Vorwort zur 39. Aktualisierungslieferung

Die 39. Aktualisierungslieferung enthält im nationalen Teil die neue Klinische Prüfung-Bewertungsverfahren-Verordnung – KPBV sowie diverse Stellungnahmen des Arbeitskreises Blut, u. a. zur Vorgehensweise bei Variante Creutzfeldt-Jakob-Krankheit (vCJK) im Zusammenhang mit Blut, Plasma und Blutprodukten und zu Pathogen-Inaktivierungssystemen für Thrombozytenkonzentrate. Weiterhin wurden die Übersichten über die Bescheide des Paul-Ehrlich-Instituts (PEI) im Bereich Hämovigilanz und über die Bewertungen des Arbeitskreis Blut von Krankheitserregern, die durch Blut übertragen werden, auf den neuesten Stand gebracht.

Im Bereich der EU sind diverse neue oder revidierte Guidelines erschienen, unter anderem zur Qualitätsdokumentation für klinische Prüfpräparate, zu Biosimilars mit rekombinatem Erythropoietin bzw. mit Somatropin und zu Qualitäts-, präklinischen und klinischen Aspekten von Gentherapeutika. Die alphabetische Liste zu Produkt-spezifischen Bioäquivalenzleitlinien wurde aktualisiert. Eine neue ICH-Leitlinie befasst sich mit der Planung und dem Design multiregionaler klinischen Prüfungen

Erwähnung verdienen außerdem einige neue und aktualisierte europäische Leitlinien zur klinischen Prüfung für bestimmte therapeutische Klassen, darunter zum Morbus Crohn, zu onkologischen Arzneimitteln, Alzheimer-Präparaten und Arzneimitteln gegen Autismus, ulzerative Colitis, zur Respiratory Syncytial Virus (RSV)-Erkrankung und zur rheumatoiden Arthritis.

Weiterhin aufgenommen wurden einige EU-Leitlinien zu Tierarzneimitteln, u. a. zur Chemie von Wirkstoffen, zur Bewertung von Umwelt-und Gesundheitsrisiken für den Menschen durch Tierarzneimittel im Grundwasser und zur Kontrolle von Element-Verunreinigungen in Tierarzneimitteln. Darüber hinaus enthält diese Lieferung eine aktualisierte Liste der Substanzen, die nicht von der Verordnung über die Festlegung von Grenzwerten für Tierarzneimittelrückstände in Lebensmitteln ((EC) No. 470/2009) erfasst sind.

Ferner wurden vierzehn aktualisierte oder neue europäische Pflanzenmonographien (European Union/Community herbal monographs) aufgenommen.

Einen wichtigen Mehrwert schafft das Kompendium durch seine Register. Diese wurden mit der vorliegenden Aktualisierungslieferung ebenfalls überarbeitet und ergänzt.

Remagen, im April 2019 Die Herausgeberin und Bearbeiterin

1.189 g Vorgehensweise bei Variante Creutzfeldt-Jakob-Krankheit (vCJK) bei Blut, Plasma und Blutprodukten (Votum 46)

Bundesgesundheitsbl 2018 · 61:1052–1057

Bei der 85. Sitzung des Arbeitskreises Blut am 18.04.2018 wurde folgendes Votum (V46) (Aktualisierung des Votums 33) verabschiedet:

Die Variante Creutzfeldt-Jakob-Krankheit (vCJK) ist bisher die einzige Erkrankung humaner transmissibler spongiformer Enzephalopathien (TSE), für die eine Übertragbarkeit durch Blut, Blutprodukte und Plasma als sehr wahrscheinlich gilt. Für alle anderen TSE werden ausschließlich andere Übertragungswege berichtet.
Durch das nachfolgende Verfahren sollen Übertragungen von vCJK durch noch nicht angewendete Blutprodukte verhindert, weitere potentiell infektiöse Spenden vermieden und eventuell stattgefundene Übertragungen aufgeklärt werden.
Das Verfahren gilt, wenn

a) bei einem Spender oder einer Spenderin von Blut, Plasma oder anderen Bestandteilen aus Blut eine vCJK wahrscheinlich ist oder gesichert wurde.
b) bei einem Empfänger oder einer Empfängerin von Blut, Plasma oder Blutprodukten eine vCJK wahrscheinlich ist oder gesichert wurde.

1. Feststellung einer vCJK

Wird bei einer Person eine wahrscheinliche oder gesicherte vCJK festgestellt, soll vom behandelnden Arzt ermittelt werden, ob diese Person jemals Blut, Plasma oder andere Komponenten aus Blut gespendet (*Spender/in*) oder Blut oder Blutprodukte erhalten hat (*Empfänger/in*).
Die Erkrankung sollte durch ein ausgewiesenes Zentrum für spongiforme Enzephalopathien bestätigt worden sein. Gemäß § 6 Infektionsschutzgesetz muss der Krankheitsverdacht, die Erkrankung und der Tod an vCJK namentlich an das Gesundheitsamt gemeldet werden.
Eine kontinuierliche bundesweite Surveillance von CJK-Verdachtsfällen wird vom Nationalen Referenzzentrum für die Surveillance transmissibler spongiformer Enzephalopathien (NRZ TSE) realisiert. Angaben zum Blutspenderstatus des Verdachtsfalles bzw. zum Erhalt von Blutprodukten sollten als Teil der epidemiologischen Surveillance an das NRZ TSE übermittelt werden.

1.220

Stellungnahme zu Pathogen-Inaktivierungssystemen für Thrombozytenkonzentrate

Bundesgesundheitsbl 2018 · 61:874–893

Bei der 85. Sitzung des Arbeitskreises Blut am 17./18.04.2018 wurde folgende Stellungnahme (S 18) verabschiedet:

Abkürzungen

ATCC	American Type Culture Collection
ATK	Apherese-Thrombozytenkonzentrat/e
CCI	Corrected count increment
CE	CE-Kennzeichnung nach REGULATION (EU) 2017/745 [6]
DSM	Deutsche Sammlung für Mikroorganismen und Zellkulturen (Leibniz-Institut)
EK	Erythrozytenkonzentrat/e
HPLC	High Performance Liquid Chromatography
INTERCEPT™	INTERCEPT™ Blood System
ISBT	International Society for Blood Transfusion
LRF	log10 Reduktionsfaktor/en
MIRASOL®	MIRASOL® Pathogen Reduction Technology System
PBMC	Peripheral Blood Mononuclear Cells
PI	Pathogeninaktivierung
PTK	Pool-Thrombozytenkonzentrat/e
TA-GvHD	Transfusions-assoziierte Graftversus-Host-Disease
TBBI	Transfusionsbedingte Bakterielle Infektionen
THERAFLEX	THERAFLEX UV-Platelets system
TK	Thrombozytenkonzentrat/e
WHO	World Health Organization
AdV-5	Adenovirus Typ 5
B19V	Parvovirus B19
BFV	Barmah Forest Virus

2.68

Manufacture of the Finished Dosage Form*

July 2017

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* Doc. Ref. EMA/CHMP/QWP/245074/2015, this guideline replaces the "Note for Guidance on Manufacture of the Finished Dosage Form" (CPMP/QWP/486/95)

Executive Summary

This guideline replaces the note for guidance on the manufacture of the finished dosage form (CPMP/QWP/486/95). The note for guidance has been updated to reflect the requirements as laid down in the current legislation Directive 2001/83/EC, and to follow the format and content of the Common Technical Document (CTD) Module 3 dossier. It also addresses current manufacturing practices in terms of complex supply chains and worldwide manufacture. In addition, the content and principles of the ICH Q8 guideline [ref 1] are also taken into account.

This guideline does not introduce new requirements on authorised medicinal products for human use. However as stated in article 23 of Directive 2001/83/EC, after a marketing authorisation (MA) has been approved, the authorisation holder should, in respect of the methods of manufacture and control take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and controlled by means of generally accepted scientific methods.

1 Introduction (Background)

The objective of the guideline on the manufacture of the finished dosage form is to provide clarification on the type and level of information that should be included in the CTD Module 3 of the marketing authorisation application (MAA) dossier with respect to the manufacturing process description. This description should include information about critical steps and intermediates and provides a link between the pharmaceutical development, the proposed control strategy and process validation. The guideline also addresses aspects related to outsourcing and new manufacturing practices such as complex manufacturing chains or issues with prolonged holding times and transportation conditions. Detailed information about requirements of the sterilisation process is provided in a separate guideline.

2 Scope

This guideline is applicable to the manufacture of the finished dosage form of chemical and herbal medicinal products for human use intended for marketing authorisation. It also applies to variations for authorised products in cases where changes to the manufacturing process affecting the MA are proposed.

The principles described are in general also applicable to biological medicinal products. Where relevant, the principles of this guideline may also be applied to radiopharmaceuticals and to chemical investigational medicinal products.

3 Legal Basis

This guideline should be read in conjunction with Directive 2001/83/EC Article 8.3 (d), as amended where it is stated that the application for a marketing authorisation shall contain a description of the manufacturing method.

The requirements on the description of the manufacturing method in the CTD Module 3 of marketing authorisation dossier are described in Annex 1, Part 1 (section 3.2.2.3) to this Directive. Further details on the information to be provided are outlined in this guideline.

2.81b

Non-clinical and Clinical Development of Similar Biological Medicinal Products Containing Recombinant Erythropoietins

EMEA/CHMP/BMWP/301636/2008 Rev. 1

This is a technical update to reflect current best practise with regard to implementation of 3Rs approaches and it is not intended as a full revision of this guideline (only section 4 is affected). These changes are considered to be minor and uncontroversial and consequently a consultation phase was considered unnecessary.

June 2018

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Executive summary
The main aim of the guideline is to address the non-clinical and clinical requirements for recombinant human erythropoietin (epoetin)-containing medicinal products claiming to be similar to another one already marketed. The non-clinical section addresses the pharmaco-toxicological assessment and the clinical section the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as the risk management plan. Criteria for extrapolation of clinical data to other indications approved for the reference medicinal product are discussed.

1. Introduction (background)

Human erythropoietin is a 165 amino acid glycoprotein mainly produced in the kidneys and is responsible for the stimulation of red blood cell production. Erythropoietin for clinical use is produced by recombinant DNA technology using mammalian cells as expression system and termed epoetin.

All epoetins in clinical use have a similar amino acid sequence as endogenous erythropoietin but differ in the glycosylation pattern. Glycosylation influences pharmacokinetics and may affect efficacy and safety including immunogenicity. Physico-chemical and biological methods are available for characterisation of the protein.

Epoetin-containing medicinal products are currently indicated for several conditions such as anaemia in patients with chronic renal failure, chemotherapy-induced anaemia in cancer patients, and for increasing the yield of autologous blood from patients in a pre-donation programme. The mechanism of action of epoetin is the same in all currently approved indications but the dosages required to achieve the desired response may vary considerably and are highest in the oncology indications. Epoetin can principally be administered intravenously (IV) or subcutaneously (SC).

Epoetins have a relatively wide therapeutic window and are usually well tolerated provided that the stimulation of bone marrow is controlled by limiting the amount and rate of haemoglobin increase. The rate of haemoglobin increase may vary considerably between patients and is dependent not only on the dose and dosing regimen of epoetin but also other factors, such as iron stores, baseline haemoglobin and endogenous erythropoietin levels, and the presence of concurrent medical conditions such as inflammation.

Exaggerated pharmacodynamic response may result in hypertension and thrombotic complications. Moreover, pure red cell aplasia (PRCA) due to neutralising anti-epoetin antibodies has been observed, predominantly in renal anaemia patients treated with subcutaneously administered epoetin. Because antibody-induced PRCA usually is a very rare event taking months to years of epoetin treatment to develop, such events are unlikely to be identified in pre-authorisation studies. In addition, possible angiogenic and tumour promoting effects of epoetin might be of importance in selected populations.

The Marketing Authorisation (MA) application dossier of a new epoetin claimed to be similar to a reference product already authorised, shall provide the demonstration of comparable quality, safety and efficacy of the product applied for to a reference product authorised in the EU.

2.81d

Similar Medicinal Products Containing Somatropin

Annex to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
(EMEA/CHMP/BMWP/94528/2005 Rev. 1)

June 2018

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Executive summary
The main aim of the guideline is to address the non-clinical and clinical requirements for somatropin-containing medicinal products claiming to be similar to another one already marketed. The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as the risk management plan. Criteria for extrapolation of clinical data to other indications approved for the reference medicinal product are discussed.

1. Introduction (background)

The Marketing Authorisation (MA) application dossier of a new recombinant human growth hormone (rhGH, somatropin) claimed to be similar to a reference medicinal product already authorised shall provide the demonstration of comparability of the product applied for to a reference medicinal product authorised in the EU.

The principal bioactive human growth hormone (hGH) is a single chain non-glycosylated 191 amino acid, 22 kD polypeptide produced in the anterior pituitary gland. Growth hormone for clinical use has an identical amino acid sequence and is produced by recombinant technology using E. coli, mammalian cells or yeast cells as expression system. The structure and biological activity of somatropin can be characterised by appropriate physico-chemical and biological methods. Several techniques and bioassays are available to characterise both the active substance and product-related substances/impurities such as deamidated and oxidized forms and aggregates.

Growth hormone has potent anabolic, lipolytic and anti-insulin effects (acute insulin-like effect). The effects of GH are mediated both directly (e. g. on adipocytes and hepatocytes) and indirectly via stimulation of insulin-like growth factors (principally IGF-1). Somatropin-containing medicinal products are currently licensed for normalising or improving linear growth and/or body composition in GH-deficient and certain non GH-deficient states. The same receptors are thought to be involved in all currently approved therapeutic indications of rhGHs.

Somatropin has a wide therapeutic window in children during the growth phase whereas adults may be more sensitive for certain adverse effects. Antibodies to somatropin have been described, including, very rarely, neutralising antibodies. Problems have been associated with the purity and stability of the formulations. Somatropin is administered subcutaneously; possible patient-related risk factors of immune response are unknown.

In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on protection of animals used for scientific purposes, the 3R principles (replacement, reduction and refinement) should be applied to development of medicinal products.

2. Scope

The guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

2.86f

Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products

EMA/CHMP/BPWP/144533/2009 rev. 2

This guideline (EMA/CHMP/BPWP/144533/2009 rev. 2) replaces 'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products rev.1'

July 2018

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GLOSSARY
AUC – Area under the Curve
BU – Bethesda Unit
CI – Confidence Interval
E – Efficacy
ED – Exposure Day
HAART – Highly active anti-retroviral therapy
ITI – Immune Tolerance Induction
IU – International Units
MA – Marketing Authorisation
MAA – Marketing Authorisation Application
p-d – plasma-derived
PhVWP – Pharmacovigilance Working Party
PK – Pharmacokinetics
PMI – Post Marketing Investigation
PTP – Previously Treated Patient (defined as > 150 EDs)
PUP – Previously Untreated Patient
RMP – Risk Management Plan
S – Safety
SAE – Serious Adverse Event
TSE – Transmissible spongiformencephalopathy
SmPC – Summary of Product Characteristics
y – years

Executive summary
This guideline describes the information to be documented when an application for a marketing authorisation for recombinant or human plasma-derived factor VIII products is made for use in treatment and prevention of bleeding in patients with haemophilia A. The guidance covers clinical investigations to be conducted pre- and post-marketing authorisation. Guidance is also provided for authorised products where a significant change in the manufacturing process has been made.
Timeline history of guideline: The original Note for Guidance on Clinical Investigation of Human Plasma Derived FVIII and FIX Products (CPMP/BPWG/198/95) came into operation on 14 February 1996. The first revision (CPMP/BPWG/198/95 Rev. 1) came into operation in April 2001. The original Note for Guidance on Clinical Investigation on Recombinant FVIII and FIX Products (CPMP/BPWG/1561/99) came into operation in April 2001. Draft revisions of CPMP/BPWG/1561/99 and CPMP/BPWG/198/95 were released for public consultation in July 2007. Following this consultation, it was decided to reorganise the guidance to have separate documents: The Guideline on clinical investigation of recombinant and plasma derived factor VIII products (EMA/CHMP/BPWP/144533/2009) and the Guideline on clinical investigation of recombinant and plasma derived factor IX products (EMA/CHMP/BPWP/144552/2009). EMA/CHMP/BPWP/144533/2009 came into effect on 1 February 2012. Revision 1 is a rapid revision following the 2013 EMA/EDQM workshop on potency assays. In July 2015 an EMA workshop exploring on registries in hemophilia came to the recommendation that the clinical trial concept requiring PUP studies for FVIII products needs to be reconsidered. In light of increasing scientific knowledge

[1,2,3,4] the number of suitable patients especially previously untreated patients (PUPs) to be enrolled in clinical trials is problematic. Hence, the conduct of sufficiently informative clinical trials in PUPs to estimate important characteristics of single products is considered difficult. Therefore the obligation to perform clinical trials in PUPs for marketing authorisation purposes has been deleted. Furthermore, a core parameter set for registry data collection in Hemophilia is introduced. The opportunity is taken to make other minor editorial updates.

1. Introduction (background)

The purpose of this guideline is to provide applicants and regulators with harmonised requirements for applications for marketing authorisation for recombinant or plasma-derived factor VIII products.

In plasma, factor VIII occurs as a heterodimer, consisting of a light chain (domains A3, C1 and C2), and a heavy chain (domains A1 and A2) and domain B. The occurrence of an antibody against factor VIII, a so-called inhibitor, is the most important complication in haemophilia treatment. Inhibitors occur very commonly in previously untreated patients (PUP) with severe haemophilia A, usually within the first 50 exposure days.

These inhibitors have mainly been observed in previously untreated children, and approximately one third disappeared on continued treatment with the same product. It now appears that in cases in which inhibitors occur in PUP, patient related factors (certain types of mutations in the factor VIII gene, the family history for inhibitors and intensive treatment appear to be important determinants of inhibitor development. Patients treated with factor VIII products should be carefully monitored for the development of inhibitory antibodies by appropriate clinical observations and laboratory test.

Two inhibitor 'outbreaks' occurred in the early 1990's in previously tolerant patients who had been treated for a number of years following exposure to plasma-derived factor VIII products subjected to a modified virus inactivation method. Hence, the incidence of inhibitor formation may be affected by the specific product used for treatment and its potential for alteration of factor VIII molecules and generation of 'neoantigens'.

An EMA expert meeting on factor VIII products and inhibitor development was held in 2006 to provide a forum with experts from EU, USA, Japan and Canada, representatives from the International Society for Thrombosis and Haemostasis (ISTH), the World Health Organisation (WHO), patient organisations and industry to discuss the international standardisation and harmonisation of requirements for clinical studies on factor VIII inhibitor development in haemophilia A patients. The objective was to provide expert advice on the collection of meaningful and comparable clinical data on the immunogenicity of recombinant and plasma-derived factor VIII products in the future. The outcome of this meeting has been taken into account for the guidance provided within this document[1].

1 Report of Expert Meeting on Factor VIII Products and Inhibitor Development (EMEA/CHMP/BPWP/123835/2006) and publication in Haemophilia (see References)

2.94e

Good Pharmacogenomic Practice

EMA/CHMP/718998/2016

February 2018

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Executive summary
Genomic data have become important in the evaluation of efficacy and safety of medicinal products for regulatory approval. Genomic information in the product information (PI) influences patient treatment decisions. Therefore, use of genomic biomarkers in drug development, should, in order to be of value, follow certain principles which are outlined in this guideline.
This guideline provides recommendations for the conduct of genomic studies in relation to medical therapy in order to provide high quality information on the impact of genomic variability on drug response. Primary focus is on the analysis of genomic germline DNA. The analysis of somatic DNA and genomic biomarkers for cancer treatment is not being discussed and might be developed as an Annex or in separate guidance.
Some methodological issues with respect to genomic clinical study design highlighted in this guidance is complementary to the what is described in the *Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection* (see section 3).

1. Introduction (background)

There has been an increase in our understanding of how inter-individual differences in DNA sequences, or 'genetic variants', link to drug response. As a consequence, there is now the opportunity to incorporate the genomic information as a basis for an estimated individual response to drug treatment, leading to a transition from population-based prescribing with a one-size-fits all dosing to a more individualized treatment.
The identification of genomic variability for explaining or predicting the response of a patient to a specific medicinal product has focused mainly on variation in genes encoding: (i) drug-metabolizing enzymes (ii) drug transporters, and (iii) drug targets. For prediction of adverse drug reactions, the analyses of specific (host) HLA haplotypes also play an important role for specific medicinal products.
Often, previous studies in this area have not been optimally designed e. g. retrospective in nature, often driven by association alone and not causality or functionality, low statistical power and use of inappropriate technology (see Annex I). Thus, there is a need for a guideline addressing factors of importance to consider in pharmacogenomics investigations.

2. Scope

The document provides guidance on methods of evaluation of genetic variations related to pharmacokinetics and response, where this could affect efficacy and/or safety
The guidance primarily focusses on the analysis of genomic germline DNA and does not discuss somatic DNA and genomic biomarkers for cancer treatment, RNA variations, proteomics or metabolomics, which are outside the scope of this document, however some principles might apply.