



European Medicines Agency  
*Pre-authorisation Evaluation of Medicines for Human Use*

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**COMMITTEE FOR HUMAN MEDICINAL PRODUCTS  
(CHMP)**

**CHMP SCIENTIFIC ARTICLE 5(3) OPINION ON  
THE POTENTIAL RISKS OF CARCINOGENS, MUTAGENS AND  
SUBSTANCES TOXIC TO REPRODUCTION WHEN THESE  
SUBSTANCES ARE USED AS EXCIPIENTS OF MEDICINAL  
PRODUCTS FOR HUMAN USE**

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## EXECUTIVE SUMMARY

The EMEA received on 17 October 2006 a request from the European Commission (EC) for the CHMP to draw up an opinion on the basis of Articles 5(3) and 57(1) of Regulation (EC) No 726/2004, on the potential risks of carcinogens, mutagens and substances toxic to reproduction (CMR) when these substances are used as excipients of medicinal products for human use.

This request was considered by the CHMP and its relevant Working Parties.

The current legal and regulatory framework establishes the basis for the safe use of excipients in medicinal products.

In the vast majority of medicinal products in the EU, well-known, established, standard excipients are used in the formulations of medicinal products, and these are described in the European or the National pharmacopoeias. The accumulated safety data for these established substances is already comprehensive, and is largely confirmed by many years of use in patients.

When a new excipient is introduced on the market, it has to be appropriately characterised by physico-chemical means and evaluated by general toxicity studies, genotoxicity (including mutagenicity), reproductive toxicity and for chronic administration carcinogenic potential, according to the Directive 2001/83/EC, as amended, and its Annex I. As for any active substance, the principles of risk-benefit assessment apply to excipients included in medicinal products.

In the event that CMR toxicity has been identified for an excipient, the rule is to avoid and replace this excipient. In the rare cases where this would not be possible, the use of such CMR excipients in a medicinal product would only be considered after careful evaluation of the benefits of the medicinal product in the target patient population versus the potential risks.

As a matter of fact, in over 400 dossiers evaluated within the Centralised procedure during the last 12 years, there has been only one identified case of a (new) excipient with potential genotoxic properties for which the risks were addressed during the normal evaluation process.

Following discussion by CHMP at the October 2007 plenary meeting, the opinion of the CHMP may be summarised as follows:

Directive 2001/83 EC and Directive 78/25/EEC and/or 94/36/EC as amended and several guidelines support the rigorous evaluation for safe use of excipients in medicinal products.

The benefit-risk evaluation is a continuous process where new data on the safety of medicinal products and/or their excipients are regularly supplied and evaluated. Should any safety concern arise from this evaluation, appropriate safety measures would be taken on the concerned medicinal product(s) consistent with the current legal and regulatory framework in order to protect public health.

## 1 INTRODUCTION

### 1.1 The European Commission Request

The EMEA received on 17 October 2006, a request from the European Commission (EC) for the Committee for Medicinal Products for Human Use (CHMP) to draw up an opinion on the basis of Articles 5(3) and 57(1) of Regulation (EC) No 726/2004, on the potential risks of carcinogens, mutagens and substances toxic to reproduction when these substances are used as excipients of medicinal products for human use.

This request was also included as a Commission Statement (OJ L378, 27.12.2006, p.19) with the Regulation (EC) No 1901/2006 of 12 December 2006 on medicinal products for paediatric use, where it was stated that:

*'In view of the risks of carcinogens, mutagens and substances toxic to reproduction, the Commission will request the Committee for Medicinal Products for Human Use of the European Medicines Agency to draw up an opinion on the use of these categories of substances as excipients of medicinal products for human use, on the basis of Articles 5(3) and 57(1)(p) of Regulation (EC) No 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.*

*The Commission will transmit the opinion of the Committee for Medicinal Products for Human Use to the European Parliament and the Council.*

*Within six months of the opinion of the Committee for Medicinal Products for Human Use, the Commission will inform the European Parliament and the Council of any necessary action it intends to take to follow-up on this opinion.'*

The contents of this opinion as requested by the European Commission (EC) will be restrained to those excipients that are used in medicinal products for human use.

### 1.2 Definition of an excipient

The CHMP Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (CHMP/QWP/39695/2006) defines excipients as the constituents of a pharmaceutical form that are not the active substance.

Excipients include e.g. fillers, disintegrants, lubricants, colouring matter, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances as well the constituents of the outer covering of the medicinal products, e.g. gelatine capsules.

In general, it is important to realise that excipients are necessary ingredients of medicinal products. In some cases they are essential ingredients in order to ensure the stability of the active substance, or to protect against adventitious contamination during use, or to optimise the delivery or the kinetics of the active substance and therefore have an important effect on bioavailability.

### 1.3 The CHMP action plan

In the light of the European Commission request received in October 2006, the CHMP, in its meeting in November 2006, discussed and agreed an action plan, where it was stated that the following would be addressed:

- The legal and regulatory framework addressing the evaluation of excipients used in medicinal products for human use, including legal provision, scientific and technical requirements,
- Existing guidelines and other scientific CHMP documents in which the safety of excipients is discussed,
- Examples of safety measures already taken for some excipients included in marketed medicinal products,
- Conclusions

It was also agreed that the CHMP Working Parties to be involved in this scientific opinion would be: the Quality Working Party (QWP), Biotechnology Working Party (BWP) and the Safety Working Party (SWP).

The other group consulted was the Pharmacovigilance Working Party (PhVWP).

## 1.4 Objectives

The objectives of this scientific opinion according to Articles 5(3) and 57(1) of Regulation (EC) No 726/2004 will be the review of the current scenario of the evaluation of excipients used in medicinal products for human use within the current legal and regulatory framework. In this context, the possible conditions of use of a carcinogen, mutagen or substance toxic to reproduction (CMR) as excipient in a medicinal product will be discussed.

The recent Regulation (EC) No 1901/2006 of 12 December 2006 on medicinal products for paediatric use, which came into force in January 2007, also calls for further attention to the evaluation of excipients to be used in paediatric formulations.

Finally proposals for any further follow-up actions and the actual need for their implementation will be considered.

## 2 METHODOLOGY

A review of the current system of evaluation of medicinal products and its constituents (active substance and excipients) in the EU was performed taking into account the current legal requirements. The scientific opinion was lead by the Safety Working Party with involvement of several other working parties as well as EMEA experts on quality and safety of medicines.

## 3 RESULTS

### 3.1 Legal and regulatory framework

#### 3.1.1 Legal Background

The legal requirements for marketing authorisation applications of medicinal products for human use are set down in Directive 2001/83/EC, as amended (by Directive 2004/27/EC) and its Annex I (Directive 2003/63/EC).

In the Directive, the requirements for excipients are described in relation to:

- the product information. Article 11 states that the summary of the product characteristics shall contain in section 6.1 the list of excipients. Also, the package leaflet shall be drawn up in accordance with the summary of the product characteristics as stated in Article 59.
- the manufacturing: Article 46(f) second paragraph, states that GMP principles shall be applicable to certain excipients, the list of which as well as the specific conditions of application shall be established by a Directive adopted by the Commission in accordance with the procedure referred to in Article 121(2).
- the particulars to appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging. Article 54 states in paragraph (d) that: "*a list of those excipients known to have a recognized action or effect and included in the detailed guidance published pursuant to Article 65. However, if the product is injectable, or a topical or eye preparation, all excipients must be stated;*"
- the information contained in the package leaflet as describe in Article 59, where reference is also made to the detailed guidance published pursuant to Article 65.

Furthermore, Article 65 states that: "In consultation with the Member States and the parties concerned, the Commission shall draw up and publish detailed guidance concerning in particular: ...*(e) the list of excipients which must feature on the labelling of medicinal products and the way in which these excipients must be indicated;* (see section Quality guidelines)

The detailed scientific and technical requirements of an application of marketing authorisation are described in Annex I to Directive 2001/83/EC.

It is important to highlight in this context, the requirements for the control of excipients in Module 3 section 3.2.2.4 (d), regarding novel excipients:

*“For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.”*

and

*“Additional information on toxicity studies with the novel excipient shall be provided in Module 4. Clinical studies shall be provided in Module 5.”*

The requirements for Module 2 (2.4 non-clinical overview) are that *“any novel excipient shall be the subject of a specific safety assessment.”*

In Module 4, section 4.2(3), it is stated that *“The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.”*

Concerning established excipients in general, many of these are the subject of monographs in the European Pharmacopoeia (PhEur) and have been in use for many years. It is a legal requirement according to Directive 2001/83/EC as amended that such excipients which are used must comply with the relevant PhEur monograph.

In addition, specific requirements for colouring agents are set down in Directives 78/25/EEC and/or 94/36/EC as amended.

### 3.1.2 Regulatory Background

As stated in the introduction and general principles, paragraph (4), of Annex I to Directive 2001/83/EC, as amended, *“In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.”*

#### Quality guidelines

It is a general principle in the evaluation of pharmaceutical formulations that the presence of each excipient must be justified both in qualitative (functional) terms and quantitative terms (optimal amount). This principle is contained in the ICH Q8 Note for Guidance on Pharmaceutical Development (CHMP/ICH/167068/04). An explanation of the choice of the excipient (and grade where necessary) should be provided. Compatibility of excipients with other excipients and active substances should be established.

The guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (CHMP/QWP/396951/06) outlines the information that must be provided and emphasises the quality standards that are expected for the non-“active substance” part of a formulation. This is a key guideline on the quality aspects of excipients, and deals with both established and novel excipients.

This guideline sets out the principle that it is not usually necessary to carry out identity testing and an assay of the excipients in the finished product at release. However, antioxidants and antimicrobial preservatives (and any other important functional excipient), should comply with the requirements outlined in the ICH guideline mentioned above and should be identified and quantitatively controlled in the product specifications.

It should be noted that this guideline makes no specific mention of the safety issues concerning the use of certain excipients. This is addressed in a separate Commission guideline on specific safety warnings relating to excipients: “Excipients in the Label and Package leaflet of Medicinal Products for Human Use” (Eudralex 3BC7A) (see below).

The guideline CPMP/ICH/283/95 on residual solvents prohibits the use of known toxic solvents (e.g. benzene) in the manufacture of medicinal products and excipients and aims to control the use and limits of other solvents from a safety point of view. This is a joint Quality/Safety guideline.

### Safety guidelines

#### *General principles*

For an excipient used for the first time in the pharmaceutical field, toxicology and pharmacokinetics should be investigated, as stated in the basic principles and requirements for Module 4 Non-clinical reports set out in Annex I of the Directive, and also in the SWP Note for Guidance on Repeated Dose Toxicity.

In addition the mentioned Note for Guidance also states that in principle, the same pivotal studies as for a new active substance should be performed for a new excipient, and that in certain cases, studies with the active substance together with the excipient(s) used in the final product may also be needed. In particular safety pharmacology studies with the finished (final) product should be conducted for formulations that substantially alter the pharmacokinetics and/or pharmacodynamics of the active substance in comparison to formulations previously tested (i.e. through essential excipients such as penetration enhancers, liposomes and other changes such as polymorphism).

In the case of vaccines, documentation is provided to support the safety of adjuvants and preservatives (e.g. by using mock vaccines i.e. vaccine formulation without antigen).

#### *Local tolerance*

In general, local tolerance is to be determined at those sites which come into contact with the medicinal product (both active substances and excipients). Commission Directive 2003/63/EC specifies that local tolerance testing is conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). In planning local tolerance testing, the Note for Guidance on Non-Clinical Local Tolerance Testing states that the pharmacodynamic, toxicological and pharmacokinetic data for the active substance(s) and excipient(s) should be taken into consideration.

The design of these local tolerance tests (choice of species, duration, frequency and route of administration, doses) will of course depend upon the proposed conditions of administration in clinical use, the potential toxicity and the reversibility of the local lesions. For substances applied to the skin (e.g. dermal, rectal, vaginal), currently available test systems investigating the sensitising potential is also required.

### Labelling guideline

The Commission Guideline "Excipients in the Labelling and Package Leaflet of Medicinal Products for Human Use" (Eudralex 3BC7A, July 2003), contains warning statements to be included in the presence of certain excipients known to have a recognised action or effect, which is important for the safe and effective use of the medicinal product. The Annex of this guideline contains information on the route of administration, the threshold of effect, and safety information of listed excipients. It provides a list of the excipients that should be stated on the labelling and also outlines the information which should appear in the package leaflet, for these excipients.

A list of relevant guidelines is provided in this document (see section 6: References).

## **3.2 Evaluation process**

### *3.2.1 Quality evaluation*

The CHMP Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (CHMP/QWP/39695/2006) defines excipients as the constituents of a pharmaceutical form that are not the active substance. It also describes the information that needs to be submitted in relation to excipients including antioxidants and antimicrobial preservatives, in the context of applications for or variations to marketing authorisations processed according to the centralised procedure.

Whatever the function of an excipient, its presence must always be justified in a given formulation, and the smallest amount must be used in order to achieve the desired function. Since it is acknowledged that some excipients are not completely inactive with regard to pharmacological activity (e.g. penetration enhancers), the acceptability of the excipients used in the formulation is judged on the basis of the overall benefit/risk analysis, taking into account the intended patient population, the seriousness of the indication etc. Particularly in medicines for paediatric use, it is good pharmaceutical practice to reduce the number and levels of excipients to a minimum or to reformulate to a pharmaceutical form where they are not necessary. (See also section non-clinical safety evaluation).

### 3.2.1.1 General requirements

With regard to the pharmaceutical development of the medicinal product covered in Module 3 of the Marketing Authorisation Application (MAA), the requirements for the chemical, pharmaceutical and biological information for the active substance(s) as well as excipients are outlined. This Module of the MAA is expected to supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.

Where the excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant is highly recommended (but not obliged) to apply for a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines (EDQM), is expected to be presented in the MAA (Module 3). However if the excipient(s) are described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, Commission Directive 2003/63/EC states that compliance with the monograph of a third country pharmacopoeia is considered as being acceptable. In such a case, the applicant is expected to submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph.

In the case of a novel excipient, the amount of information required is much more comprehensive than for an established excipient. The basic principles and requirements are outlined for supplying such detailed information on any new excipients incorporated in the formulation of the finished medicinal product.

For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data, both non-clinical and clinical, are expected to be provided according to the active substance format and to be presented as a stand-alone document. Additional information on toxicity studies with the novel excipient is expected to be provided in the non-clinical (Module 4) part of the dossier.

### 3.2.2 *Safety evaluation before placing on the market (pre-authorisation)*

#### 3.2.2.1 General principles for quality

##### Standard, Established Excipients

It is important to emphasise that in the vast majority of medicinal products in the EU, applicants of Marketing Authorisations use well-known, established, standard excipients in their formulations, and these are described in the PhEur or the National pharmacopoeias. The accumulated safety data for these established substances is already comprehensive, and has been confirmed by many years of use in patients. Some general monographs, other than individual monographs on substances, are applicable to established excipients described in the PhEur. In particular, the PhEur general monograph on Substances for Pharmaceutical Use is applicable to active substances as well as excipients that are the subject of individual monographs. The requirements in this general monograph should be read in conjunction with individual monographs on substances, in the Pharmacopoeia. Information on the quality and possible use of excipients used in particular kinds of preparations or dosage forms can also be found in other general monographs, such as Homeopathic preparations, Eye preparations, Extracts etc.

From both a quality and safety point of view, compliance with the PhEur monograph is generally taken as proof of acceptable quality and safety without further detailed evaluation. Therefore, such established excipients are generally not assessed.



However, there may be departures from this general acceptance:

1. A standard excipient with an established use is used in a new route of administration.

E.g. Lactose PhEur is an established tableting excipient for oral use, but it has more recently been used in dry powder inhalers resulting in pulmonary exposure. Consequently there have been some reports of allergic reactions to lactose by this new route of administration.

A more detailed assessment of the quality characteristics of this milk sugar, also taking into account the manufacturing process, has revealed that the reactions could be due to residual milk proteins not removed by the purification process during manufacture. Therefore, manufacturing conditions should also be considered.

2. A standard excipient is used in an established context, but at a different (higher) concentration

For example preservatives and antioxidants in liquid formulations are normally used at accepted levels which have been developed over the years and are described in the standard textbooks such as Martindale, etc. Higher than normal levels, for whatever reason, need to be assessed from a safety point of view if it is not possible to reduce them.

3. A standard excipient is used in an established context but in a different patient population

For example an excipient may be shown to be safe in adults, but when present in a formulation for paediatric use, its safety profile would need to be reassessed for this new (and possibly more sensitive) patient population.

#### Novel Excipients

Due to the need for more focussed or targeted drug delivery and evolution of new technology to meet these needs, it is becoming more common now for companies to develop more sophisticated delivery systems utilising new excipients which have a more active role, e.g.

- polymers to control the release of the active substance from the formulation in the body with consequent effects on disposition and kinetics.
- liposome stabilising agents which also determine the disposition and clearance kinetics

According to current EU legislation, such novel excipients which are used for the first time in medicines must be subjected to a full evaluation, similar to new active substances. Indeed they are new substances, even if not active in the way that the active substance is. Applicants must provide full data on manufacturing, quality control, reproducibility of purity and important functional characteristics, animal toxicology etc., and these data are evaluated in order to confirm acceptable quality and safety.

As an example, there was one case (out of over 400 centrally authorised products) of a cyclodextrin excipient in an antifungal product formulated as a powder for solution for infusion. The particular excipient, sulphobutylether beta cyclodextrin sodium (SBECD), was found to contain an impurity which is a potential genotoxic carcinogen. In this particular case of a potentially harmful excipient, since there was no other suitable cyclodextrin and since it was not possible to remove this impurity completely, the CHMP required the applicant to reduce as much as possible the levels of this genotoxic substance in the medicinal product. Then, following a comprehensive review of the available safety data, a positive opinion was reached, based on the judgement that the favourable benefit/risk balance for the medicinal product as a whole outweighed the potential safety concern over the excipient in this particular case.

#### 3.2.2.2 Non-clinical safety evaluation

According to the Directive 2001/83/EC, as amended, and its Annex I, any new excipient should be appropriately characterised by physico-chemical means and evaluated by general toxicity studies, genotoxicity (which includes mutagenicity), reproductive toxicity and for chronic administration carcinogenic potential. As for any active substance, the principles of risk-benefit assessment apply to excipients included in medicinal products. Where deemed necessary, additional non-clinical safety studies may be requested by the CHMP during the course of the evaluation.

For excipients known/suspected to cause toxicity to reproductive function their inclusion in a pharmaceutical product should take into consideration the intended patient population (age, reproductive status, specific susceptibilities), the reversibility of the effects and the intended duration of the treatment. The reproductive status of the target population (developing, non-fertile) needs special consideration when deciding on the acceptability of a potentially reprotoxic excipient.

In the rare case where a genotoxic excipient would need to be included in a pharmaceutical product because it is necessary and cannot be substituted (see above the example of cyclodextrin), the risk would be weighed against the clinical benefit, taking into consideration the duration of exposure and the seriousness of the disease.

For non-genotoxic rodent carcinogens (which are known to be around 50% of molecules tested in life span rodent carcinogenicity studies) only those for which the mechanism of tumorigenesis (including the route of administration) has been identified as relevant for man, should be carefully considered before a decision is taken to include them in a pharmaceutical product. It is important to highlight that many of the substances positive in the carcinogenicity studies are specific rodent carcinogens with no relevance to humans. In addition, the 'safety ratios' (e.g. the relation between the exposures that were tumorigenic in rodents and those to be reached in patients) should be taken into consideration.

Therefore, in the event that CMR toxicity has been identified for an excipient, the rule is to avoid and replace this excipient. In the rare case where this would not be possible, the use of such CMR excipients in a medicinal product would only be considered after careful evaluation of the benefits of the medicinal product in the target patient population versus the potential risks.

### 3.2.2.3 Safety evaluation after placing the product on the market

When a medicinal product is placed on the market, new information about its undesirable effect under normal conditions of use needs to be collected, collated and evaluated. For this purpose, pharmacovigilance and risk management systems were established.

The setting up of a pharmacovigilance system is a legal obligation according European pharmaceutical legislation (Directive 2001/83/EC, as amended and Regulation (EC) No 726/2004). The pharmacovigilance requirements apply to both medicinal products and excipients which are included in medicinal products (see reference: Eudralex, Volume 9A).

A risk management system, which includes routine pharmacovigilance activities and in most cases a risk management plan, is required for any new marketing authorisation. The risk management plan may contain a list of studies to further characterise known or potential risks, as well as a plan for risk minimisation activities.

If there is a known potential for mutagenicity, carcinogenicity, or for an effect on human reproduction, then a risk management plan is always required. Risk minimisation measures, like pregnancy prevention programmes and birth registries should be put in place. In general, such risks are acceptable only for active substances or essential excipients in medicinal products used in life-threatening indications without safer alternatives. In other situations, such excipients would not be accepted. For example, some glycol ethers which were used as excipients in topical medicinal products raised safety concerns in relation to their toxicity to the reproduction based on clinical and non-clinical data generated after their national marketing authorisation. Consequently pharmacovigilance measures were taken (removal from the national market) in relation to this toxicity.

Risk management plans are regularly updated, usually at the time of Periodic Safety Update Reports submission, when an important milestone of a planned action is reached, or when a new important safety concern arises.

## 4 DISCUSSION

As explained in this document, the pharmaceutical legal and regulatory context and the evaluation process imply that similar principles of risk assessment are applied to excipients as for active substances when appropriate. However excipients have only an indirect benefit for the patient, as part of a medicinal product. Therefore any risk identified for an excipient and in particular a CMR substance, would be acceptable only on condition that this excipient cannot be substituted with a safer

available alternative, or that the toxicological effects in animal models are considered not relevant for humans (e.g. species specific, very large safety ratio), or where the overall benefit/risk balance for the product outweighs the safety concern with the product.

Overall, the use of any excipient with a known potential toxicity, and which could not be avoided or replaced, would only be authorised if the safety profile was considered to be clinically acceptable in the conditions of use, taking into account the duration of treatment, the sensitivity of the target population and the benefit-risk ratio for the particular therapeutic indication.

## **5 RECOMMENDATIONS**

Directive 2001/83 EC and Directive 78/25/EEC and/or 94/36/EC as amended and several guidelines support the rigorous evaluation for safe use of excipients in medicinal products.

The benefit-risk evaluation is a continuous process where new data on the safety of medicinal products and/or their excipients are regularly supplied and evaluated. Should any safety concern arise from this evaluation, appropriate safety measures would be taken on the concerned medicinal product(s) consistent with the current legal and regulatory framework in order to protect public health.

## **6 REFERENCES**

### **QUALITY GUIDELINES**

Impurities: Residual Solvents (ICH Q3C)

CPMP/ICH/ 283/95-ICH Q3C (R3)

<http://www.emea.europa.eu/pdfs/human/ich/028395en.pdf>

Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product

CHMP/QWP/396951/06

<http://www.emea.europa.eu/pdfs/human/qwp/39695106enfin.pdf>

Pharmaceutical Development (EMEA/CHMP/167068 /2004-ICH Q8)

<http://www.emea.europa.eu/pdfs/human/ich/16706804en.pdf>

Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials

CHMP/QWP/185401/2004

<http://www.emea.europa.eu/pdfs/human/qwp/18540104en.pdf>

Summary of Requirements for Active Substances in the Quality Part of the Dossier

CHMP/QWP/297/97 Rev. 1

<http://www.emea.europa.eu/pdfs/human/qwp/029797en.pdf>

Reflection Paper on the formulations of choice for medicinal products for paediatric use

<http://www.emea.europa.eu/pdfs/human/peg/19481005en.pdf>

Impurities in new drug products (Revision)

CPMP/ICH/2738/99

<http://www.emea.europa.eu/pdfs/human/ich/273899en.pdf>

## **LABELLING GUIDELINE**

Excipients in the label and package leaflet of medicinal products for human use  
(EUDRALEX 3BC7A)

[http://www.emea.europa.eu/pdfs/human/productinfo/3bc7a\\_200307en.pdf](http://www.emea.europa.eu/pdfs/human/productinfo/3bc7a_200307en.pdf)

## **NON CLINICAL GUIDELINES**

Safety pharmacology studies for human pharmaceuticals (ICH S7A)  
CPMP/ICH/539/00

<http://www.emea.europa.eu/pdfs/human/ich/053900en.pdf>

Single dose toxicity  
EUDRALEX 3BS1A

<http://www.emea.europa.eu/pdfs/human/swp/3bs1aen.pdf>

Repeated dose toxicity  
CPMP/SWP/1042/99

<http://www.emea.europa.eu/pdfs/human/swp/104299en.pdf>

Non-clinical local tolerance testing of medicinal products  
CPMP/SWP/2145/00

<http://www.emea.europa.eu/pdfs/human/swp/214500en.pdf>

Pre-clinical pharmacological and toxicological testing of vaccines  
CPMP/SWP/465/95

<http://www.emea.europa.eu/pdfs/human/swp/046595en.pdf>

Comparability of medicinal products containing biotechnology-derived proteins as active substance -  
annex on non-clinical and clinical issues

CPMP /3097/02

<http://www.emea.europa.eu/pdfs/human/ewp/309702en.pdf>

## **PHARMACOVIGILANCE GUIDELINES**

EUDRALEX Volume 9A. The Rules Governing Medicinal Products in the European Union  
– Guidelines on Pharmacovigilance for Medicinal Products for Human Use –

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