex IB), as bioequivalence vis-à-vis the EU reference medicinal products has not been demonstrated. The Committee recommends that these marketing authorisations (annex IB) should be suspended unless the medicinal product is considered critical by the relevant national competent authorities. For marketing authorisation(s) of a medicinal product considered critical, the suspension may be deferred in the relevant EU Member State(s) for a period which shall not exceed twenty-four months from the Commission Decision. Should during this period the EU Member State(s) consider a medicinal product not critical anymore, the suspension of the concerned marketing authorisation shall apply.

For these medicinal products considered critical by EU Member States, the marketing authorisation holders shall submit a bioequivalence study conducted vis-à-vis the EU Reference Medicinal Product within 12 months following Commission Decision.

An authorised medicinal product listed in Annex IB may be considered critical by the EU Member State(s) based on the evaluation of the potential unmet medical need, considering the availability of suitable alternative medicinal products in the respective EU Member State(s) and, as appropriate, the nature of the disease to be treated.

For all other marketing authorisation applications (annex IB), the CHMP considers that 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 Semler, Bangalore, India;
- The CHMP reviewed available data and information provided by the MAHs/applicants, as well as information provided by Semler Research Centre Private Ltd;
- 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:
  - Authorised medicinal products and marketing authorisation applications for which alternative bioequivalence data or a justification was submitted but considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (annex IB);

- Authorised medicinal products and marketing authorisation applications for which no alternative bioequivalence data or a justification was submitted (annex IB).

- The CHMP concluded that, for both marketing authorisations and marketing authorisation applications referred to in annex IA, there was alternative data to establish bioequivalence vis-à-vis the EU reference medicinal product.

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 IB) 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.

   Some of these authorised medicinal products may be considered critical by the individual EU Member States on the evaluation of the potential unmet medical need, considering the availability of suitable alternative medicinal products in the respective EU Member State(s) and, as appropriate, the nature of the disease to be treated. Where on the basis of these criteria the relevant national competent authorities of the EU Member States consider that a medicinal product is critical, the suspension of the concerned marketing authorisation(s) may be deferred by the period for which the medicinal product is considered critical. This period of deferral shall not exceed twenty-four months from the Commission Decision. Should during this period the EU Member State(s) consider a medicinal product not critical anymore, the suspension of the concerned marketing authorisation(s) shall apply. For these medicinal products considered critical by EU Member State(s), the marketing authorisations holders shall submit a bioequivalence study conducted vis-à-vis the EU Reference Medicinal Product within 12 months from the Commission Decision.

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 IB) do not satisfy the criteria for authorisation, as the particulars supporting the marketing authorisations are incorrect and the benefit-risk balance of these marketing authorisation is considered not favourable pursuant to Article 26 of Directive 2001/83/EC.

c. Marketing authorisations for medicinal products for which the bioequivalence vis-à-vis the EU reference medicinal product has been established (annex IA) should be maintained, as the benefit risk balance of these marketing authorisation is considered favourable.

d. Bioequivalence vis-à-vis the EU reference medicinal product has been established for marketing authorisation applications listed in annex IA.