**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 Spain:

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

The Spanish Agency of Medicines and Medical Devices (AEMPS) has conducted a GCP inspection of the bioequivalence (BE) facilities in Synapse Labs Pvt. Ltd., a contract research organisation (CRO) located at Majestic Plaza, S. No. 21/5, Nr. Nyati Empire, Kharadi-Mundhwa Bypass, Kharadi, Pune – 411014, Maharashtra (India) and Krushna Complex, Kharadi-Mundhwa Bypass, Kharadi, Pune-411014, India).

The findings reported during the inspection cast serious doubts on the validity and reliability of the data of BE studies (clinical and bioanalytical part) conducted at the CRO. The inspection examined [redacted] studies over the 2009 - 2019 period and Synapse quality management system (QMS) over the 2009-2023 period. Five (05) critical findings (CF) and one (01) major finding were identified:

- The CRO failed to demonstrate the adequacy of the Computerized Systems/Bioanalysis and Data Management to ensure bioanalytical and clinical data integrity. Overall, up to 2023, the CRO lacked robust QMS measures, procedures and control over the data integrity of the data generated (4 CF).
- Significant pharmacokinetics anomalies were observed in over 20 studies conducted from 2013 to 2018 (i.e. multiple pairs of subjects with overlapping plasma time-concentration profiles). This fact, in absence of other acceptable justification would be considered coherent with profile duplication (1 CF).
- Source documentation for clinical and bioanalytical research was not clearly and unequivocally established (1 major finding).
- The CRO acknowledged most of the findings identified. No major disagreement or factual error were reported. The CRO failed to rule out possible intentional misrepresentation of data, which is also considered to potentially compromise the CRO's QMS and the investigations conducted by the CRO as a result of the inspection.

Due to the transversal and systematic nature of the findings observed over several years, in which the QMS has also been compromised, those are considered to have a direct impact on GCP compliance and the data reliability, which would cast serious doubts on the acceptability of both analytical and clinical data generated by Synapse.

It is noted that all the BE activities conducted by Synapse are governed under the same QMS. Further, upper management is common to clinical and bioanalytical activities. Considering that the concerns raised point towards a CRO system issue rather than isolated findings/cases, an at-risk period cannot be defined. It is noted that Synapse Labs was set up in 2007.

Overall, the reliability and the quality of the data (both clinical and analytical) generated by Synapse since its set up do not suffice to support the BE clinical trial results obtained on their basis thereof.

In view of the above and the necessity to take an action at EU level, Spain considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of these findings on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of studies performed at these Synapse Labs facilities and also 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.

[redacted]

agencia española de medicamentos y productos sanitarios

Signed Date