

Regulatory Update on eSubmissions in Balkans

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ABSTRACT

Electronic submissions of medicinal products are becoming mandatory for all types of Applications. Regional regulatory aspects are moving towards global electronic submissions/eCTD worldwide. The readers will get an indepth look at regulation compliance from the emerging markets like North Macedonia, Serbia, Montenegro, Bosnia and Herzegovina, Albania and Kosovo and keep up to date on country-specific environments concerning submissions of medicinal products and medical devices.

Keywords: Regulation, Electronic Submissions, Medicinal Products, Medical Devices, Harmonization.

INTRODUCTION

The Common Technical Document (CTD) describes the organisation of modules 1-5, sections and documents to be used by an Applicant for a Marketing Authorisation for a medicinal product for human use agreed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The electronic Common Technical Document (eCTD) allows for the electronic submission of the Common Technical Document (CTD) from applicant to regulator. While the table of content is consistent with the harmonised CTD, the eCTD also provides a harmonised technical solution to implementing the CTD electronically. eCTD represents the submission of PDF documents, stored in the eCTD directory structure, accessed through the XML backbone and with the files integrity guaranteed by the MD5 Checksum/eValidator [1,2].

Pharmaceutical filings have evolved considerably over the past half century in terms of content, process, and underlying supporting technologies. The industry as a whole has moved globally from primarily paper to mostly electronic submissions, and from almost entirely free-form text to an increasing amount of structured data for advanced internal analysis. In the meanwhile, the size and overall complexity of these submissions continues to increase.

Obtaining marketing authorization can be a significant barrier to market entrance. A good knowledge of the medicinal products and medical devices

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regulation is very important component of a product's marketing strategy, because there are differences in non-European Union countries in comparison with EU countries. Development of a regulatory strategy early in the product life cycle can greatly accelerate time of commercial entrance.

This paper discusses this background along with current events and trends impacting the industry today. These include changes to processes, such as the various expedited review processes used recently to address the COVID pandemic, the increasing interest of agencies in shared reviews, and the broad desire to reduce the time and costs of the submission review process.

The main goal of this article is to make comparative analysis of regulatory submission differences for medicinal products and medical devices at their first submissions, renewals and variations. The choice of countries is based upon where the company Bionika Pharmaceuticals is mainly active.

MATERIALS AND METHODS

Analytical and comparative methodology is used, as required by the subject of the research. In this paper has been analyzed the regulation of medicinal products and medical devices.

RESULTS AND DISCUSSION

In EU eSubmissions of medicinal products are mandatory for all types of Applications: Centralised, Decentralised and Mutual Recognition Procedures, as well as National

Procedures (new submissions, renewals and variations). The emergence of the first electronic submission in Europe happened in 1995; the earliest electronic submissions in the US in the late 1980s, a bit earlier than Europe, but different in structure [3].

NeeS (non-eCTD format) has been used as a transitional format towards the mandatory use of eCTD and is now only accepted in some specific cases.

Countries of interest

All countries of interest follow the European regulation for medicinal products and medical devices, but there are differences, also between countries. There is no mutual recognition between countries of interest, like in EU.

North Macedonia

In North Macedonia eSubmissions are mandatory for all types of Applications starting from 18.09.2018 (new submissions, renewals and variations). For renewals are requested only Module 1 & 2 and PSUR, if there are no changes in the other modules since the last marketing approval. Usually after renewal, the Agency - MALMED issues the marketing authorization on unlimited period [4, 5].

e-portal for submissions for medical devices is created on 01.08.2021, started with applications of already registered medical devices from 01.04.2022, but submissions via the e-portal are still not active.

The screenshot shows the MALMED e-portal interface. At the top, the date is 3/16/22, 2:42 PM and the user is logged in as marjan.dzeparoski@bionikapharm.com (Marjan Džeparoski). The main content area is titled 'My requests' and has tabs for 'Basic data', 'Documentation', 'Correspondence', and '???baranjePoraka???'.

Under the 'Documentation' tab, there is a section for 'Административна техничка документација' (Administrative technical documentation) with a table of requests:

Title	Set by	Data	Type	Size	Valid to date
<ul style="list-style-type: none"> ▼ АДМИНИСТРАТИВНО ТЕХНИЧКА ДОКУМЕНТАЦИЈА * 01. ПРОПРАТНО ПИСМО.pdf * 02. ДЕТАЛЕН ПРЕГЛЕД НА СОДРЖИНАТА НА ДОКУМЕНТАЦИЈАТА.pdf 02. ДОПОЛНИТЕЛЕН ОБРАЗЕЦ.pdf * 03. ИЗЈАВА ЗА ВЕРНОСТ НА ДОСТАВЕНИ КОПИИ.pdf * 04. EAN КОД.pdf * 05. ОВЛАСТУВАЊЕ НА ЛИЦЕТО ОДГОВОРНО ЗА ФАРМАКОВИГИЛАНЦА.pdf * 06. ДОКАЗ ДЕКА ЛИЦЕТО ИМА ВРАБОТЕНИ ЛИЦА ЗА ФАРМАКОВИГИЛАНЦА.pdf * 07. ОВЛАСТУВАЊЕ НА ЛИЦЕ ЗА КОМУНИКАЦИИ.pdf 08. а ДОКАЗ ЗА ПЛАТЕНА АДМИНИСТРАТИВНА ТАКСА И ПЛАТЕНИ НАДОМЕСТОЦИ УПЛАТА ЗА СТРУЧНИ ПРОЦЕНКИ НА АГЕНЦИЈАТА.pdf 	Цепароски Марјан	17.02.2022 02:05:07	pdf	385KB	
	Цепароски Марјан	17.02.2022 02:05:30	pdf	3KB	
	Цепароски Марјан	17.02.2022 02:07:29	pdf	139KB	
	Цепароски Марјан	17.02.2022 02:13:54	docx	29KB	
	Цепароски Марјан	17.02.2022 02:14:08	pdf	399KB	
	Цепароски Марјан	17.02.2022 02:14:25	pdf	1606KB	
	Цепароски Марјан	17.02.2022 02:36:30	pdf	5490KB	
	Цепароски Марјан	17.02.2022 02:39:24	pdf	107KB	

Figure 1. MALMED – view of agency e-portal (new submission).

Serbia

In Serbia partial eSubmissions are accepted from 20.12.2016 (e-appointments, cover letters and application forms, CPPs, advertising of medicinal products, variations*, renewals*), although “paper” CTD format is still in force for medicinal products. Full submissions are expected to be functional until end of 2024/early 2025.

*If the files are too large, they should be submitted in “paper format” (*10 MB max. file data).

For renewals are requested only Module 1 & 2 and PSUR, if there are no changes in the other modules since the last marketing approval. After renewal the Agency - ALIMS can issue the marketing authorization on unlimited period [6, 7].

Variation approvals take too long, far beyond the legal timeframes.

From 02.12.2018 eSubmissions of medical devices are mandatory via e-portal.

Figure 2. ALIMS – view of agency e-portal (application).

Bosnia and Herzegovina

In Bosnia and Herzegovina *NeeS is mandatory for all types of Applications starting from 01.01.2015, for variations from 01.06.2015 (first country from the region). On the Agency website is uploaded NeeS Checker (validation software) for checking whether there is an error in the submission dossier. For renewals are requested only Module 1 & 2 and PSUR, if there are no changes in the other modules since the last marketing approval. There is no practice after renewal,

that Agency - ALMBiH issues the marketing authorization on unlimited period [8, 9].

eSubmissions of medical devices are mandatory via e-portal from 01.2017 (also first country from the region).

*The company Bionika Pharmaceuticals has developed its own in-house software for creation of NeeS format for submissions in Bosnia and Herzegovina and for the other countries of interest (Figure 3).

Nees submission

Module 1 Administrative Information and Prescribing Information
 Module 2 Common Technical Document Summaries
 Module 3 Quality
 Module 4 Nonclinical Study Reports
 Module 5 Clinical Study Reports

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Figure 3. View of Nees submission (non-eCTD format).

Kosovo

In Kosovo eSubmissions are mandatory only for new marketing authorisations from 01.04.2018.

For renewals and variations eSubmissions are possible starting from 11.2021 only for medicines which are in the database (which have obtained marketing authorisations starting from 06.2018).

For renewals are requested only Modules 1 & 2.3 and PSUR, if there are no changes in the other modules since the last

marketing approval. There is no practice after renewal, that Agency - KMA issues the marketing authorization on unlimited period [10].

Grouping of variations is only possible for 1 medicinal product in the portal, so otherwise the company should submit the variations as paper documents.

In Kosovo there is no need for registration of medical devices if they are CE certified, so they are marketed based on import licences.

Figure 4. AKPPM – view of agency e-portal (variation)

Montenegro

“Paper” CTD format is only accepted in Montenegro. For renewals are requested only Module 1 & 2 and PSUR, if there are no changes in the other modules since the last marketing approval. After renewal, the Institute - CInMED can issue the marketing authorization on unlimited period [11].

Paper documentation is needed also for the medical devices.

There is service for monitoring status of applications via portal available for registered responsible regulatory person.

Albania

“Paper” CTD format is only accepted in Albania (evaluation in 2 separate consecutive phases). For renewals are requested Modules 1-3. There is no practice after renewal, that Agency - AKBPM issues the marketing authorization on unlimited period [12].

Grouping of variations is not possible (only country from the region).

Paper documentation is needed also for the medical devices.

Regional National Agencies have developed customized softwares for electronic submissions, but also documents in NeeS and eCTD format can be used for upload.

It is expected that all countries will develop similar network and management system in the near future.

CONCLUSION

There are differences concerning medicinal products and medical devices regulation and submissions for obtaining marketing authorization in non-European Union countries in comparison with EU countries.

For medicinal products in Serbia are accepted only partial eSubmissions, paper format is still in force in Montenegro and Albania. For medical devices paper format submission is still in force in Montenegro and Albania, there is no need for registration of CE marked Medical Devices in Kosovo.

Regional aspects are moving towards Global aspects – on which way harmonization will be achieved.

In “near” future eCTD format is expected to be mandatory for all submissions. Benefits are well-known, such as data quality, structured content, reusability, faster access, more office space.

Submission of products for obtaining marketing authorization

by companies must be planned early in the product life cycle and in accordance with the current country regulation for specific product category.

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