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Challenges of safety evaluation ☆

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ABSTRACT

Each application for authorisation of a medicinal product must be accompanied by the particulars and documents referred to in Directive 2001/83/EC on the Community code relating to medicinal products for human use. Details on the documentation needed for traditional herbal medicinal products (THMP) are given in article 16c of the above mentioned Directive. It is pointed out that a bibliographic review of safety data together with an expert report and additional data, if necessary, are required.

The Committee on Herbal Medicinal Products (HMPC) provides in its "Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products" (EMA/HMPC/71049/2007 Rev. 1) guidance on how to present the information and the dossier needed for an application. There, in agreement with the Directive 2001/83/EC, a bibliographical review of safety data is required within the "Non-clinical Overview". However, it is assumable that for such products, with a long tradition of usage bibliographical information relating to non-clinical safety are available, even if incomplete or not in accordance with today's state of the art. In the "Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration" (EMEA/HMPC/32116/2005) it is reflected how to deal with such an incomplete set of data for traditional herbal medicinal products and crucial information are highlighted.

This article will focus on the explanation of the requirements needed for the non-clinical safety evaluation of THMPs and some detailed explanations of the performance and interpretation of the mutagenicity studies.

1. Introduction

The basic requirements for the safety evaluation of (herbal) medicinal products are laid down in the Directive 2001/83/EC. Besides the examinations of primary/secondary pharmacodynamics which can add valuable information about safety aspects basically tests/studies on safety pharmacology, pharmacodynamic and pharmacokinetic interactions, single-dose and repeat-dose toxicity, genotoxicity and carcinogenicity as well as reproductive and developmental toxicity are required for a marketing authorisation. Further investigations such as studies concerning local tolerance, immunotoxicity, phototoxicity might be necessary, depending on the active pharmaceutical ingredient. According to the Directive also for traditional herbal medicinal products a bibliographic review of safety data is needed.

2. General aspects

In the "Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration" (EMEA/HMPC/32116/2005) the HMPC refers also to traditional herbal medicinal products (THMPs) which are already in medical use since at least 30 years and to the question, if all of these examinations originally required are still necessary for such products. While this guideline is not intended to relax the requirements set out by the Directive 2001/83/EC as amended it is seen as an additional guidance to prepare and assess applications for herbal preparations which are used over such a long period of time, sometimes even over centuries. It is assumed that for such products bibliographical information relating to non-clinical safety is available, even if they are often incomplete or not in accordance with today's state of the art. If such data are available (e.g. in scientific literature, including handbooks and

Abbreviations: CTD, Common Technical Document; DER, drug-extract-ratio; EMA, European Medicines Agency; EC, European Community; DNA, deoxyribonucleic acid; HMPC, Committee on Herbal Medicinal Products; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; OECD, Organisation for Economic Co-operation and Development; THMP, traditional herbal medicinal product

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monographs) it should be assessed whether the expected effects in newly performed animal studies would modify the benefit/risk assessment and would lead to a negative decision for the granting of a marketing authorisation or registration keeping in mind the clinical experience (with regard to the time and extent of use in humans), perhaps existing epidemiological studies and data as well as post-marketing experience gained by the wide spread use in humans which may contribute to the avoidance of unnecessary tests in animals (HMPC, 2005).

Therefore the HMPC tried to state the minimum requirements for THMPs within the non-clinical documentation. If such minimum requirements for non-clinical data cannot be fulfilled by published literature, additional non-clinical tests might be necessary, to solve safety concerns.

In the Guideline EMEA/HMPC/32116/2005 it is stated that where there is sufficient and well-documented experience available in humans to cover organ toxicity, single dose and repeated dose toxicity, immunotoxicity as well as local tolerance testing of traditional herbal preparations is not necessary. Also pharmacological tests including safety pharmacology and pharmacokinetics are not necessary, if there are no reasons to expect a specific risk while the potential for pharmacokinetic interactions between the herbal substance/preparation and other medicinal products must be discussed, and the possibility to perform pharmacokinetic interactions investigations in in vitro test considered. Even if some of the tests are not necessary, the expert report must address all these aspects and available literature must be discussed. Since the documented experience gathered during the long-standing use will be the main basis of the non-clinical assessment of traditional herbal medicinal products, particular attention should be paid to effects that are difficult or even impossible to detect clinically. These effects would include toxicity to reproduction, genotoxicity and carcinogenicity.

3. Genotoxicity

In contrast to other toxicity tests, where effects are evaluated, genetic toxicology refers to potential effects. They are thought to be important steps in the development of adverse health effects, such as cancer but also in germinal cells the induction of mutations can result in increased frequencies of genetic diseases or even in the introduction of new genetic diseases into the human gene pool. Therefore genotoxicity testing is an important part of the preclinical assessment of (herbal) medicinal products.

While the term “mutagenic” refers to substances which are seen to cause detectable permanent changes within a single gen/block of genes or its/their regulating sequence(s), the term “genotoxic” represent a broader term which refers to any deleterious change in in the genetic material regardless of the mechanism by which the change is induced (Maurici et al., 2005a). A number of short-term tests are available and necessary to the assessment of the genotoxic potential, to cover different endpoints.

In the Guideline EMEA/HMPC/32116/2005 it is stated that the genotoxic potential of a traditional herbal substance/preparation should be assessed. If the information available in literature is insufficient tests have to be performed, starting with in-vitro tests and here initially with a bacterial reverse mutation test using a test battery of different bacterial strains and metabolic activation. Further considerations are described below.

4. Carcinogenicity

Carcinogenic substances induce tumours (benign or malignant), increase their incidence or malignancy, or shorten the time of tumour occurrence (Maurici et al., 2005b). While genotoxic carcinogens interact directly with the DNA, non-genotoxic carcinogens are, at least initially, devoid of direct interaction with DNA but indirect alter DNA structures, amount or function and may so result in altered gene expression and/or signal transduction (OECD, 2007). It is known from animal studies that most potent mutagens are also found to be carcinogenic and it is anticipated substances that induce tumours in animals in relevant exposures are considered (presumed or suspected) human carcinogens until convincing evidence to the contrary is presented in humans. Conventional test to detect carcinogenicity in animals are long-term (2-years) rodent carcinogenicity bioassays.

In the Guideline EMEA/HMPC/32116/2005 it is stated that for traditional herbal medicinal products carcinogenicity studies are not needed if no suspicion for a carcinogenic potential could be derived from literature data and knowledge about chemical structures of constituents contained in the herbal substance/preparation. In the Guideline are also several considerations mentioned which should be taken into account if a suspicion exist. Such consideration should be used to clarify the reasons for a possible carcinogenic effect. For instance is it important to reflect in the planning of further steps if the suspicion is based on genotoxicity studies and if such suspicions can it be clarified in further genotoxicity studies (mainly in-vivo).

5. Reproductive and developmental toxicity

Investigations on toxicity to reproduction include toxic effects of a substance on reproductive ability of an organism and development of its offspring reproductive toxicity. Toxicity in this field may lead to structural and/or functional alterations that may affect reproductive competence in sexually mature males and females (impairment of fertility, parturition or lactation) or to adverse effects induced prior to attainment of adult life including effects induced or manifested in the embryonic or foetal period and postnatal. A combination of different studies should allow exposure of mature adults and all stages of development from conception to sexual maturity as well as detection of immediate and latent effects of exposure (complete life cycle, i.e., from conception in one generation through conception in the following generation).

In the Guideline EMEA/HMPC/32116/2005 it is stated that for traditional herbal medicinal products investigations regarding fertility generally are not necessary. A more detailed assessment would be necessary if literature reports on hormone-like actions or on a traditional use for regulating fertility. The reproductive toxicological potential with regard to embryo-foetal and peri-postnatal development should be assessed. It was anticipated that literature data will often be incomplete or not reliable. However, a repetition of tests is only required in cases in which the significance of the results is not clear and if there are reasons for suspicion, e.g. positive signals described in literature (from non-clinical or clinical studies, epidemiological studies, post-marketing and traditional use experience). Furthermore in the Guideline are several cases are listed, for which tests in animals are not necessary, for instance: the assessment of the results of a systematic and comprehensive scientific literature search and post-marketing experience does not identify a positive signal of reproductive toxicity and the herbal medicinal product is not intended to be used during pregnancy and lactation.

6. Missing data for safety evaluation

From the experience of the HMPC in connexion to the development of Community Monographs or from the experience