
Dossier for marketing authorization in the European Union

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Abstract

Extensive and complete documentation must be presented for marketing authorization of a medicinal product in the EU. Presented documentation should prove quality, safety and efficacy of the medicinal product. It is ensured that the applicant supplies the authorities with complete information. The legislation in Federation of Bosnia and Herzegovina has also taken more steps towards those European directions.

The presentation and content of the dossier in the European Union has been redefined. The "old" EU format will be replaced with the Common Technical Document (EU CTD format) agreed in 2000, within the International Conference on Harmonization framework. These two formats are intended to coexist during the transition period until July 2003. The CTD is an internationally agreed upon format for the preparation of a well structured presentation for applications to be submitted to regulatory authorities in the three ICH regions of Europe, US and Japan.

Key words: marketing authorization, application dossier, domestic laws

Introduction

The centralized and mutual recognition procedures became applicable in the EU from 1995. In order to achieve the free movement of medicinal products within the Community, a Committee for the Proprietary Medicinal Products is set up. The Committee has a responsibility to examine any question relating to granting, variation, suspension or withdrawal of marketing authorization in EU. In order to obtain authorization to place a medicinal product on the market, an application shall be made by the competent authority of the Member State concerned, and followed by the particulars and documents (1):

- Information about the applicant and, where applicable, about the manufacturer;
- Name of the medicinal product;
- Qualitative and quantitative particulars of all the constituents of the medicinal product;
- Description of the manufacturing method;
- Therapeutic indications, contraindications and adverse effects;

- Posology, pharmaceutical form, method and route of administration and expected shelf life;
- Reasons for any precautions and safety measures, with an indication of any potential risk presented by the medicinal product for the environment;
- Description of the control methods employed by the manufacturer;
- Results of the physical-chemical biological or microbiological tests, toxicological and pharmacological tests, clinical tests;
- A Summary of the product characteristics, packaging and labelling information, with a package leaflet;
- A document showing that the manufacturer is authorized in his own country to produce medicinal products;
- Copies of the authorizations obtained in another Member State or in the third country, with a list of Member States in which an application for authorization submitted is under examination, accompanied with particulars and information about this process.

The European Commission and the European Agency for the Evaluation of Medicinal Products published The rules governing medicinal products in the European Union. Volume 2B in this series is dealing with the presentation and content of the application dossier.

Volume 2B was first published as a separate volume in 1998. It provides guidance for the compilation of dossier for applications for European marketing authorizations. This EU format of dossier will be replaced with new update in July 2003. Format of the Common Technical Document (CTD) was internationally agreed upon format for the preparation of a well-structured presentation for applications to be submitted to regulatory authorities in the three ICH regions of Europe, US and Japan (3).

Correlation between old and new format of the application dossier

According to the Common Technical Document application dossier should be presented in five Modules:

- Module 1, Administrative and prescribing information;
- Module 2, CTD Summaries;
- Module 3, Quality;

- Module 4, Non-clinical study reports;
- Module 5, Clinical study reports.

The content of the Module 1 is defined in consultations with authorities of the Member State, and Modules 2, 3, 4 and 5 are intended to be common for all regions. The first Module is containing regional and national informa-

tion. The old EU format was composed of 4 parts. First part includes administrative information, prescribing information and Expert reports on the chemical, pharmaceutical and biological documentation, toxicopharmacological documentation and clinical documentation. The content of this Part is divided into Modules 1 and 2 of the EU CTD format (table 1).

Table 1 Correlation between old and new way of presentation of the application dossier in the EU (Part I - Module 1 and 2) and FBiH

FB&H	"Old" EU format (NTA, Vol. 2B Ed.1998)	EU CTD format (NTA, Vol.2B, Ed.2001)
Code of legislation on drugs, Marketing authorization	PART I SUMMARY OF THE DOSSIER	MODULE 1 ADMINISTRATIVE AND PRESCRIBING INFORMATION
Application Certificate of quality of the medicinal product, that proves authorization of the product in the country of manufacture and respecting the GMP rules List of the countries where the authorization is obtained, with the current prices Certificate of Manufacturers authorization for the name of the medicinal product Package Leaflet text; The way of safe disposal of expired drug	Administrative data and Table of Contents for remainder of the dossier Summary of Product Characteristics, Packaging, Labelling and Package Leaflet Expert Report on the chemical, pharmaceutical and biological documentation, with Product profile, Critical Assessment, Information on the Expert, Tabular Formats and the Written Summaries Expert Report on the toxicological-pharmacological documentation, with Product profile, Critical Assessment, Information on the Expert, Tabular Formats, Tabular Overview and the Written Summaries Expert Report on the clinical documentation, with Product profile, Critical Assessment, Information on the Expert, Tabular Formats and the Written Summaries	Comprehensive Table of Content Application Form Summary of Product Characteristics, Labelling and Package Leaflet Information about the Experts Specific Requirements for different types of applications Annex 1, Environmental risk assessment Annex 2, Orphan medicinal products/ Demonstration of significant benefit
		MODULE 2 COMMON TECHNICAL DOCUMENT SUMMARIES
The information from the Summaries is in the Expert reports on the chemical, pharmaceutical and biological documentation, toxicological-pharmacological documentation and clinical documentation, that are requested with the considered documentation		Overall Table of Contents of Modules 2,3, 4 and 5 Introduction Quality Overall Summary Non-clinical Overview Clinical Overview Non-clinical Summary (Pharmacology, Pharmacokinetics and Toxicology Written and Tabulated Summaries) Clinical Summary (Summary of biopharmaceutics and associated analytical methods, of clinical pharmacology studies, clinical efficacy, clinical safety, Synopses of individual studies)

Table 2 Correlation between old and new way of presentation of the application dossier in the EU (Part II - Module 3) and in the FBiH

FB&H	"Old" EU format (NTA, Vol. 2B Ed.1998)	EU CTD format (NTA, Vol.2B, Ed.2001)
Code of legislation on drugs, Marketing authorization	PART II CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL DOCUMENTATION	MODULE 3 QUALITY
Documentation on laboratory evaluation with Expert Report	Composition of medicinal product, Container, Clinical trial formulae, Development pharmaceuticals Method of preparation Control of starting materials (Specifications, routine tests and Scientific data for Active substance and Excipients) Control tests of intermediates Control tests on the finished products (Specifications, routine tests and Scientific data) Stability Bioavailability/Bioequivalence Data related to the environmental risk assessment for products containing genetically modified organisms (GMOs) Other Information	Module 3 table of contents Body of data Drug substance (General information, Manufacture, Characterization, Control of drug substance, Reference Standards or Materials, Container, Stability) Drug Product (Description and composition, Pharmaceutical Development, Manufacture, Control of excipients, Control of drug product, Reference Standards or Materials, Container, Stability) Appendices Regional Information Literature References

The qualitatively different approach can be seen in Module 1, which is including the Environmental risk assessment and Demonstration of significant benefit for Orphan medicinal products in the Annexes. A space for Environmental risk assessment describes present attitude in valuing drugs, regarding their influence on the environment. The task of this evaluation is to discuss possible risks to the environment from the point of view of products use and disposal, with proposition of measures for reducing this risk. In the EU format the Environmental risk assessment was divided and placed in Part II or III, depending on the presence of GMOs (genetically modified organisms) in the medicinal product.

There is another change in organization of the dossier in Module 2. Here should be presented the CTD Summaries, prepared by suitably qualified Experts. The classical "Expert Report" known from the EU format does not exist here. The term "Expert Report" is maintained for legal reasons, but the information is given in the form of Overviews and Summaries.

The Quality Overall Summary present information that provides an overview of Module 3, and discuss key issues that support information from other Modules. The Non-clinical Overview is continuing with presentation of assessment of the non-clinical evaluation. The quality of

batches of active substance used in this study should be discussed, so as the effects seen with related products. The Clinical Overview should be a critical analysis of the clinical data. It should include: description of the overall approach to the clinical development of the medicinal product, a brief overview of the clinical findings, an evaluation of benefits and risks of the medicinal product in its intended use, and description how the study results support critical parts of the prescribing information.

The content of the Module 3, 4 and 5 is parallel to the information from Part 2, 3 and 4 of the EU format. Mentioned parts include chemical, pharmaceutical and biological documentation, toxicological-pharmacological documentation and clinical documentation.

The scientific information from both versions of application dossier can be globally divided on: Quality, Non-clinical and Clinical information. The quality Part/Module is dealing with the quality of the manufacture series and the characteristics of the used test samples that can affect the results of evaluation process (table 2). The information on bioequivalence was more present in the pharmaceutical documentation of EU format and in EU CTD format is primary discussed inside of the clinical information and in Biopharmaceutical studies of Module 5.

Non-clinical documentation should present the advantages of the new product pharmacological-toxicological profile, compared with the existing similar medicinal products, and define needed specific conditions and safety issues regarding the administration of the drug (4). The role of clinical documentation in the dossier is to provide information for analysis of one medicinal product with grading its effectiveness, safety and global therapeutic value (5). There has been an organizational change in the CTD format, regarding clinical information. The Tabular Overview of the Expert Report on the Clinical

Documentation of Part I is now formed as Tabular listing of all clinical studies in Module 5 (table 3).

Correlation between the application dossier in the European Union and the Federation of Bosnia and Herzegovina

In the Federation of Bosnia and Herzegovina were discussed the differences between European and domestic

Table 3 Correlation between old and new way of presentation of the application dossier in the EU (Part III and IV - Module 4 and 5) and in the FBi H

FB&H	"Old" EU format (NTA, Vol. 2B Ed.1998)	EU CTD format (NTA, Vol.2B, Ed.2001)
Code of legislation on drugs, Marketing authorization	PART III TOXICO-PHARMACOLOGICAL DOCUMENTATION	MODULE 4 NONCLINICAL STUDY REPORTS
Documentation on pharmacological-toxicological evaluation (Pharmacodynamics, Pharmacokinetics, Toxicology), Expert Report and Literature references	Toxicity (Single-dose and Repeated-dose toxicity, reproductive function, Embryo-foetal and perinatal toxicity, Mutagenic potential, Carcinogenic potential) Pharmacodynamics (relating to the proposed indication, General, Drug Interactions) Pharmacokinetics (after a single dose and after repeated administration, Distribution, Biotransformation) Local tolerance Other Information Environmental risk assessment (non GMOs) *	Module 4 Table of Contents Study Reports Pharmacology (Primary and Secondary pharmacodynamics, Safety pharmacology, Pharmacodynamical Drug interactions) Pharmacokinetics (Analytical method, Absorption, Distribution, Metabolism, Excretion, Pharmacokinetic Drug Interactions, Other studies) Toxicology (Single-dose and Repeated-dose toxicity, , Carcinogenicity, Reproductive and developmental toxicity, Local tolerance, Other studies) Literature References
Code of legislation on drugs, Marketing authorization	PART IV CLINICAL DOCUMENTATION	MODULE 5 CLINICAL STUDY REPORTS
Documentation on clinical evaluation, Expert Report and Literature references	Clinical pharmacology (Pharmacodynamics and pharmacokinetics) Clinical experience (Clinical trials, Post-marketing experience, Other) Other Information	Module 5 Table of Contents Tabular listing of all clinical studies Clinical study reports (Biopharmaceutical studies, Pharmacokinetic studies with human material, pharmacokinetic studies, pharmacodynamical studies, efficacy and safety studies, post marketing experience) Literature References

rules for authorization, and some propositions that are in our country possibilities are adapted. In order to obtain marketing authorization, Applicant is considered to submit the following to the Regulatory authorities (2):

- Application with basic information about Manufacturer and medicinal product;
- Documentation on clinical, pharmacological-toxicological and laboratory evaluation;
- Certificate of quality of the medicinal product according to the World Health Organization rules for quality of the products intended for international trade, that proves authorization of the product in the country of manufacture and that the manufacture process was by the rules of the Good manufacture practice;
- List of the countries where the authorization is obtained, with the current prices;
- Certificate of Manufacturers authorization for the name of the medicinal product;
- Package Leaflet text;
- The way of safe disposal of expired drug;
- Manufacturers price of the medicinal product;
- Samples of the medicinal product.

Conclusion

There are no substantial changes regarding the content of old and new EU format, but the way of presentation and organization of the files is redefined. The parts of the dossier that describes in details all characteristics of the medicinal product are more strictly defined in the EU CTD format, so the new way of presenting information has less space for improvisation.

If we compare the legislation of the content of the application dossier in the EU and Federation no substantial difference in the content of documentation is present. But application and presented information about the medicinal product are more defined and extensive in the dossier for European Union marketing authorization process. Generally, our legislation is trying to keep step with EU. One of the goals of our health management policy is to develop the legislation in this segment that will correspond to European standards.

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