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Committee for Medicinal Products for Human Use (CHMP)

Final assessment report following the re-examination procedure

Referral under Article 31 of Directive 2001/83/EC

Medicinal products for which the clinical part of bioequivalence studies has been carried out by GVK Biosciences Hyderabad during the time period 2004-2014

Procedure number: EMEA/H/A-31/1408

Note

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

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

Following the serious findings identified during an inspection performed by the ANSM at GVK Biosciences Private Limited, Swarna Jayanthi commercial complex, Ameerpet, Hyderabad 500 038, India, the European Commission initiated a referral under Article 31 of Directive 2001/83/EC on 04 August 2014.

For the purpose of this report, GVK Biosciences Private Limited/Clinogent will be hereafter referred to as 'GVK Bio'.

The Committee for Medicinal Products for Human Use (CHMP) was requested to give its opinion on whether the marketing authorisations for medicinal products for which the clinical part of bioequivalence studies has been carried out by the GVK Bio-Hyderabad site (since July 2008) should be maintained, varied, suspended or withdrawn. In addition, the European Commission asked the CHMP whether or not the scope of the procedure should be extended to studies conducted before 2008.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

2.1. Introduction

The French Agency on medicinal products (ANSM) conducted an inspection on 19-23 May 2014 (inspection reference GCP-141001-FR) at GVK Biosciences Private Limited, Swarna Jayanthi commercial complex, Ameerpet, Hyderabad 500 038, India.

The following findings were reported in the French inspection report dated 02 July 2014, to which GVK Bio have responded on 18 July 2014 and in the final inspection report, which was issued on 21 July 2014: data manipulations of electrocardiograms (ECGs) were detected in each and every one of the 9 trials inspected by the ANSM. These data manipulations cast doubts on the authenticity of all other clinical records of these nine clinical trials. They were therefore considered by the ANSM as not compliant with Good Clinical Practice (GCP) and were considered not reliable to support marketing authorisation applications (MAAs). The data manipulations took place between at least July 2008 and 2013. The systematic nature of the data manipulations of ECGs, the extended period of time during which they took place and the number of members of staff involved highlight critical deficiencies in the quality system in place at GVK Bio's clinic in Hyderabad. They also show a lack of GCP training, awareness and understanding of members of GVK Bio staff, a lack of understanding by them of the importance of data integrity and of the possible consequences of their acts, as well as a lack of overview of clinical trial activities by the investigators.

The seriousness of the deficiencies identified and the lack of GCP compliance at GVK Bio's clinic at Hyderabad site raise questions as to the reliability of studies conducted between 2008 and 2014 at the site inspected, as well as the clinical part of all other bioequivalence trials performed prior to 2008.

The European Commission initiated a referral under article 31 of Directive 2001/83/EC on 4 August 2014. The CHMP was asked to assess the potential impact of the findings on the benefit risk balance of products authorised on the basis of studies with clinical activities performed at the inspection site. The medicinal products concerned are listed in Annex I.

2.2. Discussions

The procedure started on 25 September 2014. During September 2014 CHMP plenary meeting, the CHMP adopted a LoQ to the CRO to clarify whether the findings should be confined to the period 2008-2014, to specific clinical trials and/or specific clinical activities at the Hyderabad site.

During the November 2014 meeting, after GVK Biosciences' submission of responses as well as providing information relating to the matter before the CHMP on 22 October 2014, the CHMP determined that GVK Biosciences Pvt. Ltd. did not provide evidence to demonstrate that the problem was confined to a specific time period or specific clinical trials or specific individuals and clinical activities. The CHMP therefore concluded that all bioequivalence studies with clinical activities carried out at GVK Biosciences Pvt. Ltd. site in Hyderabad, India, since GVK Biosciences Pvt. Ltd. started these activities in 2004 are considered unreliable to support the benefit risk balance of the medicinal products they relate to. The CHMP therefore decided to extend the scope of the review by also including studies performed between 2004 and 2008. A list of questions to MAHs was adopted to request them to submit data to prove bioequivalence for their medicinal products vis-à-vis the EU reference medicinal product, as appropriate.

Following submission of MAHs' responses, and whilst due consideration was given to every MAHs' replies, the arguments and data provided were classified into three categories.

- Category 1: No new biowaiver request or data to establish the bioequivalence vis-à-vis the EU reference medicinal product (apart from BE studies conducted at GVK Biosciences Hyderabad site)
- Category 2: New biowaiver request submitted
- Category 3: New bioequivalence vis-à-vis the EU reference medicinal product study submitted

Discussions on the above took place during the December 2014 CHMP plenary meeting during which the CHMP endorsed the above mentioned classification.

2.2.1. Considerations to all products reviewed within the framework of this procedure

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 product was higher than the bioavailability of the reference medicinal product, this would result in a higher than intended exposure of patients to the active substance, leading potentially to an increase in the incidence or severity of the adverse effects. If the bioavailability of the product was lower than the bioavailability of the reference medicinal product, this would result in a lower than intended exposure of patients to the active substance, leading potentially to a decrease in efficacy, a delay or even a lack of therapeutic efficacy.

Taken into account the above, the benefit-risk balance of the medicinal product where the bioequivalence is not established is not positive as it cannot be excluded that it would lead to safety/tolerability or efficacy issues.

In addition to the submitted studies, some MAHs have highlighted that some audits and inspections with a positive outcome were carried out at GVK Biosciences Pvt. Ltd. facility in Hyderabad, India, and argued that, in view of this, the bioequivalence studies conducted at the site can be relied upon as sufficient to support a Marketing Authorisation. However, in light of the nature, the severity and the

extent of the GCP findings identified in the ANSM's inspection in May 2014, these arguments do not demonstrate that the said studies can be relied upon. Indeed, any mentioned audits and inspections, including those that have been done at the site since the GCP findings by the ANSM's inspection, do not provide sufficient reassurance since they may not have detected serious GCP violations, even if present. Hence, the CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have affected the said studies. 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.

The plausibility of results and controls of data integrity by MAHs were not considered sufficient to establish the bioequivalence based on studies performed at GVK Bio-Hyderabad site and therefore acceptable as basis for a marketing authorisation.

A number of MAHs have also argued that pharmacovigilance data collected on their medicinal products have not indicated any problems, which could be attributed to non-bioequivalence, such as reduced efficacy or worsened safety and tolerability. However, 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.

Some MAHs have provided results from bioequivalence data using non-EU Reference Medicinal Products. According to article 10 of Directive 2001/83/EC, the bioequivalence vis-à-vis an EU reference medicinal product needs to be established and therefore the abovementioned studies can not be considered fulfilling the criteria of article 10.

Some MAHs have submitted bioequivalence data from a study associated with unresolved, critical GCP findings. The CHMP concluded that the critical GCP findings did not allow these studies to be relied upon to establish the bioequivalence vis-à-vis the EU reference medicinal product.

2.2.2. Category 1 medicinal products

The category encompasses products for which MAHs have not provided any biowaiver request or bioequivalence study vis-à-vis the EU reference medicinal product generated elsewhere than at GVK Biosciences Pvt. Ltd. facility in Hyderabad, India, or where MAHs have not responded. Nevertheless many MAHs provided miscellaneous statements, as described in the previous section, concerning benefit risk balance of the medicinal products. These statements were carefully assessed.

In conclusion, in the absence of demonstration of the bioequivalence vis-à-vis the EU reference medicinal product, the CHMP concluded that the efficacy and safety of the concerned category 1 medicinal product can not be established, and hence the benefit-risk balance cannot be considered positive.

2.2.3. Category 2 medicinal products

This category encompasses medicinal products for which MAHs have provided biowaiver request (i.e. claims to fulfil the criteria for a Biopharmaceutics Classification System (BCS)-based biowaiver as described in Appendix III of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) to establish bioequivalence to an EU Reference Medicinal Product.

The applicability of a BCS-based biowaiver has been claimed for medicinal products with the active substances Donepezil, Levetiracetam, Levocetirizine, and Metoclopramide.

Levetiracetam: Procedures PT/H/0495, PT/H/0496 National Procedure (Croatia) MA Numbers UP/I-530-09/11-01/549; UP/I-530-09/11-01/550; UP/I- 530-09/11-01/551; UP/I-530-09/11-01/552

Marketing Authorisation Holders: Hormosan, Alkaloid-INT, Alkaloid d.o.o., Mylan, Lupin, Welding, Generics UK. Levetiracetam may be safely classified as a BCS-class 1 drug substance and therefore eligible for the BCS based BW approach (irrespective of its indication as an antiepileptic drug and in line with US-FDA recommendations). The submitted BCS-based biowaiver documentation fulfils guideline requirements related to the BCS based biowaiver approach for immediate release products containing BCS class 1 compounds which are somewhat less strict than for BCS class 3. In order to support the BCS-based biowaiver approach for the product series, product comparison in terms of comparative in vitro dissolution data have to be provided for each particular strength. Product comparison at pH 4.5 has been submitted for 250 mg and 1000 mg strength but not for 500 mg and 750 mg strengths. The bioequivalence demonstrated for the highest and lowest strengths of the product permits a preliminary interpolation to the strengths in between. With bioequivalence of the 1000 and 250 mg strengths the CHMP considers that bioequivalence can be shown for the 500 mg and 750 mg strengths as well, since all strengths are dose proportional in terms of composition. The CHMP is of the view that the comparative in vitro dissolution data for the 1000 mg strengths performed in pH 4.5 and 6.8 should be confirmed in that 6/12 and 4/12 test tablets, respectively, exhibit in vitro dissolution < 85 % at 15 min. Accordingly, such comparison should be repeated with different batches in order to verify adequate and consistent performance of 1000 mg test product batches.

The CHMP considers that the bioequivalence has been established for all strengths. The MAH(s) are requested to provide the study reports of the above mentioned in vitro studies within 2 months from the European Commission Decision to the relevant national competent authorities.

Levocetirizine: Procedures DK/H/1900, DK/H/1901, DK/H/1531. Marketing Authorisation Holders: Alfred E. Tiefenbacher (GmbH&Co.KG), Biofarm Sp.z o.o.; Delorbis Pharmaceuticals Ltd. (DK/H/1531). Based on the review of data on the BCS-based Biowaiver it is concluded that bioequivalence is supported of the above named product with Xysal/Xusal (UCB Pharma). Levocetirizine is not considered a narrow therapeutic index drug and may be cautiously classified as a BCS-class 3 drug substance. However, there is some evidence for at least a borderline case to BCS-class 1. The submitted BCS-based biowaiver report has been part of the initial marketing authorisation application and fulfils guideline requirements related to the BCS based biowaiver approach for immediate release products containing BCS class 3 compounds, i.e. similarity between test and reference in terms of composition and very rapid in vitro dissolution. The CHMP considers that the bioequivalence has been established and that there are no remaining issues.

Metoclopramide: Procedure DK/H/2296/001/DC. Marketing Authorisation Holder: Orifarm Generics A/S. Based on the review of the BCS-based biowaiver data it is concluded that bioequivalence is supported of the above named product with Primperan. The drug substance can be safely classified into BCS class 3 and is therefore eligible for the BCS-based biowaiver approach. The immediate release product(s) concerned can be considered bioequivalent based on respective comparative in vitro data. However, this conclusion is not completely in line with guideline requirements regarding immediate release products containing BCS class 3 drug substances since test and reference differ qualitatively in one excipient (test: pregelatinized starch; reference: microcrystalline cellulose) and it is not possible to finally conclude on close similarity in terms of the quantity of those excipients that are identical. Comparative in vitro dissolution results indicate very rapid dissolution of test and reference batches investigated at all pH conditions as requested, i.e. at least 85 % at 15 min. Hence, the BCS-based biowaiver approach is supported concerning product comparisons in this respect. The CHMP considers that the bioequivalence has been established and that there are no remaining issues.

For the remaining medicinal products in category 2 (i.e. products of Annex IB containing Donepezil), issues precluding the establishment of bioequivalence to an EU Reference Medicinal Product were

raised and therefore in the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal product, the efficacy and safety of these medicinal products can not be established.

Conclusion:

For products of Annex IA containing Levetiracetam, Levocetirizine and Metoclopramide, the CHMP considers that the biowaiver request is acceptable. The bioequivalence is therefore established and the benefit-risk balance for these products remains positive. The CHMP recommends therefore the maintenance of the concerned marketing authorisations.

For the remaining medicinal products in category 2 (i.e. products of Annex IB containing Donepezil), the following issues precluding the establishment of bioequivalence to an EU Reference Medicinal Product were raised:

- Absorption through the oral cavity for an orodispersible formulation cannot be excluded
- Composition differences – the test product contains critical excipients that may affect the pharmacokinetics profile of the medicinal product (absorption).

In the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal product, the efficacy and safety of these medicinal products can not be established, and hence the benefit-risk balance cannot be considered positive. The CHMP recommends therefore the suspension of the concerned marketing authorisations.

2.2.4. Category 3 medicinal products

This category encompasses products for which MAHs have provided data from other bioequivalence studies vis-à-vis the EU reference medicinal product than the one performed at GVK Biosciences Pvt. Ltd.'s site in Hyderabad, India.

For a number of medicinal products, the MAHs submitted data from bioequivalence trials, conducted elsewhere than GVK Biosciences Pvt. Ltd.'s site in Hyderabad, India.

Bendroflumetiazid Procedure: National procedure in Sweden (Asp no: 2013-0337, 2013-0338) Marketing Authorisation Holder: Alternova A/S, Denmark. Study code: BE-048-BEND-2003. The assessment of the submitted data supports the bioequivalence of these medicinal products with the reference product Aprinox tablets. The CHMP considers that the bioequivalence has been established and that there are no remaining issues.

Bosentan Procedures: CZ/H/0456/001-002/DC, CZ/H/0457/001-002/DC, CZ/H/0461/001/DC Marketing Authorisation Holders: Sandoz, Teva, Abdi, UAB Noramed, Celon Pharma. Study code: ABH-P9-096. The assessment of the submitted data supports the bioequivalence of these medicinal products with the reference Tracleer 125 mg. The CHMP considers that the bioequivalence has been established and that there are no remaining issues.

Fexofenadine hydrochloride Procedures: DK/H/1087/001-002/MR, DK/H/1088/001-002/MR, DK/H/1089/001-002/MR, DK/H/1090/001-002/MR, DK/H/1091/001-002/MR, DK/H/1106/001-002/MR, national applications in PT. Marketing Authorisation Holders: Chanelle, Biogaran, Orifarm Generics, Teva, Mylan, Dermapharm, Polpharm, Ewopharm, Apothecon, Cipla Chanelle, Costanzafarma, Farmaceutyczna Spółdzielnia, Generics UK, Norton Healthcare, Pharmachemie, Ratiopharm. Study code: 13-04-033. The assessment of the submitted data supports the bioequivalence of the medicinal product with the reference Telfast film-coated tablets. The CHMP considers that the bioequivalence has been established and that there are no remaining issues.

Lansoprazole Procedure: NL/H/0802/01-02, NL/H/0827 and national procedures in RO.

Marketing Authorisation Holder: Ranbaxy. Study codes: CR-BE-057-LANS-2003, 242_LANSO_06. The submitted data support the bioequivalence of the medicinal product with the reference Zoton. Only study BE-163-04, a study in which the formulation was evaluated against the comparator Zoton under fed conditions, was performed at GVK Biosciences Pvt. Ltd.'s site in Hyderabad. The other bioequivalence studies (performed in other CROs) were part of and assessed with the original application and demonstrated bioequivalence of the medicinal product with the reference product. As the product should be taken at least 30 minutes before food, the data from the GVK study (fed conditions) are not pivotal for the licencing decision and the benefit risk balance remains positive. The CHMP considers that the bioequivalence has been established and that there are no remaining issues.

Nebivolol: Procedure: DE/H/1454/01, DE/H/0759, DE/H/1656 and national authorisation in AT, BG, FR, PT. Marketing Authorisation Holders: G. L. Pharm, Teva, Labesfal, Aristo-Iberia, Plus Pharmacie, Heumann, Genericos Portugueses, Ecopharm, Generis Farmaceutica SA, Germed, GP – Genericos Portugueses, Heumann, Lannacher, Ratiopharm, Torrent Pharma. Study code: PK-05-035. The MAH submitted documentation for study number PK-05-035 as well as comparative data on the qualitative and quantitative composition and on the manufacturing processes. This documentation was considered acceptable to the CHMP, supporting the bioequivalence of the medicinal products with the reference product Nebilet 5 mg tablets. The CHMP considers that the bioequivalence has been established. The CHMP is of the view that a statement with respect to GCP compliance is missing in the study report. The MAH is requested to submit such a statement to the relevant national competent authorities.

Venlafaxine Procedures and Marketing Authorisation Holders: DE/H/1277 (Worwag Pharma), FR/H/0505 (Ranbaxy, Terapia SA, Basics), NL/H/1359 (Farmaprojects, Pensa, Pharmazac), FI/H/0789 (Orion Pharma), DE/H/1377 (AAA pharma), UK/H/1148 (Morningside healthcare), UK/H/1400 (Bluefish), National procedures (Heumann Pharma, Labesfal Genericos, Bluefarma, Eurogenus, Aristo Iberia, FB Health, Farmagenus, Progefarm, Forum Products). Study codes: 203-13, 204-13, 205-13. The assessment of the submitted data supports the bioequivalence of these medicinal products with the reference Trevilor retard extended release capsules. The CHMP considers that the bioequivalence has been established and that there are no remaining issues.

For the remaining medicinal products in category 3 (products of Annex IB containing Clindamycin, Esomeprazole, Phenoxymethylpenicillin, Trimetazidine), the issues precluding the establishment of bioequivalence to an EU Reference Medicinal Product were raised and therefore in the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal product, the efficacy and safety of these medicinal products can not be established.

Conclusion:

For the following medicinal products in category 3 (products of Annex IA containing Bendroflumetiazid Bosentan, Fexofenadine, Lansoprazole, Nebivolol and Venlafaxine), the CHMP is of the opinion that the results of the provided trials establish the bioequivalence vis-à-vis the EU reference medicinal product. The benefit-risk balance for these medicinal products remains therefore positive. The CHMP recommends therefore the maintenance of the concerned marketing authorisations.

For the remaining medicinal products in category 3 (products of Annex IB containing Clindamycin, Esomeprazole, Phenoxymethylpenicillin, Trimetazidine), the issues precluding the establishment of bioequivalence to an EU Reference Medicinal Product pertain to:

- The identity of test product in the study with the authorized (marketed) product is not clear.

- The full study report of the bioequivalence study is missing, only a study synopsis has been submitted.
- The reference product is not authorized in the EU.
- The steady state study for a modified release product is missing.
- The single-dose study for a modified release product is missing.
- Only a synopsis of a pilot study has been submitted.
- The test product was expired at the time of study.
- The full bioanalytical report is missing.
- A biowaiver for a lower strength is not acceptable, as comparative dissolution according to bioequivalence guideline were not submitted.

Further to the assessment, the CHMP noted that medicinal products containing Pravastatin were to be excluded of this procedure as out of the scope of the procedure.

2.3. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Overall benefit / risk assessment

Having taken into account the ANSM's inspection report, the available data and all arguments presented in the MAHs' replies, the CHMP concluded in its plenary meeting on January 2015 that in the absence of demonstration of bioequivalence to an EU Reference Medicinal Product, the efficacy, safety and tolerability of the concerned medicinal product cannot be established.

Indeed, where the bioequivalence is not established, the efficacy, safety and tolerability cannot be extrapolated from the reference medicinal product to the generic product as the bioavailability of the active substance between the two medicinal products may differ. If the bioavailability of the product was higher than the bioavailability of the reference medicinal product, this would result in a higher than intended exposure of patients to the active substance, leading potentially to an increase in the incidence or severity of the adverse effects. If the bioavailability of the product was lower than the bioavailability of the reference medicinal product, this would result in a lower than intended exposure of patients to the active substance, leading potentially to a decrease in efficacy, a delay or even a lack of therapeutic efficacy. In the light of these uncertainties and consequent potential efficacy, safety and tolerability concerns, the benefit-risk balance of the concerned medicinal products is not positive.

The following conclusions were adopted by CHMP accordingly based on the assessment of the MAHs' replies and after having given due consideration to all arguments presented by MAHs:

- For medicinal products (Annex IA) for which other bioequivalence studies than the one(s) performed at GVK Biosciences Hyderabad site or claims that the medicinal products fulfil the criteria for a Biopharmaceutics Classification System (BCS)-based biowaiver as described in Appendix III of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) were submitted, assessed and considered positive by the CHMP (i.e. medicinal products containing Bendroflumetiazid, Bosentan, Fexofenadine, Lansoprazole, Levetiracetam, Levocetirizine, Metoclopramide, Nebivolol and Venlafaxine), the CHMP is of the opinion that the bioequivalence has been established.

The benefit-risk balance for the products of Annex IA remains positive and the CHMP recommends therefore the maintenance of the concerned marketing authorisations.

- With regards to medicinal products (Annex IB) for which bioequivalence data was not submitted or considered insufficient by the CHMP to support a positive benefit risk balance of the concerned medicinal products, the CHMP is of the opinion that the bioequivalence with an EU authorised reference medicinal product has not been established and therefore concluded that the particulars supporting the marketing authorisation are incorrect and that the benefit-risk balance of the concerned medicinal products is not positive as pursuant to Article 116 of Directive 2001/83/EC.

The Committee therefore 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 Member State(s) for a period which shall not exceed twenty-four months from the Commission Decision. Should during this period the 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 Member States, the marketing authorisations holders shall submit a bioequivalence study conducted vis-à-vis the EU Reference Medicinal Product within 12 months following Commission Decision.

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

For marketing authorisations recommended for suspension, the CHMP concluded the suspension could be lifted when bioequivalence to an EU Reference Medicinal Product has been established based on a bioequivalence study conducted vis-à-vis the EU Reference Medicinal Product.

2.5. Re-examination procedure

Following the adoption of the CHMP opinion during the January 2015 CHMP meeting, requests for re-examination were received from the following MAHs:

1. Ranbaxy, Basics GmbH, Takeda Belgium, Pensa Pharma and Labesfal Genéricos (for Alendronate);
2. Heumann Pharma GmbH & co. Generica KG, and Torrent Pharma GmbH / Torrent Pharma SRL (for Irbesartan/ hydrochlorothiazide and Irbesartan);
3. Dr. Reddy's Laboratories (UK) Ltd and betapharm Arzneimittel GmbH (for Dipyridamole and Levetiracetam);
4. Neo Balkanika (for Nebivolol);
5. Genericon Pharma Austria (for Nebivolol).

In support of their request for re-examination, MAHs submitted grounds to argue that the benefit risk balance of their products subject to a suspension of MA is positive. The grounds submitted were taken into consideration and assessed by the CHMP.

The CHMP conclusions on the points raised in the MAH's grounds are given below.

2.5.1. Request for re-examination for Alendronate:

Importance of alendronate therapy for patients: The MAHs argue on the importance of the alendronate therapy for patients and continuous availability of the medicine to safeguard public health.

It is recognised that alendronate occupies an important place in the treatment of post-menopausal osteoporosis. However, prescription of the suspended MAs can be reported to another generic or the innovator brand. In addition, reference is made to the CHMP opinion in which it is stated that individual Member States may consider medicinal products critical based on the evaluation of the potential unmet medical need, considering the availability of suitable alternative medicinal products in the respective 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 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 (period which can not exceed twenty-four months from the Commission Decision).

The CHMP is of the view that this argument does not substitute the need to establish bioequivalence with an EU reference medicinal product in order to conclude on the positive benefit-risk balance of the concerned medicinal products.

Not all phases of the study performed at GVK Bio: For the original submission, the MAH had conducted a bioequivalence study that compared its test product Alendronate Sodium 70 mg Tablets with the European innovator, Fosamax 70 mg tablets in healthy, adult, male, human subjects under fasting condition. The clinical phase was conducted at GVK Bio; the bioanalytical, pharmacokinetic and statistical phases of the study were carried out by another CRO.

Serious findings were identified at the clinical site where the study was carried out, and in view of the seriousness of the deficiencies identified, the obtained data at the clinical site are considered not reliable by the CHMP. Therefore the CHMP is of the view that analysing the plasma samples at another CRO cannot overcome the fact that the generated data are unreliable.

The CHMP is of the view that the argument presented by the MAHs above does not substitute the need to establish bioequivalence with an EU reference medicinal product in order to conclude on the positive benefit-risk balance of the concerned medicinal products and therefore should be rejected.

Submission of new scientific data: The MAHs informed the CHMP that they have initiated activities for a new bioequivalence study. The information was noted, but as no data of this bioequivalence study have been submitted within the article 31 procedure, it was not considered in the review.

Therefore the MAH still needs to establish bioequivalence with the EU reference medicinal product in order to conclude on the positive benefit-risk balance of the medicinal product.

Post-marketing experience: The MAH argues on the long term post marketing experience of almost seven years for Alendronic acid containing formulations.

The CHMP noted that pharmacovigilance data reported to the competent authorities have not indicated any problems which could be attributed to non-bioequivalence, such as reduced efficacy or worsened safety and tolerability. However, the CHMP considers that the pharmacovigilance activities may likely have lacked the ability to detect a signal with regard to efficacy or safety and tolerability, and the lack of any pharmacovigilance signal does not offer sufficient reassurance to conclude on a positive benefit risk in the absence of the demonstration of bioequivalence with the EU reference medicinal product.

Finally, it is noted that bioequivalence for a generic product should be proven in line with the criteria as outlined in article 10 of Directive 2001/83/EC and the Guideline on the investigation of bioequivalence.

For the above reasons, the lack of proof of bioequivalence can not be substituted by post marketing experience data.

2.5.2. Request for re-examination for Irbesartan and Irbesartan / hydrochlorothiazide:

BE established versus non-EU RMP for Irbesartan: For the EU MA dossier for Irbesartan 75, 150 and 300 mg tablets, the following bioequivalence study has been performed: bioequivalence study for Irbesartan Film-coated Tablets using 300mg strength against EU reference product APROVEL 300 mg Film-coated Tablets. Subsequently, for Australian (AU) generic dossier submission, a bioequivalence study was performed using Irbesartan Film-coated Tablets 300 mg against the AU reference product AVAPRO 300mg Film-coated Tablets sourced from the Australian market.

The MAH claims that the data obtained in the AU study are still applicable for the EU. In addition, the MAH claims that in art 10 of Directive 2001/83/EC there is 'room for interpretation', and it is not specifically mentioned that an EU reference product must be used. According to the MAH, this is only mentioned in the Guideline on the Investigation of Bioequivalence. Finally, the MAH states that repeating the bioequivalence study would result in confirming what the MAH already knows, i.e. that the test Irbesartan product is bioequivalent with the EU reference product. That being the case, volunteers would be unnecessarily exposed to a medicinal product without a clear need, which is not acceptable from an ethical point of view.

For generic products authorised under Article 10(1) of Directive 2001/83/EC, establishment of bioequivalence vis-à-vis a reference medicinal product is a pre-requisite. This reference medicinal product has to be authorised in the EU under the EU procedures described in Article 6 and in accordance with the EU requirements defined in Article 8 of the said Directive.

Without prejudice to the above requirement, the CHMP reviewed the MAHs argumentation and considered from a scientific perspective that it is not established with the provided data that both AU and EU reference medicinal products are identical (e.g., the manufacturing sites are unknown, the quantitative compositions are unknown).

The provided study does not establish the bioequivalence with a reference medicinal product authorised in the EU. In conclusion, the CHMP is of the view that the data submitted by the MAHs are not suitable to support the positive benefit-risk balance of the medicinal product.

BE established versus non-EU RMP for Irbesartan/hydrochlorothiazide: For the EU MA dossier for Irbesartan/hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg the following bioequivalence study has been performed: bioequivalence study for Irbesartan + Hydrochlorothiazide Film-coated Tablets using 300/25mg strength against EU reference product COAPROVEL 300/25mg Filmcoated Tablets. Subsequently, for AU generic dossier submission, a bioequivalence study was performed using Alembic's Irbesartan Hydrochlorothiazide Film-coated Tablets 300mg/25 mg against the AU reference product AVAPRO HCT 300mg Film-coated Tablets sourced from Australian market.

Based on the same argumentation as described above for Irbesartan, the MAH claims that the data obtained in the AU study are still applicable for the EU. Having considered the MAHs' argumentation, the CHMP confirms its opinion and concludes that the data submitted by the MAHs are not suitable to support the positive benefit-risk balance of the medicinal product.

2.5.3. Re-examination request for Levetiracetam and Dipyridamole:

New scientific data: The MAHs have submitted a biowaiver request for levetiracetam and a new bioequivalence study for dipyridamole. The MAHs did not submit the above mentioned scientific data before the adoption of the initial opinion.

As stated in Article 62(1) paragraph 4 of Regulation (EC) No 726/2004 and Article 32(4) paragraph 3 of Directive 2001/83/EC, *“the re-examination procedure may deal only with the points of the opinion initially identified by the applicant/MAH and may be based only on the scientific data available when the Committee adopted the initial opinion.”* Therefore these scientific data can not be considered during the re-examination procedure.

Positive inspection and audit history of the GVK Bio Hyderabad site: The MAHs argue that based on the fact that a GCP audit by the MHRA of a study conducted at the site failed to identify any critical or major breaches of GCP, the CHMP conclusions that studies conducted at GVK Bio facility cannot be relied upon to demonstrate bioequivalence cannot be justified. The MAHs also state that they note the opinion regarding GCP audits conducted by GVK Bio's clients (i.e. implying that these audits were substandard as they did not identify any serious violations of GCP at the GVK Bio facility). The MAHs argue that this generalisation can only be justified if evidence is provided that individual audits were not conducted to the appropriate standard, and that no such evidence has been provided.

The CHMP acknowledges that a number of audits by GVK's clients and inspections by competent authorities were carried out at GVK Bio-Hyderabad over a large period without identifying critical findings. However the CHMP is of the view that the findings by ANSM in 2014 were serious in terms of the impact on the integrity of the studies.

The results and controls of data integrity by MAHs were not considered sufficient to override the findings of the ANSM inspection at GVK Bio-Hyderabad site.

In addition, inspections by regulatory authorities follow a sampling process in which specific parts of a particular activity are looked at in detail to establish whether its conduct complied with all relevant guidelines and regulations. This means that a successful outcome in a particular inspection cannot be taken as a guarantee that all processes are properly run and GCP compliant. Nor does it allow for the findings of a previous inspection to be ignored.

Finally, the CHMP determined that GVK Bio did not provide evidence to demonstrate that the problem was confined to a specific time period or specific clinical trials or specific individuals and clinical activities. The CHMP therefore concluded that all bioequivalence studies with clinical activities carried out at GVK Bio site in Hyderabad, India, since GVK Bio started these activities in 2004 are considered unreliable to support the benefit risk balance of the medicinal products they relate to.

The CHMP therefore confirms that it cannot be ruled out beyond reasonable doubt that critical GCP violations at the site have not affected the integrity of the scientific data of other bioequivalence studies conducted at the site, and that the studies therefore remain unreliable. The CHMP is of the opinion that these studies can not be used to establish bioequivalence with the EU reference medicinal product and therefore to support a generic marketing authorisation.

2.5.4. Re-examination request for Nebivolol Neo-Balkanika:

The MAH claimed that it had not received the official notification of the inclusion of the product in the Article 31 Referral procedure. Therefore the information submitted at the stage of re-examination was taken into consideration in order to safeguard the right of defence of the company.

Neo-Balkanika submitted the bioequivalence study (PK-05-035) which had already been submitted during the referral procedure in support of marketing authorisations for Nebivolol 5 mg tablets, with the same qualitative and quantitative composition and same manufacturers. The CHMP had already assessed this study and concluded that it can be considered as acceptable proof of bioequivalence and the benefit risk balance of the respective marketing authorisations can be considered positive.

In conclusion, bioequivalence with an EU authorised reference medicinal product is confirmed and therefore it can be concluded that the benefit/risk balance of Nebivolol / Neo Balkanika is positive.

2.5.5. Re-examination request for Nebivolol Genericon Pharma Austria:

The MAH has submitted a bioequivalence study for Nebivolol during the course of the re-examination. The MAH did not exercise the right to submit the above mentioned scientific data for assessment before the adoption of the initial opinion.

As stated in Article 62(1) paragraph 4 of Regulation (EC) No 726/2004 and Article 32(4) paragraph 3 of Directive 2001/83/EC, *“the re-examination procedure may deal only with the points of the opinion initially identified by the applicant/MAH and may be based only on the scientific data available when the Committee adopted the initial opinion.”* Therefore these scientific data can not be considered during the re-examination procedure.

2.5.6. Overall conclusion of the re-examination

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

- Concluded that the benefit risk of Nebivolol/Neo Balkanika is positive, therefore Nebivolol/Neo Balkanika is included in the list of medicinal products recommended for maintenance of the marketing authorisation;
- Confirmed its previous recommendation to suspend the marketing authorisations for medicinal products for which bioequivalence vis-à-vis the EU reference medicinal product was not established.

3. Overall conclusion

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for medicinal products concerned by the GVK Bio procedure;
- The Committee reviewed all available data and information provided by the MAHs, as well as information provided by GVK Bio;
- The Committee considered the grounds for re-examination provided by the MAHs in writing;
- the Committee concluded in accordance with Article 116 of Directive 2001/83/EC that the particulars supporting the marketing authorisation are incorrect and that the benefit-risk balance is not positive for marketing authorisations of medicinal products for which bioequivalence

data or justification was not submitted or considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (Annex IB);

- the Committee concluded for marketing authorisations of medicinal products of Annex IA containing Bendroflumetiazid, Bosentan, Fexofenadine, Lansoprazole, Levetiracetam, Levocetirizine, Metoclopramide, Nebivolol and Venlafaxine that the benefit risk balance is positive in the approved indications.

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the CHMP recommends:

- a. To suspend the 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), as the particulars supporting the marketing authorisations are incorrect and that the benefit-risk balance of these marketing authorisation is not positive pursuant to Article 116 of Directive 2001/83/EC.

Suspension of the MAs should be lifted when bioequivalence to an EU Reference Medicinal Product has been established based on a bioequivalence study conducted vis-à-vis the EU Reference Medicinal Product.

The CHMP therefore recommends by consensus the suspension of the Marketing Authorisations for the medicinal products referred to in Annex IB.

Some of these medicinal products may be considered critical by the individual Member States on the evaluation of the potential unmet medical need, considering the availability of suitable alternative medicinal products in the respective 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 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 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 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. To maintain the marketing authorisations for medicinal products for which the bioequivalence vis-à-vis the EU reference medicinal product has been established (Annex IA) as the benefit risk balance of these marketing authorisation is positive.