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Professional Paper

NEW EUROPEAN COMMISSION REGULATION ON VARIATIONS TO THE TERMS OF MARKETING AUTHORISATION FOR MEDICINAL PRODUCTS AND ITS IMPACT ON CROATIAN LEGISLATION

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Variations introduced to medicinal product documentation must not affect the quality, efficacy, and safety of the product. Croatian Medicinal Products Act and accompanying ordinances are largely aligned with the EU regulations. The EU has now tried to simplify the issue of variations with a new Regulation, creating differences in the definition of and approach to resolving certain types of variations between Croatia and the EU. These differences could hinder the approval procedure for variations in Croatia, particularly for medicines already approved in the EU. Amending the Croatian Ordinance on medicines already authorised in the EU would be one way of maintaining the efficiency of the Croatian regulatory system.

KEY WORDS: *efficacy, Medicinal Products Act, quality, registration documentation, safety*

Marketing authorisation of a medicinal product is granted based on the product documentation, which must contain all data and documents confirming its quality, efficacy, and safety. In the Republic of Croatia, the content of this documentation is determined by the Medicinal Products Act and subordinate legislation. Pursuant to the Act, the Minister responsible for health and social welfare issues ordinances which describe procedures set by the law with greater clarity and in more detail. Since 1997, relevant legislation has been amended several times in the EU and Croatia, in line with new findings pertaining to medicinal products, public health, and regulations. Most of the medicinal products from the EU Member States are available in Croatia alongside our own medicinal products. As Croatia has applied for the EU membership, its legislation concerning medicinal products has largely been aligned with that of the European Union.

Documentation for medicinal products is subject to change. Handling of variations requires significant administrative and regulatory efforts which involve both competent authorities and industry (1-3). Variations have to be implemented in such a way not to affect the quality, efficacy, and safety of the medicinal product.

According to the 2007 Medicinal Products Act still in force, marketing authorisation holder for a medicinal product is required to keep up with scientific and technical advancements and to introduce appropriate variations to assure that the manufacture and quality control of the medicinal product are in line with generally accepted scientific principles (4, 5). Variations to medicinal product data can result from amendments to regulations, operations of the manufacturer or marketing authorisation holder, market demand, or other economic reasons. Furthermore, certain variations may result from regulatory action initiated by competent authorities or marketing authorisation holder, in line with the new safety information that could affect the risk/benefit ratio of the product.

The objective of this article is to give a chronological overview of provisions concerning variations in documentation on medicinal products for human use in the Croatian legislation from 1997 to 2009. It also brings an overview of the most important provisions of the new Commission Regulation (EC) No. 1234/2008 on variations and a comparison with current Croatian regulations.

OVERVIEW OF THE PROVISIONS ON VARIATIONS IN THE CROATIAN LEGISLATION FROM 1997 TO 2009

The Croatian legislation classifies variations into several categories, depending on their impact on the quality, efficacy, and safety of a medicinal product and related risks. Variations are primarily regarded as minor (types IA and IB) or major (type II).

The procedure, conditions, and documentation for granting, renewal, revocation, and transfer of marketing authorisation for a medicinal product in Croatia, and for acceptance and approval of variations to the authorisation and documentation on a medicinal product are defined by the 2007 and 2009 Medicinal Products Act and two ordinances (4-7).

According to these regulations, marketing authorisation holder is required to submit an application to the Agency for Medicinal Products and Medical Devices for approval of variations of the marketing authorisation or medicinal product documentation before the variations are applied. A separate application for each variation is required, except in cases of consequential variations (6).

The first Croatian Act on Medicinal Products and Medical Devices from 1997 and its amendment from 2001 did not contain any provisions on variations of the marketing authorisation or medicinal product documentation (8, 9).

The Ordinance on the procedure and method for granting marketing authorisations for medicinal products came into effect in 1998. In addition to defining the procedure and documentation required for issuing marketing authorisation for medicinal products, it also laid down provisions on variations to medicinal product documentation. It became mandatory for marketing authorisation holder to submit an application to the minister of health for each variation in accordance with authorisation granted (10). Until the establishment of the Agency in 2003, marketing authorisations were granted by the Ministry of Health of the Republic of Croatia.

The Ordinance distinguished two types of variations, minor and major, and listed the documentation to be submitted with the application for approval of the variation (10). It listed all minor variations and conditions that each variation had to meet to be considered a minor variation. However, documentation to be submitted with the application for approval of the variation was not clearly defined. Major variations were considered all those not included in the group of minor variations. These were further divided into those requiring a new application for marketing authorisation, which were clearly listed, and those requiring an application for approval of variations, which were not clearly listed (10). The Ordinance also defined the content of the documentation to be submitted for switching from prescription to over-the-counter issuance of a product.

The 2003 Act on Medicinal Products and Medical Devices and its 2004 amendment (11, 12) brought significant changes to the regulation of medicinal products for human use. The Act established the Agency for Medicinal Products and Medical Devices, modelled after similar agencies of the EU Member States, to carry out the complete procedure of issuing marketing authorisation. The provisions of the Act were largely aligned with the EU Directives (18-20).

Unlike the earlier Act, this Act contained provisions important for variations and defined the application procedure and time for approval of variations to the medicinal product documentation or marketing authorisation (Table 1). The Act foresaw a new ordinance that would define the procedure and content of the documentation for issuing, renewing or changing authorisations, but the new ordinance was not passed and a series of discrepancies arose between the provisions of the new Act and the old Ordinance which was in force at the time. This made variation approval difficult.

This situation partly improved with the 2004 Ordinance on special conditions for placing medicinal products authorised in the Member States of the European Union on the market of the Republic of Croatia (13). However, this Ordinance laid down provisions applicable to medicinal products approved in the EU Member States pursuant to the centralised procedure, mutual recognition procedure, and national procedures of the United Kingdom, Ireland, Sweden, Denmark, and the Netherlands, but did not apply to

Table 1 *Comparison of legal provisions from 1997 to 2009*

Considered parameter	Act on Medicinal Products and Medical Devices (8, 9)	Act on Medicinal Products and Medical Devices (11, 12)	Act on Medicinal Products (4, 5)
Assessment of validity of the application	No specific provisions on variations	30 days	Agency requests amendment of incomplete application within 30 days
Deadline for assessment of variations		90 days	90 days from receipt of valid application
Types of variations		Not classified	Not classified New: contains provisions on the transfer of authorisation to another legal person in Croatia, and provisions concerning extraordinary safety measures that could result in variations to authorisation or documentation

medicinal products of domestic manufacturers and those from non-EU countries (13). Its objective was to simplify and speed up assessment and approval of medicinal products previously assessed and approved by the competent authorities in the EU Member States. Accordingly, the applicant was required to demonstrate previous approval in the EU with appropriate documentation. The Ordinance clearly defined conditions and documents needed for authorising variations in these circumstances. It stipulated that documentation submitted to competent authorities in Croatia was to be identical to the one submitted in the EU and that the authorisation holder was to report all variations to both the Agency and a competent authority in the EU Member State (13).

The new, 2008 Ordinance (7) has established special conditions for marketing medicinal products in Croatia that have been approved in the EU Member States through a centralised procedure (the European Medicines Agency is responsible for this procedure which results in a single marketing authorisation valid across the EU), mutual recognition procedure (after one EU Member State has authorised a medicine in accordance with its national procedure, other EU countries may recognise the validity of the original, national marketing authorisation) or a decentralised procedure (a medicine is authorised in several EU countries at the same time). The last two procedures are used where the centralised procedure is not mandatory. This Ordinance more clearly defines variations and is

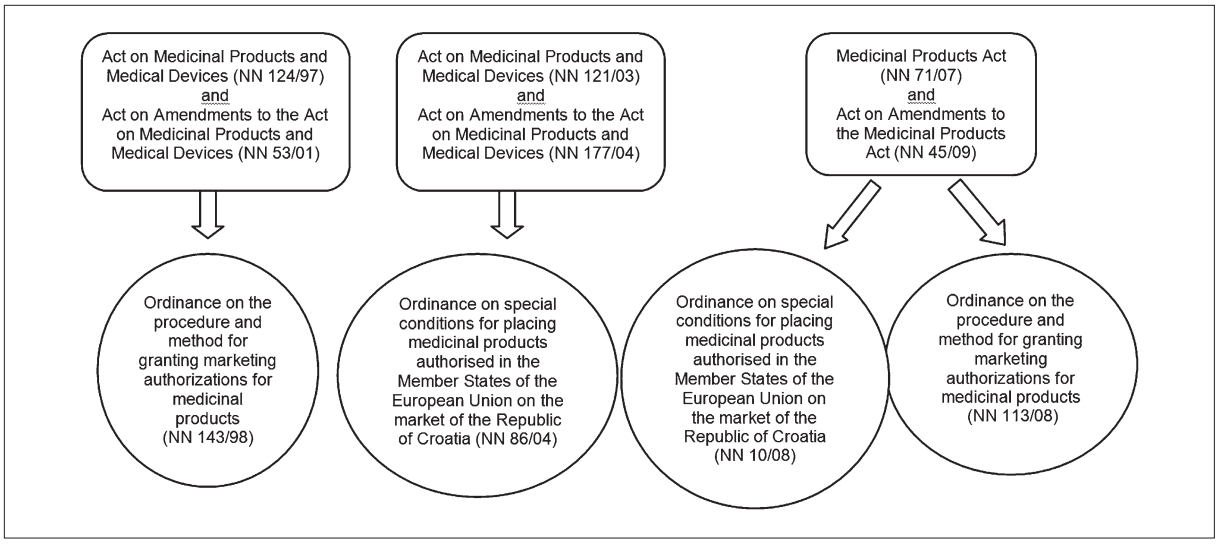

Figure 1 *Review of Croatian laws on medicinal products for human use from 1997 to 2009 relevant for variations to marketing authorisation or medicinal product documentation from 1997 to 2009*

the first to distinguish minor (types IA and IB) and major (type II) variations, and variations due to urgent safety restrictions. However, the Ordinance does not provide a list of variations. It defines the time and documents needed for the application for approval of variations to be submitted to the Agency (Table 2) and an application form for every pharmaceutical form, strength, or packaging (7).

The current 2007 Medicinal Products Act and its 2009 amendment (4, 5) for the first time in Croatia brings provisions related to medicinal products only and continues the alignment with the EU legislation. Provisions on variations are now more complete and precise. The Act also defines the transfer of authorisation to another legal person seated in Croatia and urgent safety restrictions that could lead to variations to the marketing authorisation or documentation (4, 5). Table 1 outlines the differences in respect to earlier acts.

The approval process and content of the documentation submitted for changing the authorization are outlined in detail in the 2008 Ordinance on the procedure and method for granting marketing authorizations for medicinal products (6). In comparison with the 1998 Ordinance, it more precisely defines the procedure, conditions, and documentation necessary for approval of variations to the marketing authorisation and documentation on a medicinal product. It distinguishes minor (IA and IB) and major (II) variations and consequential variations and defines procedures for certain pharmacovigilance variations (Table 2) (6).

The Ordinance gives a detailed list of minor variations (IA, IB), reporting conditions, and documentation to be submitted depending on the reported variation. Major variations (II) are defined as those that cannot be considered minor variations and as those not requiring initiation of a new marketing authorisation procedure, or those requiring initiation of a new marketing authorisation procedure (6).

The Ordinance defines a consequential variation as a variation ensuing from other variations that cannot be avoided. For example, a type IA variation may be a consequential variation of another type IA variation, a type IB variation may be a consequential variation of another type IB or IA variation, while other consequential variations are reported as part of type II variations (6).

Variations due to urgent safety measures are variations introduced on account of new information on the use of a medicinal product due to which urgent restrictions must be imposed on the authorised use of the medicinal product in the interest of public health protection. Such measures include narrower therapeutic range, changes in posology, restriction of use to a limited group of patients, extension of contraindications or precautionary measures.

Unlike the 1998 Ordinance, the 2008 Ordinance provides a special form for variations to be submitted with the application.

Provisions defining the deadlines for approval of the variations have also amended and depend on the type of variations (Table 2).

The Ordinance also defines variations to the summary of product characteristics, package leaflet, and labelling of the medicinal product that can exceptionally make part of authorisation renewal based on a conclusion in the enclosed Periodic Safety Update Report (PSUR), to align the name of a pharmaceutical form and ingredients with the Croatian pharmacopeia, and to align the format of the summary of product characteristics, package leaflet, and product labelling with the current Act and this Ordinance without affecting their content. Any other variation requires a separate application (6).

COMMISSION REGULATION NO 1234/2008 OF 24 NOVEMBER 2008 CONCERNING THE EXAMINATION OF VARIATIONS TO THE TERMS OF MARKETING AUTHORISATIONS FOR MEDICINAL PRODUCTS FOR HUMAN USE AND VETERINARY MEDICINAL PRODUCTS

The Regulation of the European Commission concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products was passed on 24 November 2008. It came into force on 1 January 2010 (14). This Regulation was preceded by Commission Regulations Nos. 1084/2003 and 1085/2003 as, following detailed analysis, it was established that these presented a burden to both industry and regulatory authorities (15-17). These regulations defined procedures for approval of variations to marketing authorisations granted based on the centralised and decentralised procedures, but not for those based on purely national procedures which differ among the EU Member States and the majority of reported variations pertain to

Table 2 *Comparison of Ordinances from 1997 to 2009*

Considered parameters	Ordinance on the procedure and method for granting marketing authorizations for medicinal products (10)	Ordinance on special conditions for placing medicinal products authorised in the Member States of the European Union on the market of the Republic of Croatia (13)	Ordinance on special conditions for placing medicinal products authorised in the Member States of the European Union on the market of the Republic of Croatia (7)	Ordinance on the procedure and method for granting marketing authorizations for medicinal products (6)
Types of variations	Minor and major variations Provisions on switching from prescription to over-the- counter issuance of a product	Provisions on variations approved in the EU No mention of the types of variations	- Provisions on variations approved in the EU - minor (IA and IB), - major (II), - variations due to extraordinary safety measures	- minor (IA, IB) - major (II), and - consequential variations Provisions on pharmacovigilance variations: - due to extraordinary safety measures, - in time of submission of Periodic Safety Update Reports (PSURs), - in the description of the pharmacovigilance system - in the risk management plan. Provisions on switching from prescription to over- the-counter issuance of a product
Application form for reporting variations	No specific form	No specific form	Specifies form	Specifies form
Deadline for assessing validity of variation or approval of variation (in addition to the Act)	No deadline	Deadline for marketing authorisation holder to complete the application: 45 days from receipt of notification from the Agency	Marketing authorisation holder submits a request to the Agency for approval of variations within 60 days of their approval in the EU Deadline to complete application: 30 days (Approval of variations according to the 2007 Act: 90 days)	Deadline for marketing authorisation holder complete application: 30 days from receipt of notification from the Agency Approval: Minor variations (IA, IB): 30 days Major variations (II): 90 days from receipt of valid application Novelty: if the Agency does not inform the applicant of approval of the variation within 30 days of receipt of application reporting a minor variation (IA) not requiring an amendment of the marketing authorisation, it is automatically granted

these procedures (1). The lack of alignment between national procedures for resolving variations can hinder free movement of medicinal products between countries (1). Therefore, the objective of the new EC Regulation was to establish a simpler, clearer and more flexible legislative framework for variations, aimed at reducing administrative burden, adopting ICH concepts, and aligning the procedures among the EU Member States, while also ensuring a uniform level of public human and animal health protection

Table 3 *Procedures and deadlines for the approval of variations to medicinal products approved through decentralised procedure (DCP)*

DCP/minor variations of type IA	Marketing authorisation holder submits notification and documents within 12 months of implementation of the variation (or immediately if necessary for continued supervision)	Competent authority informs the marketing authorisation holder and other relevant authorities within 30 days of the status of the variation and its impacts on subsequent marketing authorisation approvals		
DCP/minor variations of type IB (when the variation is approved)	Marketing authorisation holder submits notification and documents to all relevant authorities	Competent authority of the reference member state confirms validity of the notification after consulting other member states	If no authorities disagree within 30 days, the notification is accepted	Competent authority of the reference member state informs marketing authorisation holder and other relevant authorities of the member state of acceptance of the notification
DCP/minor variations of type IB (when the variation is rejected)		Competent authority informs the marketing authorisation holder and other relevant authorities of the rejection, citing reasons	Marketing authorisation holder may submit an amended notification to all relevant authorities within 30 days. The competent authority of the reference member state assesses it within 30 days and delivers its final opinion to the marketing authorisation holder and other relevant authorities	If the marketing authorisation holder does not amend the notification as required, it shall be considered rejected by all relevant authorities
DCP/major variations of type II	Marketing authorisation holder submits application for approval of variations and documents to all relevant authorities	Competent authority acknowledges receipt of the valid application and informs the marketing authorisation holder and other relevant authorities of the start of the procedure	Competent authority of the reference member state issues an application assessment report and a decision on the application, and informs other relevant authorities within 60 days (may be reduced in urgent situations or extended to 90 days for changes to therapeutic indications)	The competent authority of the reference member state may request supplementary information from the marketing authorisation holder, and inform other member states that the procedure is suspended until receipt of the requested information
	Relevant authorities of the member states recognise the decision and inform the competent authority of the reference member state within 30 days	If no authorities disagree in this period, the decision on the application is adopted	If the decision is accepted by all relevant authorities, the reference authority informs the marketing authorisation holder and other authorities of the status of the variation and possible amendments to the decision on granting marketing authorisation	If the variation represents a serious public health threat, the reference authority forwards the case to the coordination group for discussion

(1, 17). This will be achieved, among other things, through provisions on worksharing procedure and through simplified implementation of minor type IA variations. The categorisation of variations has also been amended; major variations with greater impact on the quality, efficacy, and safety of a medicinal product are clearly defined, while variations not foreseen under the Regulation are considered minor type IB variations. The Regulation does not define transfer of authorisations from one holder to another and is not applicable for variations to homeopathic or traditional herbal medicinal products approved pursuant to a simplified registration procedure (14).

Minor type IA variations

Minor type IA variations are divided into those for which competent authority can be notified at any time up to 12 months after implementation and those for which notification is sent immediately after implementation. The notification can take the form of a special notice or of an annual report containing a list of all implemented minor type IA variations. However, variations that require immediate notification and all other variations requiring approval prior to implementation are not included in this report (14).

This should simplify approval of variations, reduce the number of applications, and give competent authorities more time to concentrate on variations that really affect the quality, safety, and efficacy of medicinal products.

Major type II variations

Major variations of type II are defined as those variations that are not extensions of marketing authorisations and which could have a significant impact on the quality, efficacy, and safety of a medicinal product. These are listed in the Regulation (14).

Minor type IB variations (including article 5 recommendations)

The Regulation defines and lists minor type IA variations, major type II variations, extensions of marketing authorisations, cases for grouping variations, and minor type IB variations that are not included under any of the given lists. (14).

Earlier Regulations clumped all unforeseen variations into the category of major variations and, for that reason, some seemingly simple variations were required to undergo a complicated procedure (1). The new Regulation requires that all variations whose classification is ambiguous should be considered minor type IB variations in the sense that this category applies by default (14). However, these variations are considered major if the marketing authorisation holder or a competent authority finds them to have a significant impact on the quality, efficacy, and safety of a medicinal product (14).

The Regulation allows marketing authorisation holders before they submit an application to directly request a recommendation of the variation classification from European Medicines Agency (EMA) or from a relevant coordination group consisting of experts EU Member States authorities, who review any issues related to marketing authorisation in two or more Member States. The recommendation must be issued within 45 days of the request. Copies are delivered to the marketing authorisation holder, EMA, and the competent authorities of the EU Member States (14).

To ensure clear classification and increase the reliability of these recommendations, cooperation is essential between a coordination group and EMA. In line with this, the Regulation stipulates that these recommendations should be made public once information of commercial importance is removed (14).

Grouping of variations

In addition to the standard application for each variation, the Regulation allows for submission of a single application or notification for a group of variations to facilitate assessment of variations and reduce the administrative burden. Earlier, it was possible to report multiple variations together only if one variation led to other or multiple variations (15, 16).

Extensions of marketing authorisations

The Regulation lays down a list of variations considered to be extensions of marketing authorisations such as new doses or new pharmaceutical forms. Variations in this category are evaluated in the same procedure as the initial marketing authorisation, as they could lead to a new authorisation or amendment of the existing authorisation (14). The final decision is left to the Member State and the same variation could result in a new authorisation in one Member State or in an amendment in another.

Procedures (including worksharing)

The Regulation defines procedures for accepting variations to marketing authorisations granted pursuant to decentralised (Table 3) and centralised (Table 4) procedures. Each is divided according to the type of variation. The Regulation also defines the deadlines for implementation of each variation following approval (14).

If a variation leads to a change in the summary of product characteristics, package leaflet, or product labelling, these are to be revised with an assessment of the variation. Procedures concerning changes to an active substance for the purpose of the annual update of a human influenza vaccine, which are considered type II variations, are the same as for other medicinal products, though with shorter deadlines. The Regulation also defines the deadlines for the submission and assessment of clinical information and information on the stability of the vaccine (14).

Worksharing procedure is special procedure set by the Regulation, that involve a reference authority, selected among the competent authorities of the EU Member States or EMA, which approves variations on behalf of all involved authorities. This applies to minor type IB variations, major type II variations or a group of variations that does not include extension of marketing authorisation and which relates to several marketing authorisations of the same holder. The reference authority can be EMA if at least one of the authorisations was granted pursuant to the centralised procedure, or a competent authority of a Member State selected by the coordination group (14). Procedures depending on the type of variation are described in Table 5. Worksharing procedure is intended to avoid duplication of work and to make possible simultaneous implementation of the same variation(s) in several Member States.

LEGAL DISCREPANCIES BETWEEN THE EU AND CROATIA

Croatian Medicinal Products Act and two related ordinances were passed before the European Commission Regulation No. 1234/2008 came into effect, and there are evident differences between them. The greatest difference is in categorisation of variations and procedures for their approval. The Croatian legislation does not define "groups of variations" and "extensions of marketing authorisation" in the manner defined by the EC Regulation. Croatian legislation does not allow implementation of any type of variation before its approval. In addition, minor type IB variations do not include unforeseen variations; instead they are clearly listed in the Ordinance on the procedure and method of granting marketing authorisations for medicinal products (6). Major type II variations however include variations not considered minor. Croatian legislation also has not yet included the worksharing procedure established by the new EC Regulation. Variations to medicinal products approved in the EU, and which have been approved and are present on the Croatian market will be reported pursuant to the Ordinance on special conditions for placing medicinal products authorized in the Member States of the European Union on the market of the Republic of Croatia (7). This Ordinance distinguishes only minor types IA and IB variations, major type II variations, and variations due to urgent safety restrictions. With time these differences may hinder the implementation and approval of variations as defined by the current Croatian regulations.

To maintain the efficiency of the Croatian regulatory system, the fastest solution would be to amend the Ordinance on special conditions (7) to conform to the EC Regulation 1234/2008.

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Table 4 *Procedures and deadlines for approval of variations of medicinal products through centralised procedure (CP)*

CP/ minor variations of type IA	Marketing authorisation holder submits notification and documents to the European Medicines Agency within 12 months of implementation of the variation (or immediately if necessary for continued supervision)	European Medicines Agency informs marketing authorisation holder and European Commission within 30 days of its decision on the variation and on possible amendments to the decision on marketing authorisation approval		
CP/ minor variations of type IB (when the variation is approved)	Marketing authorisation holder submits notification and documents to the European Medicines Agency	European Medicines Agency acknowledges receipt of the valid notification	If the European Medicines Agency does not deliver an unfavourable opinion to the marketing authorisation holder within 30 days of acknowledgement of receipt, the notification is accepted	European Medicines Agency informs the marketing authorisation holder and European Commission of acceptance of the notification and of possible amendments to the decision on marketing authorisation approval
CP/ minor variations of type IB (when the variation is rejected)		European Medicines Agency informs the marketing authorisation holder of the unfavourable opinion, citing reasons	Marketing authorisation holder may submit an amended notification to European Medicines Agency within 30 days of receipt of the unfavourable opinion, which will be assessed and the final opinion delivered to the marketing authorisation holder and European Commission within 30 days	If the marketing authorisation holder does not amend the notification as required, it shall be considered rejected, and the European Medicines Agency shall inform the marketing authorisation holder and European Commission of the same
CP/ major variations of type II	Marketing authorisation holder submits application for approval of the variations and documents to the European Medicines Agency	European Medicines Agency acknowledges receipt of the valid application	European Medicines Agency issues its opinion on the valid application within 60 days of receipt (may be reduced in urgent situations or extended to 90 days for amendments to therapeutic indications)	The European Medicines Agency may request supplementary information from the marketing authorisation holder. The procedure is suspended until receipt of the requested information
	Committee for Medicinal Products for Human Use of the European Medicines Agency issues its opinion on the application, in line with Commission Regulation EC No 726/2004	European Medicines Agency informs the marketing authorisation holder and European Commission of the final opinion within 15 days		

Table 5 *Worksharing procedures*

Marketing authorisation holder submits application and documents to all relevant authorities, indicating the recommended reference authority	If the application meets the requirements, the coordination group selects the reference authority which acknowledges receipt of the valid application	If the chosen reference authority is a competent authority of an member state which has not granted marketing authorisations for all the medicinal products affected by the application, the coordination group may request assistance of another relevant authority in the evaluation	Reference authority issues opinion within 60 days in case of minor type IB variations or major type II variations (may be reduced in urgent cases or extended to 90 days for amendments to therapeutic indications)	The reference authority may request supplementary information from marketing authorisation holder and inform other relevant authorities that the procedure is suspended until receipt of the requested information
Final opinion (reference authority is European Medicines Agency)	European Commission amends where necessary the centralised marketing authorisation and updates the Community Register of Medicines within 30 days of receipt of the final favourable opinion of the European Medicines Agency	Member States approve the final opinion of European Medicines Agency within 30 days, inform European Medicines Agency and amend the concerned marketing authorisation(s) where necessary		
Final opinion (reference authority is the competent authority of the Member State)	Competent authority of the member state forwards its opinion on the valid application to the marketing authorisation holder and all relevant authorities	Relevant authorities approve the opinion within 30 days, inform the reference authority and amend the concerned marketing authorisation(s)	Member States provide information on the marketing authorisation(s) affected by the variation to verify validity of the application and issue an opinion on the application, if requested by the reference authority	

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Sažetak

NOVA UREDBA EUROPSKE KOMISIJE O IZMJENAMA – UČINAK NA HRVATSKO ZAKONODAVSTVO

Uvođenje izmjena u dokumentaciju o lijeku na temelju koje je lijek dobio odobrenje za stavljanje u promet mora biti provedeno na način da te izmjene ne utječu na kakvoću, djelotvornost i sigurnost primjene lijeka. Navedeno je u Republici Hrvatskoj regulirano Zakonom o lijekovima i pratećim Pravilnicima koji su uvelike harmonizirani s propisima Europske unije. Hrvatski propisi u zadnjih 12 godina doživjeli su niz promjena u cilju donošenja potpunijih i jasnijih odredbi. Paralelno i u Europskoj uniji nastojalo se je pojednostaviti rješavanje izmjena te je donesena nova Uredba o izmjenama.

Nova Uredba EK o izmjenama donesena je nakon stupanja na snagu važećih hrvatskih propisa s područja lijekova i njihovom usporedbom uočavaju se razlike u definiranju i pristupu rješavanja određenih vrsta izmjena u Hrvatskoj i zemljama EU.

Moglo bi se dogoditi da će navedene razlike, otežati provođenje procedura o odobravanju izmjena na način kako definiraju hrvatski propisi. Jedan od načina kako bi se mogla zadržati jednaka efikasnost hrvatskog regulatornog sustava jest pristupiti izmjeni Pravilnika o posebnim uvjetima za stavljanje gotovog lijeka u promet u Republici Hrvatskoj koji ima odobrenje u Europskoj uniji.

KLJUČNE RIJEČI: *djelotvornost, dokumentacija o lijeku, kakvoća, sigurnost, Zakon o lijekovima,*

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