Annex II

Scientific conclusions

Scientific conclusions

The Spanish Agency of Medicines and Medical Devices (AEMPS) conducted a remote GCP inspection of the bioequivalence (BE) facilities in Synapse Labs Pvt. Ltd. (henceforth referred as Synapse), 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 studies over the 2009 - 2019 period and Synapse quality management system (QMS) over the 2009-2022 period. Five (5) critical findings (CF) and one (1) 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.

On 27 June 2023, Spain 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 the medicinal products which have been authorised by the Member States on the basis of trials performed at Synapse facilities, as well as for pending procedures, and to issue a recommendation on whether the concerned marketing authorisations should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

The severity and the extent of the findings identified further to the inspection carried out by the AEMPS in November 2020 and 2022 in relation to data generated at Synapse, indicated that the quality management system was compromised and cast serious doubts on the validity and reliability of the data of BE studies (clinical and bioanalytical part) conducted at the CRO.

In order to demonstrate a positive benefit-risk balance of the concerned medicinal products, the marketing authorisation holders (MAHs) and applicants of the products concerned by this procedure were invited to comment on the impact of the serious concerns raised in relation to the suitability of the quality management system and the overall reliability of the data generated at Synapse on their marketing authorisation(s) or application(s) and provide evidence of bioequivalence (e.g. bioequivalence trials) with the EU reference medicinal product using alternative data.

Applications for generic medicinal products, i.e. under Article 10(1) of Directive 2001/83/EC, are required to demonstrate bioequivalence. 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 the bridging of preclinical tests and of clinical trials associated with the reference medicinal product. Only reference medicinal products authorised under Article 6 of said directive and in accordance with the provisions of Article 8 of the same directive are accepted.

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 not be within acceptable predefined limits. These limits are set to ensure comparable *in-vivo* performance, i.e. similarity in terms of safety and efficacy. If the bioavailability of the generic product is higher than the predefined upper limit, the bioavailability of the reference medicinal product 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 predefined lower limit, the bioavailability of the reference medicinal product 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.

In applications for hybrid medicinal products, i.e. under Article 10(3) of Directive 2001/83/EC, and for well-established use medicinal products, i.e. under Article 10a of Directive 2001/83/EC, the need for bioequivalence studies is determined on a case-by-case basis. However, where it was considered to be fundamental to demonstrate equivalence with a EU reference medicinal product or with the medicinal product referred in the scientific literature submitted in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product or of the scientific literature submitted, the same principles apply. In the absence of reliable data demonstrating bioequivalence with an EU reference medicinal product, or, for well-established use products, with the medicinal product referred in the scientific literature, the benefit-risk balance of the products either authorised or seeking a marketing authorisation based only on data generated at Synapse to demonstrate the bioequivalence could not be considered positive, as the possibility of safety/tolerability or efficacy issues cannot be excluded.

The CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have affected the validity and reliability of 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. Although it is acknowledged that audits or inspections carried out in the past at Synapse may have had positive outcomes, the absence of findings does not guarantee that the data has not been impacted since GCP violations may have not been detected even if present. The findings identified in relation to data generated at Synapse are considered to reflect broader problems concerning the suitability of the quality management system and the overall reliability of all data generated at Synapse and no review or audit of unreliable data can be used to address the concerns. Therefore, it is considered that those arguments do not demonstrate that the said studies can be relied upon.

In addition, the CHMP is of the opinion that the absence of the identification of any pharmacovigilance signals does not provide sufficient reassurance because it is not established that the pharmacovigilance activities may be designed to detect such a signal. More importantly, pharmacovigilance activities cannot substitute the demonstration of bioequivalence.

Results of bioequivalence studies with non-EU reference products have been provided. Non-EU medicinal products do not meet the definition of "reference medicinal product" provided by Article 10(2)(a) of Directive 2001/83/EC. As such, results from bioequivalence studies using non-EU reference medicinal products can therefore not be accepted for demonstrating said bioequivalence.

In conclusion, in the absence of reliably proven bioequivalence vis-à-vis the EU reference medicinal product, or, as regards well-established use products, in the absence of demonstration of how the data supporting the medicinal product referred in the scientific literature used for at least ten years is relevant to the well-established product, the requirements of Article 10 or 10a of Directive 2001/83/EC cannot be considered fulfilled. The efficacy and safety of the medicinal products cannot be established and therefore, the benefit-risk balance cannot be considered positive.

Alternative bioequivalence data or appropriate justification for BCS-biowaivers were submitted to demonstrate the bioequivalence of:

- the medicinal products:
    - Nortriptyline: Nortriptyline film-coated tablets Alissa Healthcare Research Limited and Pharmafile Limited;
    - Sitagliptin: Anau, Sitagliptin PharOS, Sitagliptin Genericon, Sitagliptin +pharma, Sitagla, Sitagliptin Sandoz GmbH, Sitagliptin Sandoz, Sitagliptin Hexal, Sitagliptin GNR, Sitagliptin 1 A Pharma, Sitagliptina Sandoz Farmaceutica, Sitagliptin Evolugen; Sitagliptin DOC Generici;
    - Sitagliptin/metformin (50/1000 mg only): Sipactimet, Sitagliptin/Metformin PharOS, Sitagliptin/Metformin hydrochlorid Genericon, Sitagliptin/Metformin +pharma, sitagliptin/metforminklorid Genericon, Sitagliptine/Metformine hydrochloride Genericon, Sitagliptin/Metforminhydrochlorid +pharma, Sitaglamet, Sitagliptin/Metformin BGR, Sitagliptin/Metformin Sandoz GmbH, Sitagliptin/ Metformin Hydrochloride Sandoz, Sitagliptin/Metformin Hexal, Sitagliptine/Metformine GNR, Sitagliptin/Metformin 1 A PHARMA, Sitagliptine/Metformine Evolugen, Sitagliptine/Metformine hydrochloride DOC Generici, Condias Combi; and of
- the marketing authorisation applications for Gitas and Condias (sitagliptin).

The CHMP considers that the bioequivalence of those products has been demonstrated and recommends the maintenance of the marketing authorisations mentioned above, and concludes that, with regards to the marketing authorisation application, bioequivalence has been demonstrated vis-à-vis the EU reference medicinal product using alternative data.

Alternative bioequivalence studies carried out at a different CRO and not the studies performed at Synapse were referred to as the pivotal evidence to demonstrate the bioequivalence of Metformin - Win Medica, Sunitinib – Bluefish Pharmaceuticals AB, Genepharm S.A., Sapiens Pharmaceuticals Ltd and Pharmevid s.r.o., Fesoterodine - Genus Pharmaceuticals Limited, and Ursodeoxycholic acid – Teva B.V, Teva UK Limited. The CHMP concluded that the benefit-risk balance of Metformin - Win Medica, Sunitinib – Bluefish Pharmaceuticals AB, Genepharm S.A., Sapiens Pharmaceuticals Ltd and Pharmevid s.r.o., Fesoterodine - Genus Pharmaceuticals Limited and Ursodeoxycholic acid – Teva B.V, Teva UK Limited, were not affected by the concerns related to the studies performed by Synapse and recommended the maintenance of the marketing authorisations.

All other MAHs/applicants did not submit evidence demonstrating the bioequivalence of their medicinal products. In the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal product, or in the absence of demonstration of how the data supporting the medicinal product vis-à-vis the medicinal product referred in the scientific literature demonstrating that the active substance of the medicinal product concerned has been in used for at least ten years is relevant to the well-established medicinal use product, the requirements of Article 10 or 10a 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 considers

that all concerned marketing authorisation applications not listed in the above paragraph of this section do not currently fulfil the criteria for authorisation, and recommended the suspension of the marketing authorisations for all concerned medicinal products not listed in the above paragraph of this section (those concerned marketing authorisation applications and marketing authorisations are listed in Annex IB).

For marketing authorisation(s) of a medicinal product considered critical by the relevant national competent authorities, the suspension may be deferred in the relevant EU Member State(s) for a period which shall not exceed 24 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.

Re-examination procedure

Following the adoption of the CHMP opinion in December 2023, the applicants/MAHs Sandoz B.V. group of companies, Farmex d.o.o., Rontis Hellas Medical and Pharmaceutical Products S.A., DOC Generici S.r.l., Elpen Pharmaceutical Co. Inc., PharOS - Pharmaceutical Oriented Services Ltd. group of companies, Aurobindo Pharma Limited group of companies and Remedica Ltd., some of which representing a number of applicants/MAHs as detailed below and in the assessment report, requested a re-examination of the CHMP opinion on the Article 31 referral for Synapse Labs Pvt. Ltd. according to Article 32(4) of Directive 2001/83/EC for their affected medicinal products containing abacavir/lamivudine, atazanavir, darunavir, deferasirox, efavirenz/emtricitabine/tenofovir, erlotinib, lapatinib, olanzapine, sitagliptin/metformin, sorafenib, and sunitinib. Detailed grounds for re-examination of the CHMP recommendation have been submitted by the applicants and MAHs on 15 January, 12 and 13 February 2024.

CHMP discussion on grounds for re-examination

The CHMP considered the detailed grounds as submitted by the applicants and MAHs within this re-examination procedure and the scientific data underlying these grounds.

Regarding the two claims based on analyses of study data, the CHMP reiterated that in light of the nature, the severity and the extent of the findings identified further to the inspection carried out by the AEMPS in November 2020 and 2022 in relation to data generated at Synapse, the quality management system was considered compromised and serious doubts cast on the validity and reliability of the data of BE studies (clinical and bioanalytical part) conducted at the CRO. Indeed, given the failure of the quality management system to prevent and detect the occurrence of the findings, failures in other areas of the trials cannot be excluded. Hence, the CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have not affected the validity and reliability of said studies and the arguments presented do not demonstrate that said studies can be relied upon. Therefore, the CHMP is of the opinion that the studies cannot be relied upon to establish bioequivalence vis-à-vis the EU reference medicinal product.

With regard to the alternative bioequivalence study conducted at a different facility for olanzapine and the data supporting a biowaiver claim for sitagliptin/metformin, the CHMP noted that these scientific data were not available for its initial assessment and before its initial opinion, and as such, in accordance with Article 62(1), fifth subparagraph, of Regulation (EC) No 726/2004, could not take

these into account in the re-examination. Further for olanzapine, it is not agreed with the MAH that the study conducted at Synapse was not pivotal to the demonstration of bioequivalence of the current olanzapine orodispersible tablets with the polymorphic Form-II of the active substance as it has not been demonstrated that the change in polymorphic form did not affect the *in vivo* availability of the product.

In the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal products, the efficacy and safety of the concerned medicinal products cannot be established and therefore, the benefit-risk balance cannot be considered positive.

The CHMP agrees that, similar to Sunitinib – Bluefish Pharmaceuticals AB, Genepharm S.A., Sapiens Pharmaceuticals Ltd and Pharmevid s.r.o., the benefit-risk balance of Nibufar (sunitinib, Farmex d.o.o) was not affected by the concerns related to the studies performed by Synapse. While the fed-state study was conducted at Synapse, a fasted-state study was performed at a different CRO and according to the EMA Product Specific Bioequivalence Guideline a fasted-state study is sufficient to support the demonstration of bioequivalence. This was not considered for the initial opinion due to a technical issue. The final opinion is updated accordingly.

Based on the totality of the data available, including the information submitted during the initial assessment procedure and the detailed grounds for re-examination put forward by the identified MAHs/applicants, the CHMP:

1. Concluded that the benefit-risk balance of Nibufar is positive, and recommends the maintenance of the marketing authorisation.

2. Confirmed its previous conclusions that bioequivalence vis-à-vis the EU reference medicinal product had not been demonstrated for the other medicinal products/marketing authorisation applications subject to the re-examination whose benefit-risk balance is considered not favourable. The CHMP therefore confirmed its conclusion that the following marketing authorisation applications do not satisfy the criteria for authorisation, whilst the marketing authorisations of the following medicinal products should be suspended:

    - Abacavir/lamivudine (MAHs: Remedica Ltd, Accord Healthcare S.L.U, Accord Healthcare B.V., Accord Healthcare Polska Sp. Z o.o., Biogaran, EG LABO – Laboratoires Eurogenerics, Aliud Pharma GmbH, betapharm Arzneimittel GmbH, Dr. Reddy's S.r.l., Stadapharm GmbH, Stada Arzneimittel AG, Stada M&D Srl, Reddy Pharma Iberia S.A., Dr Reddy's Laboratories Ltd.)

    - Atazanavir (MAHs: Remedica Ltd, Stada Arzneimittel AG, Sandoz, Sandoz S.R.L., Sandoz B.V., Arrow Génériques, Biogaran, Hexal AG, Aliud Pharma GmbH, betapharm Arzneimittel GmbH, Rowex Ltd., Sandoz SpA, Sandoz Pharmaceuticals d.d., Generis Farmacêutica, S.A., Stada M&D Srl, LABORATORIO STADA, S.L., Aurobindo Pharma B.V., Dr Reddy's Laboratories (UK) Limited, Sandoz Limited)

    - Darunavir (MAHs: Stada Arzneimittel AG, Stada Arzneimittel GmbH, Sandoz GmbH, Sandoz – SA-NV, Sandoz d.o.o., Sandoz Pharmaceuticals d.d., Sandoz A/S, Sandoz B.V., Sandoz, Sandoz SpA, Sandoz Farmacêutica, Lda., Sandoz Farmacéutica, S.A., Sandoz S.R.L., Sandoz Limited, Remedica Ltd, Biogaran, EG LABO – Laboratoires Eurogenerics, Hexal AG, Aliud Pharma GmbH, Elpen Pharmaceutical Co. Inc, Rowex Ltd., Clonmel Healthcare Ltd, EG S.p.A., LABORATORIO STADA, S.L., Zentiva k.s.,)

    - Deferasirox (MAHs: Stada Arzneimittel GmbH, Stadapharm GmbH, Aliud Pharma GmbH, Elpen Pharmaceutical Co. Inc, Centrafarm B.V., Stada Arzneimittel AG, Thornton & Ross Limited)

    - Efavirenz/emtricitabine/tenofovir (MAHs: Sandoz GmbH, EG (Eurogenerics) NV, Stada d.o.o., Remedica Ltd, Stada Arzneimittel AG, Sandoz Pharmaceuticals d.d., Sandoz, EG LABO –

Laboratoires Eurogenerics, Biogaran, Aliud Pharma GmbH, Hexal AG, betapharm Arzneimittel GmbH, Elpen Pharmaceutical Co. Inc, Clonmel Healthcare Ltd, Sandoz Farmaceutica, S.A., Reddy Pharma Iberia S.A., Sandoz B.V., Centrafarm B.V., Dr Reddy's Laboratories (UK) Limited)

- Erlotinib (MAHs: EG (Eurogenerics) NV, Sandoz – SA-NV, Sandoz Pharmaceuticals d.d., Mylan Pharmaceuticals Limited, Remedica Ltd, Mylan AB, Stada Arzneimittel AG, Sandoz A/S, Biogaran, EG – Laboratoires Eurogenerics, Viatris Sante, Sandoz Farmaceutica S.A., Hexal AG, Stadapharm GmbH, Mylan Ireland Limited, Sandoz Hungária Kereskedelmi Kft., Zentiva k.s., Viatris Limited, Mylan SpA, Sandoz SpA, Mylan, Lda., Sandoz, Centrafarm B.V., Glenmark Arzneimittel GmbH, Glenmark Pharmaceuticals Europe Limited, Sandoz B.V., Sandoz Limited, Generics (UK) Limited. Applicant: Sandoz Hungaria KFT)
- Lapatinib (MAHs: Aliud Pharma GmbH, EG S.p.A., LABORATORIO STADA, S.L., Newbury Pharmaceuticals AB, PharOS – Pharmaceutical Oriented Services Ltd., Remedica Ltd, Stada Arzneimittel AG, Stada M&D Srl, Stadapharm GmbH)
- Olanzapine (MAHs: Arrow Génériques, Aurobindo N.V., Aurobindo Pharma S.r.L., Aurobindo Pharma Limited, Aurobindo Pharma B.V., Aurobindo Pharma Limited, Aurovitas Pharma Polska Sp. Z o.o., Aurovitas Spain S.A.U., Generis Farmacêutica, S.A., Milpharm Limited, Orion Corporation, PharmConsul s.r.o., PUREN Pharma GmbH & Co. KG. Applicant: PharmConsul s.r.o.)
- Sitagliptin/metformin 50/850mg (MAHs: +pharma arzneimittel gmbh, Genericon Pharma GmbH, Sandoz GmbH, Belupo lijekovi i kozmetika, d.d., Heaton k.s., Sandoz Pharmaceuticals d.d., Hexal A/S, Biogaran, Evolupharm, Sandoz, 1 A Pharma GmbH, Hexal AG, DOC Generici S.r.l., PharOS – Pharmaceutical Oriented Services Ltd., Sandoz Farmacêutica, Lda., Sandoz S.R.L., Maddox Pharma Swiss B.V., Sandoz B.V.)
- Sorafenib (MAHs: EG (Eurogenerics) NV, G.L. Pharma GmbH, Hexal AG, LABORATORIO STADA, S.L., Laboratorios Cinfa, S.A., Remedica Ltd, Sandoz – SA-NV, Sandoz B.V., Sandoz Pharmaceuticals d.d., Sandoz d.o.o., Sandoz Farmacêutica, Lda., Sandoz GmbH, Sandoz S.R.L., Stada Arzneimittel AG, Sandoz s.r.o., Stada d.o.o., Stadapharm GmbH, Stada M&D Srl. Applicant: Sandoz A/S).

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 Synapse, a contract research organisation (CRO) located in Kharadi, Pune, India, since the set-up of the site under the name Synapse Labs Pvt. Ltd.
- The CHMP reviewed available data and information provided in writing by the applicants and MAHs, as well as information provided by Synapse. Synapse did not provide any new information that changed the conclusions laid out in the notification for this procedure.
- The CHMP also considered the grounds for re-examination submitted by the applicants/MAHs in writing.
- The CHMP concluded that, for the 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.

- The Committee 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 for which alternative bioequivalence data or a justification was not submitted, or submitted but considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product, or, for well-established use products, with the medicinal product referred in the scientific literature (Annex IB).
    - Marketing authorisation applications for which alternative bioequivalence data or a justification was not submitted, or submitted but considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (Annex IB).

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 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.

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

   For the suspension of the marketing authorisations to be lifted the MAHs shall provide evidence that bioequivalence vis-à-vis an EU reference medicinal product has been demonstrated, based on relevant data, in accordance with the requirements of Article 10 of Directive 2001/83/EC (e.g. a bioequivalence study conducted vis-à-vis the EU reference medicinal product) or, when applicable for well-established use products, bioequivalence vis-à-vis the medicinal product referred in the scientific literature has been demonstrated.

   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 24 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/medicinal product referred in the scientific literature within 12 months from the Commission Decision.

c. Marketing authorisation applications for which bioequivalence data or justification were not submitted or submitted but 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.

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