NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by: Finland

Details on the draft list of products concerned (pending applications and authorised medicinal products) are annexed to this notification.

The US Food and Drug Administration (FDA) recently rejected all clinical and bioanalytical studies conducted by Synchron Research Services, a contract research organisation (CRO) located in Ahmedabad, Gujarat, India, on the ground that inspections and analyses of study data indicated that the company was 'responsible for the creation of false data' and that all their studies were therefore 'unacceptable'.[1]

More concretely, the US-FDA recommendation is based on combination of the following:

- Outcome of US-FDA GCP inspection (18-22 November 2019):
  - The site failed to demonstrate that the analytical method used in an in vivo bioavailability or bioequivalence study to measure the concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), in body fluids or excretory products, is accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), achieved in the body.
  - Significant pharmacokinetic (PK) data anomalies were observed across multiple studies conducted at the site.
- Analysis of study data generated at Synchron (pre- and post- GCP inspection):
  - multiple pairs of subjects with overlapping time-concentration profiles;
  - distinct groups of subjects where the T/R ratio for Cmax, AUC0-t, or AUC0-∞, among other parameters, for most subjects in the subgroups is above or below 1; or
  - study data having both the above concerns.
- Lack of adequate CRO responses to explain the study data and observations.

Similar concerns have been previously raised in study data supporting marketing authorisation applications (MAAs) in the EU:

- Data manipulation has been detected in two EU inspections conducted by FR and NL in 2005 and by FR and DE in 2009. Data from the studies concerned were rejected, but these cases were treated as isolated non-compliance at that time.

The available information and data raise serious concerns related to the suitability of the quality management system and the overall reliability of data generated at Synchron, submitted in MAAs in EU Member States. Indeed, although the findings listed above relate to the bioanalytical part of the studies, given the failure of the quality management system to prevent and detect the occurrences described above, failures in other areas of the trials (including clinical parts) cannot be excluded. It should also be noted that upper management is common to clinical and bioanalytical activities. Considering that the concerns raised by the FDA, taken together with the observations in previous EU inspections of the site, point

[1] Further information about FDA's action, including letters sent to Synchron are available on FDA's website.

towards a CRO system issue rather than isolated findings/cases, an at-risk period cannot be defined.

In view of the findings described above and the necessity to take an action at EU level, Finland considers that it is in the interest of the Union to refer the matter to the CHMP and requests that CHMP 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 Synchron Research Services sites, as well as for pending procedures. The CHMP is 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.

Signed Tea Linhola, Finnish CMDh member Date 11.1.2022