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REGULATORY REQUIREMENTS FOR MARKETING AUTHOURIZATION OF GENERIC DRUGS AND COMPILATION OF DOSSIER FOR EUROPEAN MARKET IN CENTRALIZED PROCESS

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ABSTRACT

The EU has one of the most highly regarded regulatory systems in the world. The European Medicines Agency (EMA) is responsible for the scientific evaluation of centralized marketing authorization applications (MAA). Once granted by the European Commission, the centralized marketing authorization is valid in all European Union (EU) Member States. The system comprises of European parliament, the council of ministers, and the European Commission. EU consists of 27 member states: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom and three countries which are member of European. Free Trade Agreement (EFTA) Iceland, Norway, and Liechtenstein. These EFTA members are those countries which were unable to join rest of the 27 member states as common market. These three EFTA member countries along with 27 EU member states.

KEY WORDS: European market, Regulatory requirements, Generic drugs.

INTRODUCTION

In general there are 4 types of marketing authorization forthe drug product to enter into European Union drug market [1].
They are as follows,

A) Initial Marketing Authorisation

1. CENTRALISED PROCEDURE
2. MUTUAL RECOGNITION PROCEDURE
3. NATIONAL PROCEDURE
4. DECENRALISED PROCEDURE

1. CENTRALISED PROCEDURE

The 'centralized procedure' for authorizing medicinal products is laid down in Regulation (EC) No726/2004. The centralized procedure [2], which is compulsory for products derived from biotechnology, for orphan medicinal products (Fees Exemption will be given in this case) and for medicinal products for human use which contain an active substance authorized in the Community after 20 May 2004(date of entry into force of Regulation (EC) No 726/2004) [3]. And which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes. The procedure is also compulsory for the products which are used as performance enhancers or to increase yields from animals [4].

I) PRE-SUBMISSION

- a draft summary of product characteristics;
- Eligibility
- Strength
- Type of application
- Statement of intention to request for accelerated assessment
- Statement of whether Orphan designation valid or

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- Pending
- Proposed invented name
- Request for total or partial fee exemptions, etc.

When an applicant decides to apply to the EMA for the drug product authorization then at least seven months before the submission of application, the applicant should notify the EMEA of their intention to submit an application. So, the applicant will have the opportunity to meet the EMA's product team in person in a Pre-Submission meeting where the procedural, regulatory and legal advice will be provided to the applicant [5].

The applicant's request for eligibility for evaluation via the Centralized Procedure, together with a justification another documents is presented to all CHMP [Committee for Medicinal Products for Human Use] members. Following discussion at CHMP, the EMEA informs the applicant whether the product is eligible for evaluation via the Centralized Procedure. Amongst the members of CHMP a Reporter and a Co-Reporter will be appointed for the purpose of scientific evaluation and to prepare an Assessment Report for the CHMP on the application. This Assessment report will be submitted to the CHMP and EMA on DAY 80 where a peer review will be done by the members of CHMP for the validity of Scientific/Regulatory conclusions. A list of Questions raised by the CHMP along with the conclusions and review of scientific data will be sent to the applicant on DAY 120.At this point EMA stops the clock for giving time to applicant for responding to the data with proper responses. After receipt of the responses from the applicant, the CHMP adopts a timetable for the evaluation of the responses The EMEA ensures that the opinion of the CHMP is given in 90 additional days.

After the positive opinion of CHMP, the applicant provides the EMEA with final translations of the necessary documents in all EU languages and the clock resumes from this point. A draft decision will be prepared within fifteen days by the commission on the application, and then the medicinal product will be assigned by a Community registration number which will be placed on product's package if the authorization is granted. Finally, within 30 days the EMEA transmits the CHMP opinion and other required documents to the European Commission, and the Members of the Standing Committee ,and to Norway and Iceland. The applicant may go for the other procedures like Mutual Recognition Procedure (MRP) or the Decentralized Procedure (DCP) if the product does not fall within the mandatory scopes of the Centralized Procedure (CP).

Mutual Recognition Procedure

The Regulation for the mutual recognition procedure is laid down in Directive 2001/83/EC. The mutual recognition procedure is mandatory for all medicinal products to be marketed in a Member State other than they were first authorized, since 1 January 1998.The mutual recognition procedure is used in order to obtain marketing authorizations in several Member States where the medicinal product in question has received a marketing authorization in any of the Member State at the time of application.

Procedure for Mutual Recognition Procedure (MRP)

An application for this procedure can be sent to one or more Member States. The applications sent should be similar and all Member States must be informed of them. When a Member State decides to assess the application (at this point it becomes the "Reference Member State" RMS),it announces the decision to other Member States (which then become the "Concerned Member States" CMS), to whom applications have also been submitted by the applicant. At this juncture the CMS will suspend their evaluations on the particular application and waits for the RMS's decision on the application. Usually the procedure ends with the marketing authorization granted by the RMS after the evaluation of the application. In the other case RMS can be the country which had already approved the product; in such a case the RMS updates the existing assessment report in 90 days [6].

The updated report will be sent to all the member states along with the summary of product characteristics (SPC),labeling and package leaflet. After receiving the reports from RMS, the Concerned Member States will have 90days to recognize the decision made by the RMS on the report and the other documents. Upon the positive decision national marketing authorization will be granted in each of the CMS(s)

3. NATIONAL PROCEDURE

The national procedure is like the other procedures but in this case only one member state is involved. The documents submitted to an authority are very specific to that particular authority and evaluation of the application is carried out by the same member state. The evaluation time for an application for a national marketing authorization is 210 days from the receipt of the application. But this procedure is stringently limited from 1 January1998 to the early phase of mutual recognition (granting of the marketing authorization by the Reference Member State) and to medicinal products which are not to reauthorized in more than one Member State.

4. DECENTRALISED PROCEDURE

The new Decentralized procedure came into effect in the European Union in 2005 and is regulated by Directive2004/27/EC. The main purpose of this procedure is to acquire marketing authorizations in several Member States, even though there are no marketing authorization has been granted in the European area [7].

Steps involved in Decentralized procedure (DCP)

The applicant has to send an application to the respective authorities of each and every member States,

where there is plan to attain a marketing authorization. Unlike MRP, here the applicant may assign a country to act as the Reference Member State [8]. This selection can be based on many criteria like workload, previous experience, interests of the applicant and acceptance of the applied dossier by the RMS. The RMS will commence the assessment after the application is decided to be complete by both the RMS and all the CMS(s). The RMS then forwards a preliminary Assessment Report on the submitted dossier to the CMS(s) and the applicant in a period of 70 days. The CMS(s) is requested to give comments on the proposed national prescription status and to inform the RMS. On day 105, the RMS will forward all observation and remarks from the CMS(s) to the applicant and stops the clock if necessary, until the applicant prepares a response document for the comments sent. The RMS prepares a Draft Assessment Report on day 120 and may close the procedure if a consensus has been reached between the CMS(s) and the RMS. Otherwise the CMS(s) has 90 more days to approve the Draft Assessment Report, and other documents.

Authorities of the RMS and the CMS(s) agree to a decision within 30 days after acknowledgement of their agreement to the Assessment Report and other documents. Upon the positive agreement, a national marketing authorization will be issued in the RMS and each of the CMS(s) [9].

PRODUCT REGISTERATION OVERVIEW IN EU THROUGH CENTRALIZED PROCESS

Regulatory requirement for the approval of the medicinal drug in European Union was found to be more rigid. types of applications which will specify the product and time frame required for the approval of the drug which helps in tracking of life of the respective product The retaining of the current marketing authorization systems, DCP together with scope of CP provide a great flexibility of the choice between different marketing authorizations and also allowed to go for the national application of medicinal product To harmonies and fasten the process of medicinal product evaluation, the European Union adopted the e CTD format for the submission [10].

A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting clinical trials, filing of Registration Dossier/ New Drug Application (NDA) and post-marketing studies. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. The single regulatory approach for marketing authorization of a new drug product applicable to various countries (on the basis of single dossier) is utmost difficult. Therefore, the knowledge of exact and detailed regulatory requirements for Registration Dossier of each country should be known to establish a suitable regulatory strategy.

General principles

- Different licensing procedures, but identical requirements on the documentation:
- Full application: demonstration of quality, safety and efficacy
- Generic application: demonstration of quality for the generic product plus bioequivalence to the reference product (only possible once data protection period has expired
- Well-established use: demonstration of quality for the product plus literature reference establishing recognized efficacy and an acceptable level of safety marketing authorizations are granted under the responsibility of the European Commission. The main advantage of this procedure is that new, innovative medicinal products can be made available to all European residents at the same time once marketing authorization has been granted. The Centralized procedure also leads to greater efficiency in Europe, as only one or two Member States are asked to produce assessment reports for each medicinal product.

Procedure

Pharmaceutical companies that wish to follow the centralized procedure submit a dossier to the European Medicines Agency (EMA) in London. The dossier is assessed by the Committee for Medicinal Products for Human Use (CHMP), the EMA's medicines assessment committee. The CHMP has in principle 210 days to reach a final decision. This period may be suspended to allow the company to answer questions. Companies can also give verbal explanations relating to the dossier they have submitted. The CHMP produces an opinion which is sent to the European Commission and used in reaching the final decision. The European Commission usually adopts the CHMP's opinion in all respects [11].

Once a favorable decision has been made, the Summary of Product Characteristics (SmPC) and the package leaflet are determined. A European Public Assessment Report (EPAR) is produced. If the opinion is negative, information is given as to the grounds on which this conclusion was reached. The EPAR can be found on the EMA website.

Products that have obtained marketing authorization via the Centralized procedure are given a European marketing authorization number. Certain products must undergo the Centralized procedure: medicinal products that have been made using biotechnology, and new medicinal products intended to treat i.a. cancer, AIDS, neurodegenerative diseases and diabetes. In the case of other innovative products, companies are free to opt for either Centralized or National registration.

EMA and CHMP

The EMA receives applications under the Centralized procedure and controls the assessment process. The CHMP submits an opinion to the European Commission which then reaches a binding decision. Each European Member State has one representative on the CHMP and one alternate [12].

Two reporters are appointed in the CHMP for each medicinal product, and they monitor the product throughout its life cycle. CHMP members operate in their personal capacity. They act as a bridge between the European system and national systems. In the Netherlands, the Dutch CHMP members report to the Medicines Evaluation Board.

Centralized Procedure

As per the regulation (EC) No 726/2004, Centralized procedure is describe for marketing application of medicinal products, for which only one application, single evaluation and single authorization required for marketing medicinal product can be put into all member states. Application for this type of authorization is directly send to EMA Applications of medicinal product are processed by following ways,

Admissibility of application

At least 7 month before the submission of application, applicant should inform EMA about the submission of application and give estimate of month of application. After discussion with the Committee for medicinal products for human use (CHMP), EMA will inform applicant for whether application is acceptable or not. If applicant is willing to apply for multiple applications then applicant must inform EMA about the submission before at least 4 months. Before actual start of procedure reporter and Cap pointed by the CHMP members and EMA (6).

Dossier

Dossier submitted to EMA and rapporteur, co-rapporteur both parallel.

1 full copy of dossier, 2 additional copy of module 1 & 2 including draft Summary of product characteristics (SmPC), labeling and package leaflet (PL) in English, 1 electronic copy of module 1 & 2 (6).

Payment of fees

Payment of fees should be done within 45 days of notification. The invoice will be sent to the billing address indicated by the applicant and will contain clear details of the product and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment.

Conditional marketing authorization

Request for accelerated assessment can be submitted at any time of prior to the submission of application. Applicant can apply for accelerated assessment procedure if he proves that the medicinal product is in major public health interest and therapeutically effective. Request has to be send within 10working days in advance of the actual start of the evaluation procedure. The timetable for the accelerated procedure is reduced to 150days [13].

Renewal of marketing authorization

After marketing authorization expiry if applicant wants to continue sale the drug into the market then renewal of the marketing authorization is important. For the renewal of the marketing authorization applicant must apply before six month advance of the expiry of medicinal product in market. For this procedure required fees should submit within 45 days of notification date.

MARKETING AUTHORIZATION OF HUMAN MEDICINAL PRODUCTS TO EUROPEAN UNION/EUROPEAN ECONOMIC AREA

MARKETING AUTHOURIZATION

Allow all medicine to placed on the market of the sale and supply two way obtaining Marketing Authorization centralized and national authorization procedure.

In Europe today, all medicines must have a marketing authorization before they can be used by patients Through the centralized procedure, the Agency gives an opinion and it results in a single marketing authorization for the whole of the European Union. In the national procedures, individual member states authorize the medicines for use in their own territory. The centralized procedure ensures a consistent approach to medicines regulation right across the European Union One application leads to one evaluation leading to one authorization valid in the 28 Member States of the European Union as well as Iceland, Norway and Lichtenstein. Importantly it also results in a single set of product information for healthcare professionals and patients in the all the European Union official languages. These include medicines for rare diseases (sometimes called orphan drugs), and for some disease areas like HIV/AIDS, cancer, neurodegenerative disorders and diabetes. There are also some product types like those derived biotechnology and some gene therapy products that must also come to the Agency. The EMA has specific committees and working parties that specialize in evaluation of these products and disease areas [14].

The European Economic Area: (EEA)

The European Economic Area unites the 27 EU member states and the three EEA European Free Trade Association (EFTA) states (Iceland, Liechtenstein and Norway).

European Medicines Agency

The European Medicines Agency (EMA) is a decentralized body of the European Union with headquarters in London. There are 7 of these scientific

committees that evaluate medicines at the EMA – 6 of them are for human medicines and one, the CVMP irresponsible for medicines for veterinary use. The Agency secretariat supports the work of these committees in a scientific and logistic capacity. Importantly four of these committees have members representing patients' organizations and this provides important opportunities for patients to contribute their expertise and experience with their disease areas of interest

Application Process for medicinal products

For Marketing Authorization A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorization has been issued by the competent authority of a Member State (or EEA country) for its own territory (national authorization) or when an authorization has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a Community authorization). The marketing authorization holder must be established within the EEA.

GLANCE OF EUROPEAN ECONOMIC AREA

EEA constitutes total 30 countries, with 26 different languages and 14 types of currencies existing in the region. The total population is about 500 millions. EEA Languages European Economic Area. Among all the languages most commonly used language is English, German and French. In the below figure 3 we can find the other most commonly used languages in the European Union.

EEA Population

The total population of EEA is about 500 millions. Below top 5 highest populated and also lowest populated countries of EEA region. These top 5highest populated countries population constitutes 60%of total population of EEA. Considering the total population of EEA it stood above the USA population (Around 310 M).

EUROPEAN LEGAL FRAMEWORK FOR LICENSING OF MEDICINALPRODUCT

The legal framework of the EU licensing consists of three major columns: Regulations, Directives and Guidelines. The Rules Governing Medicinal Products in the European Union are issued by the EU Commission and can be downloaded from http://eudrams1.is.eudra.org/F2/eudralex/download. For human medicinal products, including all biological and biotech products, the relevant volumes are:

Volume 1 Pharmaceutical legislation (Summary of all current Regulations and Directives)
Volume 2 Notice to Applicants
Volume 2A Procedures for marketing authorization
Volume 2B Presentation and content of the application dossier
Volume 2C Regulatory guidelines
Volume 3 Guidelines medicinal products for human use
Volume 4 Good Manufacturing Practice (GMP) with in particular
Annex 01 Manufacture of sterile medicinal products
Annex 02 Manufacture of biological medicinal products for human use
Annex 13 Manufacture of investigational medicinal products
Annex 14 Manufacture of products derived from human blood or human plasma
Annex 15 Qualification and Validation
Annex 16 Certification by a Qualified Person and batch release
Annex 18 GMP for active pharmaceutical ingredients (ICH Q7A)
Volume 9 Pharmacovigilance

Regulations

Regulations are directly effective as supranational law and they are addressing the citizens of the EU Member States.

Directives

Directives are addressing the Member States and they have to be implemented in national law by the legislation of the Member States.

Guidelines

Guidelines issued by the CHMP, the European Pharmacopoeia and ICH are not legally binding but where an applicant chooses not to be compliant with a guideline, that decision must be explained and justified. Guidelines are addressing scientific staff of authorities and companies. All guidelines, points to consider or recommendations issued under the roof of the EMA can be found on the EMA web page *www.ema.europa.eu*.

PREPARATION OF DOSSIER FOR EUROPEAN MARKET IN CENTRALIZED PROCESS

Introduction

Dossier

The word 'Dossier' has the English meaning as a collection or file of documents on the particular subject, especially a file containing detailed information about a person or a topic. Any formulation is prepared for human use i.e. designated to modify or explore physiological systems or pathological states for the benefit of the recipient is called as "Pharmaceutical product for human use". Process of critiquing and assessing the dossier of pharmaceutical product containing its detailed about administrative, chemistry, preclinical & clinical information and the permission granted by the regulatory agencies of a country with a view to support its marketing or approval in a country is called as "Marketing approval or Registration" ,"Marketing Authorization or " Product Licensing".

"Registration Dossier" of the pharmaceutical product is a document that contains all technical data (administrative, quality, nonclinical, and clinical) of a pharmaceutical product to be approved / registered / marketed in a country. It is more commonly called as New Drug Application (NDA) in the USA or Marketing Authorization Application (MAA) in European Union (EU) and other countries as simply Registration Dossier.

Thus dossier is a file document that has to be submitted based on the requirement of the drug approval/ market authorization process. It is a comprehensive scientific document used to obtain worldwide licensing approval/ market authorization of a drug by diverse health authorities. Its creations, processing, compilation & dispatch to the field by a regulatory affairs department, is dependent upon many interrelated activities, the filling and authorization process in the emerging markets will be depends upon the region.

Globalization of the pharmaceutical industry has created the need to harmonize the recommendations for the development of new pharmaceuticals, as well as the regulatory requirements of various countries. Thus, a common format of submission will help in overcoming these hurdles. Through ICH process, the CTD's guidance have been developed for Japan, European Union, and United States. Almost Most of the countries have adopted the CTD format.

Guideline on the use of the CTD format in the preparation of a registration application for medicinal products

The new EU-CTD-presentation will be applicable for all types of marketing authorization applications irrespective of the procedure (CP, MRP, DCP or national) and of type of application (stand alone, generics etc). The CTD-format will be applicable for all types of products (new chemical entities, radiopharmaceuticals, vaccines, herbals etc.) To determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities.

The Common Technical Document was developed as an international document, and therefore specific European legal terms such as "active substance", "medicinal product", and "marketing authorization" were not used in its development. Applicants are reminded that the term "medicinal product" covers both pharmaceutical and biological medicinal products. Unless otherwise indicated, it should be considered to be synonymous with the term "drug product". Similarly, the term "active substance" should be considered as synonymous with "drug substance". The terms used in the ICH documents may be used in the CTD part of the application.

Presentation of European Marketing Authorization Applications: The current requirements for the content of the European application dossier are set out in Annex I to Directive 2001/83/EC as amended, as stated in Article 8.3 "the application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I" Annex I of Directive 2001/83/EC sets out the legal provision for implementation of the CTD format. The provision of this update of Volume 2B (EU CTD), which take into account the ICH agreements, replaces the previous structure of the European marketing authorization dossier described in the 1998 edition of Volume 2B. From 1st July 2003, all applications should be made entirely in accordance with the EU-CTD presentation outlined in the July 2003 edition of NTA, Vol. 2B or its subsequent updates. In order to take into account experience with CTD structure and changes of a technical or scientific nature, it is anticipated that NTA, Volume 2B will be updated regularly.

Presentation of the application

The Common Technical Document is organized into five modules. The content of Module 1 is defined by the European Commission in consultation with the competent authorities of the Member States, the European Agency for the Evaluation of Medicinal Products and interested parties. Concerning the structure of Modules 2, 3, 4, and 5 they are common for all ICH regions.

Administrative, regional or national information is provided in Module 1:

This module contains the specific EU-requirements for the administrative data (e.g. the application form, the proposed summary of product characteristics, labeling and package leaflet, etc.).

Module 2

Contains high level summaries (the Quality Overall Summary, the Non-clinical Overview / Summaries, and the Clinical Overview / Summaries), which must be prepared by suitably qualified and experienced persons (experts). Although the term "Expert Report" must be maintained for legal reasons, the content is expected to be given in the Quality Overall Summary, the Non-clinical Overview / Summaries, and the Clinical Overview / Summaries documents. Old Expert Reports are now replaced by Module 2. The experts have to sign and add brief information on their educational background and specific expertise in a special section in Module 1.4. Chemical, Pharmaceutical and Biological documentation is provided.

Module 3. This information should be structured as described in Guideline M4Q (M4Q (R1): QUALITY

Module 4: These reports should be presented in the order described in Guideline M4S (M4S (R2): SAFETY Nonclinical Summaries and Organization of Module 4 The non-clinical section of the application).The documentation on the Clinical Trials performed on the drug/medicinal product is provided in the Clinical Written Summaries (from Module 2) and in the Clinical Study Reports

Module 5: These reports should be presented in the order described in GuidelineM4E (M4E (R1): EFFICACY

Module 2 :Clinical Overview and Clinical Summary Module 5Clinical Study Reports The clinical section of the Application).

The International Conference on Harmonization (ICH) process has considerably harmonized on the organization of the registration of documents with the issuance of the Common Technical Document (CTD) guideline. This recommended format in the CTD guideline for registration applications has become widely accepted by regulatory authorities both within and beyond the ICH Regions.

1.2 Application Form

Module 1.2 is to be used for an application for a marketing authorization of a medicinal product for human use submitted to

(a) the European Medicines Agency under the centralized procedure or

(b) a Member State (as well as Iceland, Liechtenstein and Norway) under either a national, mutual recognition or decentralized procedure.

The relevant application form has to be included, depending on the type of application.

The different application forms are available on the Website of the European Commission

DG Enterprise:

 New Applications and Extension Applications

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2b

 Variation applications

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c

 Renewal applications

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c

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1.3 Product Information

In accordance with Article 8.3 (j), Article 11 and Title V of Directive 2001/83/E Applicants/marketing authorization holders must include proposals for (revised) Summary of Product Characteristics (SPC), labeling and package leaflet in their application.

1.3.1 SPC, Labeling and Package Leaflet

The national competent authorities and the EMEA have published templates in all EU languages (incl. Norwegian and Icelandic) for the presentation of product information (Summary of Product Characteristics (SPC), labeling and package leaflet):

• For mutual recognition or decentralized procedures: the templates for product information are published on the Heads of Agency website (annotated template) and on the EMEA website (clean templates)

http://heads.medagencies.org/mrfg/docs/pi/QRD_annotated_template_CMDh.pdf

http://www.emea.europa.eu/htms/human/qrd/qrdtemplate.htm

• For applications in the centralized procedure: the templates for product information are published on the EMEA website (annotated and clean templates)

http://www.emea.europa.eu/htms/human/qrd/qrdtemplate.htm

Product information must only be presented in the mandatory format and lay-out (see "QRD convention" on the EMEA Website) using the electronic product information templates provided on the EMEA Website.

A complete set of SPC/Annex II/Labelling/Package Leaflet texts, as appropriate should be presented per language (in alphabetical order). Relevant guidance documents which address the submission and presentation of product information in paper and electronic format should be consulted when preparing this section of Module 1 (*e.g*. QRD Templates, EMEA Post-Authorization Guidance document)

• For national procedures other national templates may apply these templates should be used in conjunction with the relevant guidelines. In particular with the "Guideline on Summary of Product Characteristics", the "Guideline on packaging information" and the "Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use", as published by the European Commission in the Notice

ToApplicants,Vol.2C:

(http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c).

For the paper submission of product information:

• different language versions should be separated by a tab

• SPC, (Annex II), labelling and package leaflet should be separated by a tab

• for submission to CHMP members/Member States, only the relevant language version(s) are to be provided in addition to the English product information, as required.

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1.3.2 Mock-up

In accordance with Directive 2001/83/EC, Article 8, a mock-up of the outer and immediate packaging of the medicinal product must be included with the application.

A "mock-up" is a copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/labelling of the medicinal product. It is generally referred to as a "paper copy" or "computer generated version".

Requirements for mock-up and/or specimen submission are published by the European Commission in the Notice to Applicants, Vol. 2A, Chapter 7 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2a) When mock-ups are submitted, a list detailing the mock-ups provided with the application should be included in addition to the actual mock-ups. NTA, Vol. 2B-CTD, Module 1 edition May 2008 12

Module 1.3.3 Specimen

A "specimen" is a sample of the actual printed outer and immediate packaging materials and package leaflet.

Member States/EMEA may require specimens of the sales presentation of the medicinal product to be submitted, in order to check compliance with the relevant articles in Title V of Directive 2001/83/EC (e.g. Article 56).

Requirements for mock-up and/or specimen submission are published by the European Commission in the Notice to Applicants, Vol. 2A, Chapter 7 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2a)

When specimens are submitted, a list detailing the specimens provided should be included. For the electronic submission of Module 1, only the list detailing the specimens should be included here, separate from the actual specimens provided. NTA, Vol. 2B-CTD, Module 1 edition May 2008 13

1.3.4 Consultation with Target Patient Groups

Articles 59(3) and 61(1) of Directive 2001/83/EC require that the package leaflet reflects the results of consultations with target patient groups to ensure that it is legible, clear and easy to use, and that results of assessments carried out in cooperation with target patient groups be provided to the competent authority/EMEA.

These articles do not define the precise method to be used. As a consequence, these provisions permit 'user testing' as well as other appropriate forms of consultation. This is addressed in the draft EU guidance document published on the website of the European Commission: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2005/08_05/usertesting_20050817.pdf which will be included in the Commission "Guideline on the readability of the label and package leaflet of medicinal products for human use", (see Website of the European Commission: http:// ec.europa.eu/enterprise/pharmaceuticals /eudralex/homev2.htm#2c) Information from the applicant regarding the 'user consultation' performed together with the presentation of results, or a justification not performing such consultation, is to be included in this section for all new applications and for relevant post-authorization applications introducing significant changes to the package leaflet. NTA, Vol. 2B-CTD, Module 1 edition May 2008 14

Module 1.3.5 Product Information already approved in the Member States

(Where applicable)

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Module 1.3.6 Braille

In accordance with Article 56a of Directive 2001/83/EC the name of the medicinal product must be expressed in Braille format on the packaging. This is addressed in the European Commission guidance document published on the website of the European Commission http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2005/04_05/braille_text20050411.pdf, which will be included in the Commission "Guideline on the readability of the label and package leaflet of medicinal products for human use", (see Website of the European Commission: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c) Applicants should address here the proposed implementation of the Braille requirement on the packaging of the medicinal product concerned, based on the principles set-out in the abovementioned European Commission guidance document. In addition, the Braille text (in normal font) which will be printed on the outer carton in Braille needs to be included in section 16 of the outer carton product information templates (if applicable) and should be indicated with dots on the mock-ups (where applicable and feasible). NTA, Vol. 2B-CTD, Module 1 edition May 2008 16

1.4 Information about the Experts

In accordance with Article 12 of Directive 2001/83/EC experts must provide detailed reports of the documents and particulars which constitute Modules 3, 4 and 5. In addition Article 12.1 and Part I 1.4 of Annex I of 2001/83/EC refer to signed expert reports for the different scientific parts of the dossiers. The requirement for these signed Expert Reports may be met by providing:

• The Quality Overall Summary, Non-clinical Overview / Summary and Clinical Overview / Summary in Module 2,

• A declaration signed by the experts in Module 1.4.

• A brief information on the educational background, training and occupational experience in Module 1.4.

For post-authorization applications, the relevant expert declaration(s) must be provided. In cases where marketing authorization holders wish to distinguish such declaration from any previous declarations, the relevant procedure number of the reference member state/EMEA may be included on top.

1.4.1 Quality

According to his / her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EC.

QUALITY :

Name of the expert: …….. Signature:

Address: ……..

……..

……..

……..

Date:

According to the Annex I of Directive 2001/83/EC brief information (*curriculum vitae*) on the educational background, training and occupational experience of the expert is attached. NTA, Vol. 2B-CTD, Module 1 edition May 2008 18

1.4.2 Non-Clinical

According to his / her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EC

NONCLINICAL (pharmacology, pharmacokinetic, toxicology):

Name of the expert: …….. Signature:
Address: ……..
……..
……..
……..
Date:

According to the Annex I of Directive 2001/83/EC brief information (*curriculum vitae*) on the educational background, training and occupational experience of the expert is attached.

1.4.3 Clinical

According to his / her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EC

CLINICAL:

Name of the expert: …….. Signature:
Address: ……..
……..
……..
……..
Date:

According to the Annex I of Directive 2001/83/EC brief information (*curriculum vitae*) on the educational background, training and occupational experience of the expert is attached.

1.5 Specific requirements for Different Types of Applications

1.5.1 Information for Bibliographical Applications

For bibliographical applications based upon Article 10a of Directive 2001/83/EC applicants should provide here a concise document (up to approximately 5 pages), summarizing the grounds and evidence used for demonstrating that the constituent(s) of the medicinal product have a well-established use, with an acceptable level of safety and efficacy, as outlined in Part II.1 of Annex I to Directive 2001/83/EC.]

1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications

For applications based upon Article 10(1), 10(3) or 10(4) of Directive 2001/83/EC, applicants should provide here a concise document (up to approximately 5 pages), summarizing the grounds and evidence used for demonstrating that the medicinal product for which an application is submitted, is:

• A 'generic' of a reference medicinal product (Art 10.1).

This summary should include details on the medicinal product, its qualitative and quantitative composition in active substance(s), its pharmaceutical form and its safety/efficacy profile of the active substance(s) in comparison to the active substance(s)of the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and efficacy.

• A so-called 'hybrid' of a reference medicinal product (Art 10.3).This summary should include details on the medicinal product, its active substance, pharmaceutical form, strengths, therapeutic indications, route of administration as appropriate in comparison to the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned.

• A 'similar' biological medicinal product – a so-called 'bio similar' (Art 10.4).This summary should include details on the similar biological medicinal product, its active substance, raw materials and manufacturing process. Differences with relevant attributes of the reference medicinal product should be included. Any other changes introduced during development which could affect comparability should be highlighted. The comparability exercise versus the reference medicinal product for quality, safety and efficacy should be described, and the reference medicinal product used throughout the quality, safety and efficacy development programme (as appropriate) should be defined. The table presented below should be completed and included in this section of Module 1.No copy of the information already provided in the application form (Module 1.2) should be repeated here. However, further detailed information on the elements listed in the application form should be provided here where relevant.

1.5.3 (Extended) Data / Market Exclusivity

This section is required in case the marketing authorization holder/applicant wishes to claim (additional) data / market exclusivity when applying for a new indication or change in classification, based on the following legal provisions:

In accordance with the fourth subparagraph of Article 10(1) of Directive 2001/83/EC and Article 14(11) of Regulation 726/2004, the 10- year period of marketing protection may be extended by one year in the event of authorization of new therapeutic indications representing a significant clinical benefit in comparison with existing therapies.· According to Article 10(5) of Directive 2001/83/EC a non-cumulative period of one year of data exclusivity may be granted for a new indication for a well-established substance, provided that significant pre-clinical or clinical studies are carried out in relation to the new indication.

According to Article 74a of Directive 2001/83/EC where a change of classification of a medicinal product has

been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant or marketing authorization holder for a change of classification of the same substance for one year after the initial change was authorized.

Requirements in relation to Article 10(1) of Directive 2001/83/EC and Article 14(11) of Regulation (EC) No 726/2004:

The marketing authorization holder shall provide in this section a report justifying that the application concerns a new therapeutic indication that brings significant clinical benefit in comparison with existing therapies. The report, which should in general be not more than 5-10 pages, should include:· Justification of the proposed new indication compared to the therapeutic indication(s) already authorized.

Details of existing therapies relating to the proposed new indication Justification as to why the medicinal product, for which extended marketing protection period is sought, is of significant clinical benefit in comparison to existing therapies in the new therapeutic indication. Related study reports and literature references shall be placed in the relevant Modules of the dossier and cross-referred to accordingly. NTA, Vol. 2B-CTD, Module 1 edition May 2008 2 Please also refer to the "Commission Guideline on elements required to support the significant clinical benefit in comparison with existing therapies of new therapeutic indication in order to benefit from an extended (11 years) Marketing Protection period" as published on the Commission's website (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol - 2/c/guideline_14-11-2007.pdf).

Requirements in relation to Article 10(5) of Directive 2001/83/EC

The marketing authorization holder/applicant shall provide in this section a report justifying that the application concerns a new therapeutic indication and that significant preclinical or clinical studies have been carried out in relation to this new indication. The report, which should in general be not more than 5-10 pages, should include: · Introduction.

Justification of the new indication compared to the existing therapeutic indication(s). · Justification that significant preclinical or clinical studies have been carried out in relation to this new indication. Justification that the substance can be considered as a "well-established substance" in accordance with the requirements of indent (a) in section 1 of Part II of the Annex to Directive 2001/83/EC. Related study reports and literature references shall be placed in the relevant Modules of the dossier and cross-referred to accordingly. Please also refer to the "Guideline on new therapeutic indication for a well-established substance" as published on the Commission's website (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol -2/c/10%20_5_%20guideline_11- 2007.pdf)

Requirements in relation to Article 74a of Directive 2001/83/EC

The marketing authorization holder/applicant shall provide in this section a report justifying that its application includes significant preclinical tests or clinical trials which have been carried out in relation to this change of classification.

The report, which should in general be not more than 5-10 pages, should include: A summary of the preclinical tests and/or clinical trials carried out in relation to the change of classification NTA, Vol. 2B-CTD, Module 1 edition May 2008 3 · A justification why the preclinical tests or clinical trials carried out in relation to the change of classification should be viewed as significant. Related study reports and literature references shall be placed in the relevant Modules of the dossier and cross-referred to accordingly.

Please also refer to the "Guideline on changing the classification for the supply of a medicinal product for human use" as published on the Commission's Website (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c)

1.5.4 Exceptional Circumstances

According to Article 22 of Directive 2001/83/EC and Article 14(7) of Regulation (EC) No 726/2004, an authorization may be granted in exceptional circumstances subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. Such an authorization may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Part II.6 of the Annex I to Directive 2001/83/EC.

If the applicant considers that the grounds for approval under exceptional circumstances should apply, the applicant should include a justification in this section, covering the
following aspects.

1) A claim that the applicant can show that he is unable to provide comprehensive nonclinical

1.5.5 Conditional Marketing Authorization

This section is only applicable to applications in the centralized procedure. Where the applicant requests a 'conditional marketing authorization' to be granted in accordance with Article 14(7) of Regulation (EC) No 726/2004, the applicant should include a justification in this section, covering the following aspects:

Evidence that the product falls under Article 3(1) or 3(2) of Regulation (EC) No 726/2004 and belongs to one of the categories set-out in Article 2 of Commission Regulation (EC) No 507/2006;

Evidence that the product satisfies the requirements laid down in Article 4 of Commission Regulation (EC) No 507/2006; Applicant's proposal for completion of ongoing studies, conduct of new studies and/or collection of pharmacovigilance data (as appropriate), in accordance with Article 4(1)(b) of Commission Regulation (EC) No 507/2006. Please also refer to the "Guideline on the scientific application and the practical arrangements on the Conditional Marketing Authorization" published on the EMEA website (include link to doc on Website once published).

1.6 Environmental Risk Assessment

In accordance with Article 8 (ca) and (g) of Directive 2001/83/EC an application for marketing authorization shall be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment.

The requirements in the Directive relate to those risks to the environment arising from use, storage and disposal of medicinal products and not for risks arising from the synthesis or manufacture of medicinal products.

For the paper submission of the application, extensive documentation for the environmental risk assessment should always be provided in a separate volume as part of Module 1. In case of a short statement, this can remain in the Module 1 volume(s).

1.6.1 Non-GMO

Applications for marketing authorizations for medicinal products which do not contain GMOs (Genetically Modified Organisms) should include in Module 1 an indication of any potential A dated signature of the author, information on the author's educational, training and occupational experience (CV), and a statement of the author's relationship with the applicant, shall be provided.

Please also refer to the "Guideline on the Environmental Risk Assessment for medicinal products for human use" as published on the EMEA website (http://www.emea.europa.eu/pdfs/human/swp/444700en.pdf). NTA, Vol. 2B-CTD, Module 1 edition May 2008 7

1.6.2 GMO

Applications for marketing authorizations for medicinal products which contain GMOs (Genetically Modified Organisms) should include in Module 1 an environmental risk assessment. GMO means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Environmental risk assessment means the evaluation of the risk to human health and the environment (which includes plants and animals) connected with the release of GMOs or products containing GMOs.

The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive. The information shall consist of:

• an introduction; a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC; • the complete technical dossier supplying the information required by Annexes III and IV Directive 2001/18/EC;

• the environmental risk assessment in accordance with the principles set out in Annex II to Directive 2001/18/EC; the results of any investigations performed for the purposes of research or development; taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labeling and package leaflet;

• appropriate measures in order to inform the public. A dated signature of the author, information on the author's educational, training and occupational experience (CV), and a statement of the author's relationship with the applicant, shall be provided. NTA, Vol. 2B-CTD, Module 1 edition May 2008 8

1.7 Information relating to Orphan Market Exclusivity

This section is required for **all new Applications** (not only for Designated Orphan medicinal products) as well as for Type II variations for new indications, where the indication applied for is the same as the indication of an authorized Orphan Medicinal Product.

In accordance with Article 8.1 of Regulation (EC) No 141/2000, where a marketing authorization in respect of an orphan medicinal product has been granted in all Members States, the Community and the Member States shall not, for a period of 10 years, accept another application for marketing authorization, or grant a marketing authorization or accept an application to extend an existing marketing authorization, for the same therapeutic indication, in respect of a similar medicinal product.

Where a designated orphan medicinal product has been authorized for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, the applicant must submit a report addressing the possible **"similarity"** with the authorised orphan medicinal product.

If the medicinal product, which is the subject of the application for marketing authorization is deemed to be "similar" to an orphan medicinal product covered by the above-mentioned market exclusivity provisions, the applicant must furthermore provide justification that one of the **derogations** laid down in Article 8.3, paragraphs (a) to (c) of the same Regulation applies, that is:

(a) the holder of the marketing authorization for the original orphan medicinal product has given his consent to the second applicant, or

(b) the holder of the marketing authorization for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised,is safer, more effective or otherwise clinically superior. Further details can be found in the "European Commission guideline on aspects of the application of Article 8 of Regulation (EC) No 141/2000: Assessment of similarity and/or clinical superiority of orphan medicinal products when assessing marketing authorization applications and variations."(include link to doc on Website once published) NTA, Vol. 2B-CTD, Module 1 edition May 2008 9

1.7.1 Similarity

Where a designated orphan medicinal product has been authorised for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, applicants should provide a critical report addressing the possible similarity with the authorised orphan medicinal product and concluding on similarity or "non" similarity. NTA, Vol. 2B-CTD, Module 1 edition May 2008 10

1.7.2 Market Exclusivity

If the medicinal product, which is the subject of the application for marketing authorization is deemed to be "similar" to an orphan medicinal product covered by the above-mentioned market exclusivity provisions, the applicant must furthermore provide justification that one of the **derogations** laid down in Article 8.3, paragraphs (a) to (c) of Regulation (EC) No 141/2000 applies, that is:
(a) the holder of the marketing authorization for the original orphan medicinal product has given his **consent** to the second applicant, orWhere this derogation applies, a signed letter from the holder of authorised orphan medicinal product confirming his/her consent for the second applicant to file an application for marketing authorization, in accordance with Article 8.3 (a) of the same Regulation, and with specific reference to this provision, should be provided.
(b) the holder of the marketing authorization for the original orphan medicinal product is **unable to supply sufficient quantities** of the medicinal product, or Where this derogation applies, applicants should provide a report describing why supply of the authorised orphan medicinal product is deemed to be insufficient, in accordance with Article 8.3 (b) of Regulation (EC) No 141/2000. The report should include details of the supply shortage and justify that as a result patients' needs in the orphan indication are not being met. All claims should be substantiated by qualitative and quantitative references.
(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise **clinically superior**. Where this derogation applies, applicants should provide a critical report justifying why the medicinal product which is the scope of the application is deemed to be "clinically superior" to the authorised orphan medicinal product, in accordance with Article 8.3 (c) of Regulation (EC) No 141/2000 and Article 3.3(d) of Regulation (EC) No 847/2000. NTA, Vol. 2B-CTD, Module 1 edition May 2008 11

1.8 Information relating to Pharmacovigilance

1.8.1 Pharmacovigilance System

According to Article 8 (ia) of Directive 2001/83/EC a detailed description of the pharmacovigilance system which the applicant will introduce must be provided. This should include proof that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country according to Article 8 (n) of Directive 2001/83/EC).

The description of the marketing authorization holder's pharmacovigilance system should follow the requirements and format as detailed in Volume 9A of Eudralex (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm). NTA, Vol. 2B-CTD, Module 1 edition May 2008 12

1.8.2 Risk-management System

According to Article 8 (ia) of Directive 2001/83/EC a detailed description of the risk management system which the applicant will introduce should be provided, where appropriate. The detailed description of a risk management system should be provided in the form of an EU Risk Management Plan (EU-RMP), as outlined in Volume 9A of Eudralex (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm). The EU-RMP contains 2 parts: Part I · A Safety Specification · A Pharmacovigilance Plan, and Part II · An evaluation of the need for risk minimization activities, and if there is a need for additional (ie non- routine) risk minimization activities: · A risk minimization plan An EU-RMP may need to be submitted at any time of a product's life-cycle, is during both the pre-authorization and post-authorization phases. In particular an EU-RMP should be submitted:

• with the application for a **new marketing authorization** for : any product containing a new active substance · a similar biological medicinal product ·a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product • with an application involving a **significant change** in a marketing authorization (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication) unless it has been agreed with the competent authority that submission is not required.
• on **request** from a competent authority (both pre-and post-authorization).

• on the **initiative** of a applicant/marketing authorization holder when they identify a safety concern with a medicinal product at any stage of its life cycle. NTA, Vol. 2B-CTD, Module 1 edition May 2008 13 In some circumstances, products which are not in the above categories which are seeking a new authorization may require an EU-RMP:
• known active substances
• hybrid medicinal products where the changes compared with the reference medicinal product suggest different risks
• bibliographical applications
• fixed combination applications.

It is strongly recommended that discussions with the competent authorities on the need for, and content of, an EU-RMP should take place in advance of submission, especially for situations where the submission of an EU-RMP is not mandatory. The RMP should be presented in a stand-alone format (separate volumes in paper) allowing circulation to, and evaluation by pharmacovigilance and risk management experts. It should be accompanied by other relevant documents such as study protocols, where applicable. NTA, Vol. 2B-CTD, Module 1 edition May 2008 14

1.9 Information relating to Clinical Trials

According to Article 8 (ib) of Directive 2001/83/EC a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC should be provided, where applicable.

This statement should indicate that "clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC" together with a listing of all trials (protocol number) and third countries involved. The requirement applies to **all new applications** (including extension applications), and **other** relevant post-authorization regulatory procedures (e.g. variations) for which clinical trial reports are submitted. NTA, Vol. 2B-CTD, Module 1 edition May 2008 15 or clinical data on the efficacy and safety under normal conditions of use

2) A listing of the non-clinical or clinical efficacy or safety data that cannot be comprehensively provided

3) Justification on the grounds for approval under exceptional circumstances

4) Proposals for detailed information on the specific procedures/obligations to be conducted (Safety procedures, programme of studies, prescription or administration conditions, product information) Please also refer to the "Guideline on procedures for the granting of a marketing authorization under exceptional circumstances, pursuant to Article 14 (8) of Regulation (EC) No 726/2004" published on the EMEA website NTA, Vol. 2B-CTD, Module 1 edition May 2008 5

1.10 Information relating to Paediatrics

With reference to Article 7, 8 and 30 of Regulation (EC) No 1901/2006 ('paediatric regulation'), this section is required: · as of 26 July 2008 for **all new Applications*** for a medicinal product which is not authorised in the EEA as of 26 January 2009 for applications* for **new indications, new pharmaceutical forms and new routes of administration**, for authorised medicinal products which are protected either by a supplementary protection certificate, or by a patent which qualifies for the granting of such a certificate. for Paediatric Use marketing authorization applications (**PUMA**) In accordance with Article 23 of Regulation (EC) No 1901/2006 ('paediatric regulation'), the competent authority responsible for granting marketing authorizations shall verify whether an application for marketing authorization, extension or variation complies with the requirements laid down in article 7 or 8 of that Regulation, or whether a PUMA application complies with the agreed Paediatric Investigation Plan (PIP).

For guidance on PIPs, please refer to the draft "Commission guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies", as published by the European Commission (http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/draft_guideline_pip_2007-02.pdf). Applicants should therefore include the following documents in this section, as appropriate: - copy of the product-specific waiver decision issued by the EMEA; copy of the class-waiver decision issued by the EMEA; copy of the latest version of the PIP Decision(s) (incl. deferrals, if applicable), together with -if available-: except for generic, hybrid, bio-similar and well-established use applications and traditional herbal or homeopathic medicinal products (see Article 9 of the paediatric regulation) NTA, Vol. 2B-CTD, Module 1 edition May 2008 16

• A copy of the PDCO opinion on PIP compliance + report (in case PIP compliance verification by PDCO has taken place)
• The applicant's "PIP Compliance Report" (in case no competent authority compliance verification has taken place). Please also refer to the Template for such PIP compliance reports published on the EMEA website (include link to doc on Website once published). Related study reports should be placed in the relevant Modules of the dossier and cross-referred to accordingly.
• Overview table of the PIP results, indicating in which application(s) they were/are going to be submitted, status of the application(s), as well as their location in the present application.

Module 2.3

Quality Overall Summary

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD. The QOS should include sufficient

information from each section to provide the Quality reviewer with an overview of Module 3. The QOS should also emphasise critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under the CTD-S module), including cross-referencing to volume and page number in other Modules.

This QOS normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures). The *italicised* text below indicates where tables, figures, or other items can be imported directly from Module 3.

INTRODUCTION

The introduction should include proprietary name, non-proprietary name, European
Pharmacopoeia name or common name of the drug substance, company name, dosage form(s),
strength(s), route of administration according to the current version of the Standard Terms of the
European Pharmacopoeia and proposed indication(s)

2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.S.1 General Information (name, manufacturer)

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture (name, manufacturer)

Information from 3.2.S.2 should be included:

• Information on the manufacturer;

• A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;

• *A flow diagram, as provided in 3.2.S.2.2;*

• A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3;

• A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in.
3.2.S.2.4;

• A description of process validation and/or evaluation, as described in 3.2.S.2.5.

• A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and
CTD-E modules of the dossier.

2.3.S.3 Characterisation (name, manufacturer)

For NCE:

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included. When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

For Biotech:

A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure and biological activity), as described in 3.2.S.3.1, should be included.

For NCE and Biotech:

The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

2.3.S.4 Control of Drug Substance (name, manufacturer)

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A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included. *Specification from 3.2.S.4.1 should be provided. A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.*

2.3.S.5 Reference Standards or Materials (name, manufacturer)

Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System (name, manufacturer)

A brief description and discussion of the information, from 3.2.S.6 should be included.

2.3.S.7 Stability (name, manufacturer)

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1. The post-approval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

2.3.P DRUG PRODUCT (NAME, DOSAGE FORM)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)

Information from 3.2.P.1 should be provided.

Composition from 3.2.P.1 should be provided.

2.3.P.2 Pharmaceutical Development (name, dosage form)

A discussion of the information and data from 3.2.P.2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture (name, dosage form)

Information from 3.2.P.3 should include:

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• Information on the manufacturer.

• A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.

• *A flow diagram, as provided under 3.2.P.3.3.*

• A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

2.3.P.4 Control of Excipients (name, dosage form)

A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

2.3.P.5 Control of Drug Product (name, dosage form)

A brief summary of the justification of the specification(s), a summary of the analytical
procedures and validation, and characterisation of impurities should be provided.

Specification(s) from 3.2.P.5.1 should be provided.

A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials (name, dosage form)

Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

2.3.P.7 Container Closure System (name, dosage form)

A brief description and discussion of the information in 3.2.P.7 should be included.

2.3.P.8 Stability (name, dosage form)

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.

The post-approval stability protocol, as described in 3.2.P.8.2, should be provided.

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2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (name, manufacturer)

Biotech:

A summary of facility information described under 3.2.A.1 should be included.

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

A discussion on measures implemented to control endogenous and adventitious agents in production should be included.

A tabulated summary of the reduction factors for viral clearance from 3.2.A.2, should be provided.

2.3.A.3 Excipients

2.3.R REGIONAL INFORMATION

A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.

3.2 Body of Data

3.2.S DRUG SUBSTANCE1 (NAME, MANUFACTURER)

Reference CPMP Guidelines:

"On summary of requirements for active substances in part II of the dossier",including the Certification of Suitability of monographs of the European Pharmacopoeia.(see also NTA, Vol. 2B – introduction). "Active Substance Master File procedure"

3.2.S.1 General Information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the drug substance should be provided. For example:

• Recommended International Nonproprietary Name (INN);

• Compendial name (e.g. European Pharmacopoeia) if relevant;

• Chemical name(s);

• Company or laboratory code;

• Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN), and

• Chemical Abstracts Service (CAS) registry number.

Reference CPMP-Guidelines: "Chemistry of New Active Substance" and *"Chemistry of the Active Substance"*

3.2.S.1.2 Structure (name, manufacturer)

NCE:

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

Biotech:

The schematic amino acid sequence indicating glycosylation sites or other posttranslational modifications

and relative molecular mass should be provided, as appropriate.

Reference CPMP Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

3.2.S.1.3 General Properties (name, manufacturer)

A list should be provided of physicochemical and other relevant properties of the drug

substance, including biological activity for Biotech.

Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of Active Substance"*

1**For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance**

Page 7

NTA 2B , CTD-Module 3, edition July 2004 *Reference CPMP-ICH Guidelines: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances" and "Specifications – Test Procedures and Acceptance criteria for Biotechnological, Biological products"*

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example:

NCE:

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time). Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

Biotech:

Information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest (s), purification and modification reactions, filling, storage and shipping conditions.

Batch (es) and scale definition

An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.

Cell culture and harvest Page 8

NTA 2B , CTD-Module 3, edition July 2004

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g. cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified. A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.2.S.2.3); major equipment (details provided in 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in 3.2.S.2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. (Details on shipping and storage provided in 3.2.S.2.4.)

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.S.2.4 should be identified. A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in 3.2.S.2.3, major equipment (details provided in 3.2.A.1), and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5.) The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for

process steps, equipment and intermediates (Details in 3.2.S.2.4.). Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. (Details should be given in 3.2.S.2.5.). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (details on shipping and storage provided in 3.2.S.2.4.).

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided. (Details in 3.2.S.2.4.) The container closure system(s) used Page 9, NTA 2B , CTD-Module 3, edition July 2004 for storage of the drug substance (details in 3.2.S.6.) and storage and shipping conditions for the drug substance should be described.

Reference CPMP-ICH Guidelines: "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin", "Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products".

3.2.S.2.3 Control of Materials (name, manufacturer)

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterisation. (Details in 3.2.A.2 for both NCE and Biotech).

Biotech:

Control of Source and Starting Materials of Biological Origin Summaries of viral safety information for biologically-sourced materials should be provided (Details in 3.2.A.2.). Source, history, and generation of the cell substrate Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in CPMPICH Guidelines Q5B and Q5D.

Cell banking system, characterisation, and testing Information on the cell banking system, quality control activities, and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)) should be provided as described in CPMP-ICH Guidelines Q5B and Q5D.

Module 4

Nonclinical Study Reports

NTA, Volume 2B, CTD-Module 4

This guidance presents an agreed format for the organisation of the nonclinical reports in the Common Technical Document for applications that will be submitted to Regulatory Authorities. This guidance is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired. The appropriate location for individual-animal data is in the study report or as an appendix tothe study report.

Module 5

Clinical Study Reports

NTA, Volume 2B, CTD-Module 5

Preamble

Through the ICH process, a guideline has been published on the structure and content ofclinical study reports (E3). This document provides guidance on the organisation of these study reports, other clinical data, and references within a Common Technical Document(CTD) for registration of a pharmaceutical product for human use. These elements shouldfacilitate the preparation and review of a marketing application. This guidance is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that are in the application.

Detailed Organization of Clinical Study Reports and Related Information in Module 5

This guidance recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as "not applicable" or "no study conducted" should be provided when no report or information is available for a section or subsection.

Table 1. Schematic representation of Centralized procedure

DAY	DAY
1	Start of the procedure
80	Receipt of the Assessment Report(s) or critique from Rapporteur and Co- Rapporteur(s) and EMA sends this report to applicant as preliminary conclusions

100	Rapporteur, Co-Rapporteur, other CHMP members and EMEA receive comments from Members of the CHMP (incl. peer reviewers)
115	Receipt of draft list of questions from Rapporteur and Co-Rapporteur, as discussed with the peer reviewers, by CHMP members and EMA
120	CHMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMA
	CLOCK STOP (for GMP/GLP/GCP inspection)
121	Submission of the responses, including revised summary of product characteristics labelling and package leaflet texts in English, and restart of the clock.
150	EMA sends joint Assessment Report to the applicant making it clear that it only their preliminary conclusions and that it is for information only
170	Deadline for comments from CHMP Members to be sent to Rapporteur and Co-Rapporteur, EMEA and other CHMP Members
180	CHMP discussion and decision on the need for adoption of a list of "Outstanding issues" and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation
181	Restart the clock and oral explanation (if needed)
181 to 210	210 Final draft of English summary of product characteristics, labelling and package leaflet sent by applicant to the Rapporteur and Co-Rapporteur, EMA and other CHMP members.
215	Applicant provides EMEA with final translations of summary of product characteristics, Annex II, labelling and package leaflet in the 20 languages, taking account 234comments received from Member States by Day 229.
232	Transmission of Opinion and Annexes in all EU languages to applicant, Commission, and Members of the Standing Committee, and Norway and Iceland.
By 246	Applicant provides EMEA with one final full colour 'worst-case' mock-up of outer and inner packaging for each pharmaceutical form.

Type Variations to Marketing Authorization Europe Eutypes of Application For Eu Marketingauthorization

EUROPE EU: Variations to Marketing Authorisation

A variation to the terms of a marketing authorization is an amendment to the contents of the documents of the approved dossier. Variations in European Union (EU) are regulated by following regulations and Guidelines:

•The submission of variation applications makes sure that the dossier and the Summary of Product Characteristics (SPC) are always kept up to date. During the life cycle of a medicinal product, the modifications are repeatedly made to the dossier, which may be simple changes, such as a change in the manufacturing method or a change in a manufacturer Variations in European Union (EU) are regulated by following regulations and Guidelines: • Commission Regulation (EC) No. 712/2012 of 3 August 2012 amending Regulation (EC) No. 1234/ 2008 concerning examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products

Annex I – Extensions of marketing authorizations.

Annex II – Classification of variations.

Annex III – Cases for grouping variations.

Annex IV – Elements to be submitted.

Annex V – Variations concerning a change to or addition of therapeutic indication, addition of non-food producing target species, replacement or addition of a stereotype, strain, antigen etc.

Guidelines of 16.05.2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.

Consequently, this guideline provides details of the classification of variations into the following categories as defined in Article 2 of the variations regulation: minor variations of Type IA, minor variations of Type IB and major variations of Type II and provides further details, where appropriate, on the scientific data to be submitted for specific variations and how this data should be documented. It should be noted that the general documentation accompanying every application for variations to the term of a marketing authorization is laid down on Annex IV of the variations regulation and in the Commission guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation(EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products.

Variation classification guideline for European Union
In general changes are categorized into three types

1. Administrative changes
2. Quality changes
3. (Non-) Clinical changes (safety, efficacy)

1. Administrative changes

According to the 'Variations Guidelines' 2013/C 223/01External link icon, this variation does not apply when the information has been otherwise transmitted to the authorities (e.g. through the so-called "QP declaration"). Otherwise transmitted means that the information has been provided to the competent authorities within any formal regulatory procedure e.g. renewals, variations. In these cases, no separate variation application for the change in the audit date has to be submitted. However, the change has to be mentioned in the scope of the application form as well as under "present/proposed" but not in the section "variations included in this application."

Manufacturer of finished product (as referred under documentation requirement 1 of classification category A.8) means any registered EEA manufacturers of medicinal products (finished product and batch release) which hold a valid manufacturing authorization. This is the same as manufacturing sites which are required to provide a qualified person declaration, where a single declaration may be acceptable under certain circumstances – see note below under section on Quality Changes – Classification category B.II.b.1.

2. Quality changes

The update of Module 3.2.S can be submitted as a grouped variation application, if conditions 5 or 6 of Annex III of the Variation Regulation (EC) No 1234/2008 apply. An update or change of a stand-alone ASMF is not foreseen and can only be addressed in connection with a marketing authorisation. The type of the variation(s) is dependent on the type of the single changes introduced in the updated version. The update – including changes to the open and /or restricted part - can be submitted as a grouped application, if condition 5 of Annex III of the Variation Regulation (EC) No 1234/2008 applies. However, in case of substantial changes in the updated version of Module 3.2.S or the ASMF it is recommended to submit a single type II variation under category B.I.z. However, it is a prerequisite for the validation of these single variations that the "present/proposed" section of the application form is filled in correctly and completely. In all cases, updates of the ASMF must be submitted by the ASMF holder (open and closed part to EMA, open part to marketing authorisation holder) whilst the variation as such has to be submitted by the marketing authorisation holder. We encourage a close dialogue between MAH and ASMF holder to establish the correct classification of all the changes introduced within a new version of an ASMF to avoid validation issues. Any pre-submission queries related to upcoming submissions pertaining to such changes should be addressed to the appointed Procedure Manager.

Variation scopes B.I.a.4.c, B.I.b.1.d, B.I.c.2.c, B.II.b.5.c, B.II.c.1.c, B.II.d.1.d, B.II.e.2.c and B.IV.2.f of the 'Variations Guidelines' 2013/C 223/01External link icon, deal with the deletion of a non-significant in-process control (IPC) test or specification parameter. Provided all relevant conditions and documentation requirements are met, all these variations fall under the Type IA category (do-and-tell). For the categories listed above and other variations related to specifications of active ingredients, excipients, finished product, packaging material or measuring or administration device, the deletion of an obsolete parameter is given as an example. For finished products, this is further exemplified by mentioning of odour and taste. Although it is not possible to give similar examples for all of the categories mentioned above, these examples serve as an indication of the types of changes considered to fall under this variation category, regardless if this is related to in-process controls or specifications. This is therefore intended to be used for truly obsolete tests that are no longer part of normal specifications for newer products, but have remained for historical reasons in older products. This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.

3. (Non-) Clinical changes (safety, efficacy)

In line with the 'Variations Guidelines' 2013/C 223/01External link icon all 'final' non-clinical or clinical study reports concerning a marketing authorisation granted under the centralised procedure will have to be submitted to the Agency as part of a type II variation application, unless otherwise specifically covered in the annex to the classification guideline on variations or listed. Results of imposed non-interventional safety studies covered by the Art. 107q of the Directive 2001/83/EC;

Submissions of final study results in support of extension of marketing authorisation applications, annual renewals or annual re-assessments; Submission of study results related to paediatric population in line with Article 46 of Regulation 1901/2006. Submissions pursuant to Article 46 should continue to follow the procedure for post-authorisation measures, unless the MAH concludes that changes to the product information (PI) are warranted based on the data submitted. In such cases, the relevant variation should be submitted; Studies in the context of an environmental risk assessment (ERA). These are expected to be assessed during the initial marketing authorisation or relevant post-marketing procedures (e.g. extension of indication, extension applications). In the exceptional case that ERA study results are provided stand-alone, they

should be submitted as a type IB C.1.z variation; Results including reports from bioequivalence studies to support quality changes to the marketing authorisation should be submitted under the applicable variation category for quality changes.

As a general rule, the 'final' study report is considered the one including the primary analysis of the study. In case the final study report has previously been submitted, further updates of data from the study without formal statistical significance after the primary analysis do not trigger additional variations, unless they lead to changes to the product information and/or to the Risk Management Plan (RMP). On the other hand, a formal extension study, generally with a different study design and objectives as compared to the initial study, is considered a separate study and it generally carries a separate study number. The submission of the final report for such an extension study triggers a variation.

When a change to the product information is proposed as a consequence of the final study report, the type II variation should be submitted under variation classification categories C.I.6 (extension of indication), C.I.4 (other changes involving the SmPC, Annex II, labelling and/or Package Leaflet) or C.I.11 (changes limited to the Annex II conditions). When no changes to the product information are proposed, the variation should be submitted under category C.I.13. When a final non-clinical or clinical study report is provided as part of a variation submitted under category C.I.13, it should be noted that one separate type II variation per study report is required. This requirement applies also in situations where the CHMP has requested several non-clinical or clinical studies to be undertaken as part of a specific post-authorisation measure (PAM) in order to address a specific issue; one type II variation under category C.I.13 per final study report will still be requested (provided that the product information remains unaffected). It should be noted that these requirements also apply to all non-clinical studies, including the provision of final study reports for in vitro studies. In case the final non-clinical or clinical study report leads to consequential changes to the RMP, the MAH can include an updated RMP version as part of the type II variation regardless of whether it is submitted under category C.I.6, C.I.4, C.I.11 or C.I.13. With regard to 'interim' non-clinical or clinical study results, the timelines of the progress reports for a given study should be pre-specified and indicated in the protocol. These progress reports may include available interim results, but there is in general no obligation or recommendation to include interim results in RMPs unless required as part of an agreed pharmacovigilance plan. On the other hand, such results should be reported in relevant PSURs.

When interim results have been requested by the CHMP and are provided in order to address a specific post-authorisation measure (PAM), the data should be submitted in line with the requirements of the PAM procedure, unless the MAH considers that the interim data result in consequential changes to the product information and/or the RMP in which case a type II variation should be submitted instead. With reference to analyses across studies on specific topics (e.g. a biomarker report from more than one study) for which the individual final study reports have previously been submitted, the analysis should be submitted under category C.I.4 (in case of changes to the product information), under category C.I.11 (changes limited to the Annex II conditions) or as a PAM (no changes to the product information and/or the RMP are warranted). When the analyses should be submitted as variations, one variation scope per analysis (and not per study included in the analysis) should be submitted.

Final results from an imposed non-interventional post-authorisation safety study (PASS category 1 and 2 in the RMP, and reflected in Annex II) should be submitted within 12 months of the end of data collection unless a written waiver has been granted by PRAC, as appropriate (please refer to guidance on imposed post-authorisation safety studies). Final (and also interim) results should be submitted as a variation, if the MAH considers that changes to the product information are warranted. If not, then the submission should follow the relevant Art 107q of Directive 2001/83/EC procedure (please also refer to guidance on post-authorisation safety studies).

TYPES OF VARIATIONS

Variations are broadly classified in to two categories:

Minor Variations: Type-1A & Type-1B variations

Major Variations: Type-II variations

Type lA variations: Type lA variations are the minor variations which have only a minimal impact or no impact at all, on the quality, safety or efficacy of the medicinal product, and do not require prior approval before implementation ("Do and Tell" procedure). Such a minor variations are "classified" two subcategories, which impact on their submission: • Type lA variations requiring immediate notification ('IA IN') • Type lA variations NOT requiring immediate notification ('lA') (Variations which do not require immediate notification may be submitted by the marketing authorisation holder (MAH) within 12 months after implementation).

Type IA variations

Why certain minor variations of Type IA require immediate notification?

Certain minor variations of Type IA require immediate notification after implementation, in order to ensure the continuous supervision of the medicinal product.

When should I submit my Type IAINvariation?

This should be submitted immediately and generally within 2 weeks of implementation of the change.

What is meant by 'implementation' for Type IA variations?

For quality changes, implementation is when the company makes the change in its own quality system.

EXAMPLES OF TYPE IA VARIATIONS

Type IA Changes - Only a minimal impact or no impact at all, on the quality, safety or efficacy of the medicinal product ("Do and Tell" procedure)

Examples of Type IA_{IN} variation

Change in the name and/or address of the marketing authorisation holder

♣ Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites)

♣ Changes in imprints, bossing or other markings

♣ Change in the shape or dimensions of the pharmaceutical form perticularly Immediate release tablets, capsules, suppositories and pessaries.

Examples of Type IAvariation

♣ Addition of physico-chemical test in specification. ♣ Deletion of non-significant test (ex: Identification test in Stability study).

♣ Tightening of specification limits (ex: Tightening of test limit for water content, Residual solvents and Related substances..etc.

♣ CEP updates/renewal.

♣ API and FP Batch size increase/decrease within 10 fold.

Type IB variations

Commission Regulation (EC) No 1234/2008 ('the Variations Regulation') defines a minor variation or Type 1B as a variation which is neither a Type lA variation nor Type II variation nor an Extension.

Such minor variations must be notified to the National Competent Authority/European Medicines Agency by the Marketing Authorisation Holder (MAH) before implementation.

However, the MAH must wait a period of 30 days to ensure that the notification is acceptable by the Agency before implementing the change (Tell, Wait and Do procedure)

EXAMPLES OF TYPE IB VARIATIONS

Type IB Changes - Min to moderate impact on product quality (Tell, Wait and Do procedure):

Major change the approved Analytical method
FP Mfg. site changes
Shelf-life extension
Change in storage condition
Minor changes to approved manufacturing process
Change in batch size beyond 10 fold category
SmPC /PIL changes in-line with innovator product

Type II variations

Commission Regulation (EC) No 1234/2008 ('the Variations Regulation') defines a major variation of Type II as a variation which is not an extension and which may have a significant impact on the Quality, Safety or Efficacy of a medicinal product.

EXAMPLES OF TYPE II VARIATIONS

- Type II Changes (Significant impact on product quality, safety & efficacy):
- Addition of alternate/new API DMF supplier
- Relaxation of approved specification
- Major change in approved manufacturing process
- Major change in approved composition

Extension Applications

Definition for Extension of marketing authorisation

Changes to a marketing authorisation listed in Annex I of Commission Regulation (EC) No 1234/2008 are regarded as "extensions" of the marketing authorisation.

Examples of extension changes

1. Changes to the active substance(s) – replacement of a chemical active substance by a different salt/ester complex/derivative. with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different

2. Change to strength, pharmaceutical form, route of administration

- Change of bioavailability;
- Change of pharmacokinetics e.g. change in rate of release
- Change or addition of a new strength/ potency;
- Change or addition of a new pharmaceutical form;
- Change or addition of a new route of administration.

Such applications will be evaluated in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates. The extension can either be granted as a new marketing authorisation or will be included in the initial marketing authorisation to which it relates.

Grouping of variations

- It is possible to group variations of different categories the same marketing authorisation (MA) and submit them in one submission, under a single application form, to the same relevant authority. This is permissible where variations are covered under the cases listed in Annex Ill to the variations regulation.
- Examples are any group of lA changes, a group comprising a Type IB or Type II change plus one or more of the same or lower category which are consequential to the first, and a group of administrative changes to labelling.
- If a projected group is not listed in Annex Ill, the regulation and supporting guidances permit the MAH to request agreement of the relevant authority (ies) to grouping of related changes where a single data package and evaluation are meaningful.
- 14 cases of Groupings listed in Annex Ill

- CMDh Guidance for Examples for Acceptable and Not-Acceptable Groupings for MRP/DCP Products -Doc. Ref: CMDh/173/2010/Rev.10 July 2013

Documentation required for variation filling

- The following documents should be submitted for filing of Variations applications: • Cover letter. • The completed EU variation application form
- Reference of variation guidelines, indicating that all conditions and documentation requirements are met.
- Relevant documentation in support of the proposed variation including any documentation specified in the Annex to these guidelines.
- In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised product information presented in the appropriate format.
- Update or Addendum to the detailed critical summaries (quality, safety, efficacy as appropriate)
- Examples of the variation applications:
- Type IA
- Type IB
- Type II

VARIATION APPROVAL TIMELINE

How shall my Type IA/ IA in notification be processed (timetable) by Health Authority?

A 'notification of receipt' letter would be issued by the Agency within five days of receipt of a Type IA application. Within 30 days of receipt, the notification would be reviewed. The Health authority will check the correctness of the application form, ensure the required documentation is present and compliance with the required conditions.

There will be no interaction with the marketing authorisation holder (MAH) during the procedure, and no request to provide missing information Type IA notification is a 'Do and tell' procedure, therefore changes must be implemented prior to submission of notification

How shall my Type IB notification be processed (timetable) by Health Authority?

For Type IB notifications, the target pre-assessment processing time is 14 days. Substantive assessment is done within 30 days, and leads either to approval or a request for further information (RFI) letter within that 30 days. The company's response to the RFI letter needs to be received within 30 days. Assessment of that response is within a further 30 days.

How shall my Type II notification be processed (timetable) by Health Authority?

Type II variations follow a 30-day, 60-day or 90-day procedure (Depending upon complexity of the variation application).

CONCLUSION

A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorization has been issued by the competent authority. Marketing authorization holder should follow the relevant guideline and directives for manufacturing of the medicinal products to be market in the EEA and he has select to select the relevant legal type of application and relevant procedure based on the product eligibility, for faster drug product approval. Summary of the drug approval processes of various countries similar and differ in some aspects. In all countries, information submitted to regulatory authorities regarding the quality, safety and efficacy of drug is similar. Although the requirements are harmonized in regulated countries by CTD (Common technical document) filing, yet others have enormous diversity in requirements. ACTD also accepted in other countries Finally, there needs to be a reassertion that the purpose of drug registration is to protect the public health, not to facilitate profit of pharmaceutical manufacturers. Registration should be seen as a critical step in ensuring access to safe and effective medicinal product. To assure that the drug sold to the public will have quality attributes similar to those of the drug demonstrated to be safe and effective.

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