European Medicines Agency
Inspections

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Assessment of the quality of medicinal products containing existing/ known active substances

The document on assessment of the quality of medicinal products containing existing/known active substances (e.g. generics), has been developed in order to address common issues arising in Member States, when the assessment of the quality part of such products is carried out.

The document aims to clarify the assessment strategy which should be followed by Competent Authorities when assessing quality of products containing existing/known active substances, in line with Annex I of Directive 2001/83/EC, as amended and equivalent provisions of Directive 2001/82/EC and, at the same time, includes guidance for the applicants.

Although this document addresses approaches to assessment, the approaches identified are expected to have an impact on applicants and as such, it has been agreed to publish it for a 6 months public consultation period. Stakeholders are also asked for estimates on possible economic and public health impacts of the proposed strategy.

Once finalised, following the consultation process, it is foreseen to annex the document to the current guidance for the assessors and to establish a reference to it in the Notice to Applicants.

Comments should be sent to qwp@emea.europa.eu by 31st January 2008.

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Assessment of the quality of medicinal products containing existing/ known active substances

PREAMBLE

This paper addresses in general the strategy for the assessment of the quality of medicinal products containing known active substances. These include generic medicinal products but also those medicinal products which do not fall under the legal definition of generics. These active substances can be pharmacopoeial or non-pharmacopoeial substances.

1. INTRODUCTION

The CHMP/CVMP QWP has prepared a series of guidelines, which provide recommendation on the information which has to be submitted in an application file for marketing authorisation (MA). It is assumed that these guidelines represent the current knowledge on technical and scientific progress.

Some of these guidelines are sole EU guidelines, others have been adopted through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)/International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH) processes. Although the latter guidelines mainly address the information requested for new active substances and corresponding medicinal products, some of them have also been adopted for existing products (e.g. stability, after some modifications, but without changing the principles); others have indirectly been adopted for existing products (e.g. impurities in new active substances Q3A (Vet. GL10); residual solvents, Q3C (Vet. GL18), through the policy adopted by the European Pharmacopoeia.

In Europe, the pharmaceutical legislation makes no distinction between the quality requirements for new active substances and the quality requirements for existing generic active substances (Directives 2001/83 and 2001/82 as amended). Therefore in principle (V)ICH guidelines adopted as EU guidelines may also equally apply to new products containing existing/known active substances. .

Further it should be noted that (V)ICH often comes up with new concepts or principles; there is also no scientific reason why these could not equally apply or be adapted to products containing existing/known active substances during post approval procedures. Further the association of generic products have observer status in different ICH Quality Expert Working Groups and are therefore aware of, and contribute to, the development of regulatory requirements.

For instance, the recently adopted ICH Q8 guideline (Pharmaceutical Development) is also a guideline which is applicable for Human medicinal products containing existing active substances: compared to the CHMP guideline "Development Pharmaceutics" it does not differ in its basic requirements. The more elaborated concepts (design space, process analytical technology), which are described in there, are optional.

2. PROBLEM STATEMENT

The issue to be addressed by this paper is how medicinal products containing existing active substances should be assessed within the European pharmaceutical legislative framework, taking into account both the legal requirements and the protection of European patients and animals. A harmonised approach needs to be agreed to facilitate availability of high quality medicinal products across the European Union.

Normally, the legislation foresees that the Quality of a Generic Medicinal Product is assessed on its own merit, not taking into account the Quality of the Originator Product. However, a comparison of certain aspects, such as impurities of the Active Substance might sometimes be needed, where an impact on the safety profile of the generic product cannot be excluded.

3. DISCUSSION – GENERAL CONSIDERATIONS

Article 10 of Directive 2001/83/EC, as amended by Directive 2004/27/EC, states that the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product. The definitions

of generic and reference medicinal products are provided in Article 10.2. Article 13 of Directive 2001/82 applies similarly and should be referred to for Veterinary medicinal products.

From a quality risk management (QRM) point of view, each product should be considered on its own merit.

The manufacturer/applicant has to take full responsibility for his product, especially in those areas which are "site" specific i.e. those aspects where he can only rely on his own knowledge and competence (e.g. manufacturing, development, quality control). All the critical parameters of a generic product have to be addressed in the application file in the same way as for a new product. This does not mean that for some of these parameters the applicant cannot rely for instance on literature, if available, but he has to address them specifically for his product and his environment.

Further, as the safety and efficacy of a generic product is based on the demonstration of bioequivalence to an innovator product, the link between the generic and the reference product also needs to be substantiated in the quality part of the generic application. In accordance with the Note for Guidance on Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), samples of the product from full production batches should be compared with those of the test batch in vitro, and should show similar in vitro dissolution profiles when employing suitable test conditions. Section 3.7 "In vitro dissolution complementary to a bioequivalence study" of the guideline describes in detail the data that need to be submitted. Similar principles apply to Veterinary medicinal products: see the Note for Guidance on Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMEA/CVMP/016/00).

In addition, it has to be considered that the bioequivalence waivers in the CPMP and corresponding CVMP guidelines require quality comparisons to be made between the reference and generic products (e.g. section 5.1.6 in the CPMP guideline for parenteral solutions requires that the same or comparable excipients are used). Bioequivalence waivers might therefore have implications for the quality part of the dossier and expectations towards the supporting data.

4. LEGAL ASPECTS

Annex I to Directive 2001/83 as amended, and the draft Annex I to Directive 2001/82 (Vet), both provide for the following points to be considered in the application for or assessment of a generic medicinal product.

For generic human/veterinary medicinal products the detailed and critical summaries on safety and efficacy shall particularly focus on the following elements:

- The grounds for claiming exemption from the need to perform toxicological or clinical studies;
- A summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities;
- An evaluation of the bio-equivalence studies or a justification why studies were not performed with reference to established guidance as specified in "Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products EMEA/CVMP/016/00".

The following text, from both the Human and Veterinary Notice to Applicants is also relevant:

"The requirement that the generic and reference products have the same qualitative and quantitative composition extends only to the active substance(s) and not to the other ingredients. However, differences in excipient composition or differences in impurities must not lead to significant differences as regards safety and efficacy…".

Recent case law specifies that a difference in impurity profile does not constitute a deviation from the principle of essential similarity. *"It is possible for a generic medicinal product with a different impurity profile to differ from an originator product with regard to safety. If the differences are significant in safety terms then the generic may not be considered as essentially similar (see case C-368/96 Generics [1998] ECR I-07967, paragraphs 32 to 34). In this case, the second application has*

to demonstrate quality, safety and efficacy of his product without referring to the other product". It is the scope of the assessment to confirm that the different or higher impurity level does not impact on safety considerations, hence questioning the principle of essential similarity.

In the European Pharmacopoeia it is recognised that, depending on the source and therefore on potentially different syntheses, a monograph can cover different impurity profiles which can even imply different tests. This Eur. Pharm. policy should be applicable also in the assessment of generic products for which no EP monograph exists.

As a consequence, this leads to the conclusion that each active substance with regard to impurities has ultimately to be assessed on its own merit. Of course, Competent Authorities might want to check, for confirmation reasons, to see the impurity profile of the proposed product is different from that of the reference product, but this cannot lead to a rejection if the impurities are considered qualified.

5. ASSESSMMENT STRATEGY

5.1 General considerations

Generic applications are assessed on their own merits, i.e. it is evaluated whether the dossier describes an adequate quality of the product. The applicant should submit a comprehensive dossier demonstrating the suitability of his product for its intended purpose. It is not the assessing agency's responsibility to demonstrate this suitability.

The following elements should be taken account in the assessment of applications for generic products:

1. Quality documentation of the generic product
2. The guidelines and other common requirements
3. The justification of the applicant
4. In addition, if needed: the information received from the innovator and the scientific literature and other common information might be considered by the assessing agency.

It is important to be aware, that in order for the authorities to have confidence in a medicinal product, not only at time of submission but also during the whole lifecycle, the applicant has to provide adequate justification in their dossier for all aspects of the product and this will include the area of impurities. It is not the Agency's responsibility to search for such justifications.

5.2 Assessment

The assessment of the generic product should first start based on the quality documentation of the Marketing Authorisation Application (MAA), on the common EU guidelines and pharmacopoeial requirements. It is up to the applicant/manufacturer to demonstrate that he is able to manufacture a product of consistent quality, meeting current scientific state of the art.

If guidelines are not adequately followed, this should be justified by the applicant in his dossier. He can also refer to the originator, but it is up to him to demonstrate why, for his product, he can rely on the originator product.

The assessor might want, for reasons of information, to check the information received from the originator in order to better understand and review the data received in the application file. This should be decided on a case by case basis and not be necessarily the rule. It is not the Agency's responsibility to justify the suitability of the product, but to assess if the information provided is adequate.

All these considerations should be fully documented and critically reviewed in the quality assessment report.

5.3 Specific considerations on impurities

If the following addresses mainly the medicinal product, it is in principle equally valid for the active substance, which in many cases will be covered by a pharmacopoeial monograph. The thresholds for

reporting, identification and qualification as described in the respective current (V)ICH guidelines (Q3A & Q3B for Human products; GL10 & GL11 for Veterinary) as well as in the pharmacopoeial general monograph "Substances for pharmaceutical use" are applicable.

Under the development part of the application, it should be discussed whether the product is likely to have a different impurity profile as compared to the originator product. Especially when this is the case, efforts should be made to keep the level of impurities as low as reasonably possible. Development work to keep the level of impurities low is performed for originator products, and this should not in principle be different for generic products. Where the level of impurities observed in generic products is higher than that in the originator, a discussion taking into account the active substance development and possible impurity sources (e.g. synthetic route, side reaction with excipients, production conditions during manufacture, etc.) should be provided by the applicant. The development should take into consideration knowledge gained on development of similar drug products (e.g. formulation development). Predictable degradation products should be limited to an appropriate level. Generally, the manufacturing process/packaging process should be optimised. In addition, the application and discussion of general risk assessment strategies at early stages of the development is encouraged.

It is expected that the generic applicant himself justify why he considers the impurities in his respective product safe for the intended use and qualified, either by reference to expected similarity with the originator or by other means.

It should be reminded here that toxicological studies represent a model, where, according to our current knowledge, one can reasonably assume that a specific impurity or impurity profile will not give raise to adverse reactions. It should also be reminded that impurities represent an unnecessary burden for the patients (or for Veterinary products the recipient animals and also users of the product) and as we only use a model, the "principle of precaution" might also be considered. Anyhow an adequate justification from the applicant is necessary.

In the case where the impurity profile of a generic product differs qualitatively from the originator, or where higher amount of impurities are seen, the full qualification or other adequate information about the safety of these impurities will be asked. If the level of one impurity in a generic application is higher than the threshold defined for qualification, the applicant is also expected to provide the appropriate justification. This can be by way of reference to published literature, demonstration that the respective impurity can be regarded as qualified by use as it has been already present in relevant marketed products (e.g., indicated for use in the same species, same route of administration, etc) or by respective studies as requested in the (V)ICH guidelines.

It should be kept in mind that a comparison of different impurity profiles is difficult and not necessarily meaningful. If a higher impurity level than that of the originator has been adequately discussed and qualified where necessary, the application shall not be refused where the assessor considers that the product’s safety is not adversely affected. When assigning a shelf-life to the medicinal product, consideration may need to be given to the potential cumulative safety effects of degradation products.

Where an existing medicinal product has a similar impurity profile but at a higher level than that of the generic product, no action is necessary since the impurity profile is considered adequate.

Special caution needs to be taken where new indications, or species, resulting in higher doses are applied for. This has to be kept in mind in the assessment of the safety of the product, considering the administered dose and its qualification (different thresholds). On the other hand, it should always be the highest possible dose, which determines the thresholds for identification and/or qualification of impurities/degradation products, regardless of the indications (or species) applied for in the specific product.

In all cases, it is important that all these issues are adequately and critically addressed by the reviewer in his assessment report.