European Medicines Agency

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

PREAMBLE

This paper is intended for assessors and addresses in a general way the strategy for the assessment of the quality of medicinal products containing existing/known active substances. It is not intended to give detailed guidance to the applicant, what information has to be submitted in an application file for marketing authorisation, but, for better understanding, it addresses the content of what the assessor can expect to be presented in an application file. This is described in the relevant guidelines. Medicinal products containing known active substances can either be generics or medicinal products which do not fall under the legal definition of generics. This paper only deals with active substances and corresponding products of chemical origin. Biological/biotech and herbal products are excluded from the scope of this paper.

1. INTRODUCTION

The CHMP/CVMP QWP has prepared a series of guidelines, which provide recommendation on the information that 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) or the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal 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 (keeping the same 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/known active substances (Directives 2001/83/EC and 2001/82/EC as amended). Therefore in principle (V)ICH guidelines adopted as EU guidelines may also equally apply to products containing existing/known active substances.

Further it should be noted that when (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.

For instance, the recently adopted ICH Q8 guideline (Pharmaceutical Development) is also a guideline which is applicable for Human medicinal products containing existing/known 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 the ICH Q8 document, are optional.

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2. PROBLEM STATEMENT

The issue to be addressed by this paper is how medicinal products containing existing/known 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 on to facilitate availability of high quality medicinal products across the European Union.

3. DISCUSSION – GENERAL CONSIDERATIONS

Article 10 of Directive 2001/83/EC, as amended, states that the applicant shall not be required to provide the results of pre-clinical tests and clinical trials if it is demonstrated 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/EC 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 merits. Unless explicitly recommended otherwise in the legislation/guidelines or scientifically, the principle of quality assessment should be based on the quality documentation's own merit in accordance with the principles laid down in the existing relevant quality guidance and monographs, where applicable.

The manufacturer/applicant has to take full responsibility for his product, especially in those areas which are "company" specific i.e. those aspects where he can only rely on his own knowledge and competence (e.g. development, manufacturing, 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 product containing new active substances. 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.

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. See current Note for Guidance on Bioavailability and Bioequivalence and Note for Guidance on Conduct of Bioequivalence Studies for Veterinary Medicinal Products.

4. LEGAL BASIS

Annex I to Directive 2001/83/EC (Human) as amended, and the Annex I to Directive 2001/82/EC (Vet), both provide points to be considered in the application for and the 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 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 the Guidelines on the Conduct of Bioequivalence Studies for Human and Veterinary Medicinal Products.

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 of the product.

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 necessarily 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 (see also 5.2).

For existing/ known active substances, the European Pharmacopoeia general monograph "Substances for pharmaceutical use" is applicable.

As a consequence, of the above-mentioned legal aspects, this leads to the conclusion that each active substance with regard to impurities has ultimately to be assessed on its own merits. Of course, an assessor might want to check, for confirmation reasons, to see if the impurity profile of the proposed product is different from that of the reference product, but this fact is not a ground for rejection of the application if the impurities are considered qualified.

An assessor might want to see a comparison of the formulation and means of administration (e.g. parenteral preparations, eye drops, patches), where an impact on the safety and efficacy profile of the generic product cannot be automatically excluded.

5. ASSESSMENT STRATEGY

5.1 General considerations

Medicinal products containing existing/known active substances are assessed on their own merits, i.e. it is evaluated whether the dossier describes an adequate quality of the product. The application should be a comprehensive dossier, based on the current EU guidelines and pharmacopoeial requirements. The suitability of the product for its intended purpose should be demonstrated and the manufacture of the product is of consistent quality, meeting current scientific state of the art.

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

1. Quality documentation of the generic product (Module 3/Part II)
2. The guidelines and other common requirements e.g. Pharmacopoeiae
3. Justifications made by the applicant in the application file.
4. In addition, if needed: the information submitted (in the original file) by the innovator and the scientific literature and other common information might be considered by the assessor.

It is not the responsibility of the assessor to search for justifications, interpretations or other conclusions but to assess if the information and justification provided is adequate.

All considerations from the assessors should be fully documented and adequately and critically discussed in the quality assessment report, in particular the critical aspects of the development.

In addition, the application and discussion of general risk assessment strategies at early stages of the development is encouraged.

Critical aspects arising during development studies with regard to the originator products and other similar products should not be ignored by the applicant.

5.2 Specific considerations on impurities

If the following addresses mainly the medicinal product, it will in principle be 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 European Pharmacopoeial general monograph "Substances for pharmaceutical use" are applicable. Regarding genotoxic impurities, the policy as described in the "CHMP Guideline on the limits of genotoxic impurities" should be followed.

It is expected that the applicant of a generic product justifies why he considers the impurities in his product safe for the intended use and qualified, either by reference to expected similarity with the originator or by other means e.g. compliance with relevant (V)ICH guidelines.

In the development part of the application, it is expected to find a discussion whether the product is likely to have a different impurity profile as compared to the original product. Especially when this is the case, the level of impurities should be kept as low as reasonably possible. The level of impurities for originator products is usually low, 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, it is expected that 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.) for a generic product is provided by the applicant.

It should be remembered 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 raise adverse reactions. It should also be remembered 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, it is expected that an adequate justification from the applicant would be provided..

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 requested by the assessor. 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 applied for, no action is necessary since the impurity profile is considered qualified by use.

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 according to the instructions in the SPC 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 the assessment report.