21 July 2016
EMA/633696/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Referral under Article 31 of Directive 2001/83/EC

Medicinal products for which clinical and bioanalytical parts of the bioequivalence studies were performed at the Semler Research Center Private Limited located at SRC Private Limited, 75A, 15th Cross, 1st Phase, JP Nagar, Bangalore 560 078, Karnataka, India (also known as JP Nagar site) and Semler Research Center Private Limited PA Arcade, No 21, 22, 23, Kodigehali Main Road, Sahakaranagar Post, Bangalore 560 092, Karnataka, India (also known as Sakar Nagar Clinical site)

Procedure number: EMEA/H/A-31/1443

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Information on the procedure

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 EU 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.

# 2. Scientific discussion

## *2.1. Introduction*

The findings of the FDA and WHO inspections described in section 1 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.

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

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 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.

## *2.2. Clinical aspects*

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.

The submissions from the MAHs/applicants for products are summarised below per INN.

### 2.2.1. Abacavir/lamivudine

For all abacavir/lamivudine-containing products affected by this review, bioequivalence to the EU reference medicinal product was established based on an alternative bioequivalence study conducted at a different facility. Having assessed the alternative study, the CHMP considered that it supports bioequivalence of these medicinal products to the reference medicinal product Kivexa 600mg/300mg.

### 2.2.2. Amoxicillin

The MAHs/applicant carried out a comprehensive review of the amoxicillin studies to confirm their validity and reliability, with special emphasis on the published findings. In addition audits were conducted covering all three aspects of the studies i.e. clinical, bioanalytical and statistical, focusing on data integrity and chromatographic analysis performed in the bioanalytical phase.

The MAHs/applicants also state that amoxicillin is a biopharmaceutics classification system (BCS) Class-I/III drug (*WHO Working document QAS/04.109/Rev.1, Intra-Agency Agreement Between NICHD & USFDA*) and is in fact eligible for BCS based biowaiver as per the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/ Corr). The MAHs/applicant conclude that, based on their review and assessment, validity and reliability of the bioequivalence studies for

this product can be justified to an extent that associated risk pertaining to clinical efficacy and safety can be ruled out.

The arguments of the MAHs/applicant were considered, however the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. In light of the nature, the seriousness and extent of the critical GCP findings identified by the FDA and WHO inspections, all data generated at Semler is considered unreliable and no review or audit of unreliable data can be used to address the concerns. While the active substances may be eligible for biowaiver, no formal request was submitted and the detailed information necessary to assess the appropriateness of a biowaiver was not made available.

Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for amoxicillin-containing products concerned by this referral procedure.

On 18 July 2016 the applicant further submitted the study synopsis of a new bioequivalence study performed at a different CRO. The applicant also stated that the full clinical study report will be submitted to the competent authorities of the relevant EU Member States for assessment in the context of the pending MAA. In this context, bioequivalence cannot be considered demonstrated until the full clinical study report is assessed by the relevant competent authorities.

### 2.2.3. Atovaquone/proguanil

The MAHs of atovaquone/proguanil-containing medicinal products referred to a reanalysis of study data concluding that the individual time concentration curves are different between volunteers and the chromatograms for the assay in plasma do not show any irregularity. The MAHs also stated that pharmacokinetic data obtained in the study are very similar to those found in the available literature, and that adverse events reported during the study show a comparable safety profile of both test and reference product. The MAHs further mentioned previous study-specific inspections with a positive outcome. A review of data from one of the products, particularly data on stability and/or complaints, did not indicate any product quality issues.

The arguments of the MAHs were considered, however the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for atovaquone/proguanil-containing products concerned by this referral procedure.

### 2.2.4. Ebastine

The MAHs carried out a comprehensive review of the ebastine studies to confirm their validity and reliability, with special emphasis on the published findings. In addition audits were conducted covering all three aspects of the study i.e. clinical, bioanalytical and statistical, focusing on data integrity and chromatographic analysis performed in the bioanalytical phase. The MAHs conclude that, based on their review and assessment, validity and reliability of the bioequivalence studies for this product can be justified to an extent that associated risk pertaining to clinical efficacy and safety can be ruled out.

The arguments of the MAHs were considered, however the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. In light of the nature, the seriousness and extent of the critical GCP findings identified by the FDA and WHO inspections, all data generated at Semler is considered unreliable and no review or audit of unreliable data can be used to address the concerns.

Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for ebastine-containing products concerned by this referral procedure.

### 2.2.5. Eletriptan

The MAH indicates that only the clinical and statistical parts of the relevant study were conducted at Semler, whereas the bioanalytical part was conducted at a different site. Further, reference is made by the MAH to a bioequivalence study between the US eletriptan test product and the US reference product Relpax. The MAH states that the reference product formulations in the EU and US are at least qualitatively the same, and the comparative dissolution data presented on the EU and US test and reference products show similar rapid dissolution characteristics.

The fact that the bioanalytical part of the bioequivalence study was conducted at a different facility does not change the fact that the clinical and statistical parts of the eletriptan study are unreliable.

The arguments of the MAH were considered, however an indirect comparison between the EU and US test product does not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for eletriptan-containing products concerned by this referral procedure.

### 2.2.6. Eprosartan

The MAHs clarified the basis for selecting Semler as a CRO for conducting the bioequivalence study and stated that these data were in line with regulatory requirements at the time of dossier submission. No alternative data to establish bioequivalence vis-à-vis an EU reference medicinal product was submitted. The bioequivalence to the EU reference medicinal product is therefore not established. Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for eprosartan-containing products concerned by this referral procedure.

### 2.2.7. Erlotinib

In its response, one of the applicants indicates that it has performed a risk assessment to evaluate the potential impact of the claimed data integrity issues detected at Semler on the claim for bioequivalence for Erlotinib 150 mg film-coated tablets, and it concluded that there are no grounds to question the reliability of this specific study. However the applicant has decided to repeat the bioequivalence study in a different CRO and provided the expected timeline for completion of the study.

The other applicant stated that the therapeutic equivalence of the medicinal product is not compromised by the recent GCP issues identified by FDA /WHO and thus the safety and the efficacy of the proposed product in the EU is assured. However this applicant has also decided to repeat the bioequivalence study in a different CRO and provided the expected timeline for completion of the study.

The arguments of the applicants were considered, however the information submitted does not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for erlotinib-containing products concerned by this referral procedure.

### 2.2.8. Irbesartan / hydrochlorothiazide

The applicants carried out a comprehensive review of the studies to confirm their validity and reliability, with special emphasis on the published findings. In addition audits were conducted covering all three aspects of the studies i.e. clinical, bioanalytical and statistical, focusing on data integrity and chromatographic analysis performed in the bioanalytical phase.

The applicants conclude that, based on their review and assessment, validity and reliability of the bioequivalence studies for this product can be justified to an extent that associated risk pertaining to clinical efficacy and safety can be ruled out.

The arguments of the applicants were considered, however the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. In light of the nature, the seriousness and extent of the critical GCP findings identified by the FDA and WHO inspections, all data generated at Semler is considered unreliable and no review or audit of unreliable data can be used to address the concerns. Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for irbesartan/hydrochlorothiazide-containing products concerned by this referral procedure.

On 18 July 2016 the applicants further submitted the study synopsis of a new bioequivalence study performed at a different CRO for irbesartan/hydrochlorothiazide 300 mg/25 mg tablets. The applicants also stated that the full clinical study report was submitted to the competent authorities of the relevant EU Member States for assessment in the context of the pending MAA. In this context, bioequivalence cannot be considered demonstrated until the full clinical study report is assessed by the relevant competent authorities.

### 2.2.9. Pregabalin

The MAH/applicant indicates that only the clinical part of the relevant study was conducted at Semler, whereas the bioanalytical and statistical parts were conducted at a different site. Reference was made also to bioequivalence studies conducted for the 50 mg and 300 mg strength that were conducted at another CRO. The MAH/applicant considers that bioequivalence demonstrated for the 50 mg-300 mg strengths is supportive for bioequivalence of the 25 mg strength.

The fact that the bioanalytical and statistical parts of the bioequivalence study were conducted at a different facility does not change the fact that the clinical part of the pregabalin study is unreliable. Furthermore, the conclusion for the 50 mg to 300 mg strengths cannot be extrapolated to the 25 mg strength. A bracketing approach is not possible based on the outcome of the studies with the 50 mg and 300 mg strength since the composition of the 25 mg strength does not fall within the range tested. In addition the 25 mg strength is not dose-proportional to the 50 mg or 300 mg strengths.

The arguments of the MAH/applicant were considered, however the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for pregabalin-containing products concerned by this referral procedure.

### 2.2.10. Rasagaline

The applicants carried out a comprehensive review of the studies to confirm their validity and reliability, with special emphasis on the published findings. In addition audits were conducted covering

all three aspects of the studies i.e. clinical, bioanalytical and statistical, focusing on data integrity and chromatographic analysis performed in the bioanalytical phase.

The applicants also state that rasagiline is a BCS Class III drug (*CDER Clinical Pharmacology and Biopharmaceutics review*) and is in fact eligible for BCS based biowaiver as per the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/ Corr). The applicants conclude that, based on their review and assessment, validity and reliability of the bioequivalence studies for this product can be justified to an extent that associated risk pertaining to clinical efficacy and safety can be ruled out.

The arguments of the applicants were considered, however the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. In light of the nature, the seriousness and extent of the critical GCP findings identified by the FDA and WHO inspections, all data generated at Semler is considered unreliable and no review or audit of unreliable data can be used to address the concerns. While the active substance may be eligible for biowaiver, no formal request was submitted and the detailed information necessary to assess the appropriateness of a biowaiver was not made available.

Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for rasagaline-containing products concerned by this referral procedure.

### 2.2.11. Rosuvastatin

The applicants carried out a comprehensive review of the studies to confirm their validity and reliability, with special emphasis on the published findings. In addition audits were conducted covering all three aspects of the studies i.e. clinical, bioanalytical and statistical, focusing on data integrity and chromatographic analysis performed in the bioanalytical phase.

The applicants also state that for the 40 mg strength only the analytical phase of the study was performed at Semler and that rosuvastatin is a BCS Class III drug (*Intra-Agency Agreement Between the Eunice Kennedy Shriver NICHD and the US FDA Oral Formulations Platform—Report 1*) and is in fact eligible for BCS based biowaiver as per the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/ Corr). The applicants conclude that, based on the review and assessment, validity and reliability of the bioequivalence studies for this product can be justified to an extent that associated risk pertaining to clinical efficacy and safety can be ruled out.

The arguments of the applicants were considered, however the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. In light of the nature, the seriousness and extent of the critical GCP findings identified by the FDA and WHO inspections, all data generated at Semler is considered unreliable and no review or audit of unreliable data can be used to address the concerns. While the active substances may be eligible for biowaiver, no formal request was submitted and the detailed information necessary to assess the appropriateness of a biowaiver was not made available.

The fact that the other parts of the bioequivalence study for the 40 mg were conducted at a different facility does not change the fact that the analytical part of that study is unreliable.

Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for rosuvastatin-containing products concerned by this referral procedure.

### 2.2.12. Saquinavir

For the above mentioned saquinavir-containing medicinal products, the MAH/applicant referred to a reanalysis of study data concluding that the individual time concentration curves are different between volunteers and the chromatograms for the assay in plasma do not show any irregularity. The MAH/applicant also stated that pharmacokinetic data obtained in the study are very similar to those found in the available literature, and that adverse events reported during the study show a comparable safety profile of both test and reference product.

The arguments of the MAH/applicant were considered, however the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for saquinavir-containing products concerned by this referral procedure.

### 2.2.13. Tramadol/paracetamol

The MAHs/applicant carried out a comprehensive review of the tramadol/paracetamol study to confirm its validity and reliability, with special emphasis on the published findings. In addition an audit was conducted covering all three aspects of the study i.e. clinical, bioanalytical and statistical, focusing on data integrity and chromatographic analysis performed in the bioanalytical phase. The MAHs/applicant also note that tramadol and paracetamol are BCS class-I and class-III active substances respectively (*Mohamed Ali Lassoued et al., J Pharm Pharmaceut Sci, 2011 & L. KALANTZI et al., Wiley InterScience, 2005)*.

The arguments of the MAHs/applicant were considered, however the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. In light of the nature, the seriousness and extent of the critical GCP findings identified by the FDA and WHO inspections, all data generated at Semler is considered unreliable and no review or audit of unreliable data can be used to address the concerns.

While the active substances may be eligible for biowaiver, no formal request was submitted and the detailed information necessary to assess the appropriateness of a biowaiver was not made available.

Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for tramadol/paracetamol-containing products concerned by this referral procedure.

On 18 July 2016 the applicant further submitted the study synopsis of a new bioequivalence study performed at a different CRO. The applicant also stated that the full clinical study report will be submitted to the competent authorities of the relevant EU Member States for assessment in the context of the pending MAA. In this context, bioequivalence cannot be considered demonstrated until the full clinical study report is assessed by the relevant competent authorities.

### 2.2.14. Other products

For all other products included in the referral, no data was submitted. The CHMP considered that the bioequivalence to the EU reference medicinal product is therefore not established.

## 3. Conclusions

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 of opinion document) 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 of opinion document), 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 (included in 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.

# 4. Condition for lifting the suspension of the marketing authorisations

For the suspension of the marketing authorisations referred to in annex IB to be lifted, the competent authorities of the EU Member States shall ensure that the below condition has been completed by the marketing authorisation holder(s)

- 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).

# 5. Grounds for 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 section 4 of this report.

   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.