

Generic Medicines in Croatia – Regulatory Aspects and Statistics

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ABSTRACT

A generic medicine is an equivalent of an originator pharmaceutical product. It contains the same active substance as, is »essentially similar« to, and is therefore interchangeable with, the originator product. The objective of this study was to determine the share of generic medicines of the total received marketing authorization applications in Croatia, and the specificities in the approval of generic medicines with regard to assessments of their quality documentation. We collected the information from the Agency's medicinal products databases. Absolute numbers are shown for the applications for the authorizations of medicines in total and generics in particular in the period from 2005–2009. Data were analyzed using descriptive statistics. The annual number of marketing authorization applications for generic medicines received in Croatia increased from 148 applications in 2005 to 276 applications in 2009. In the period from 2005–2009, the number of applications for the approval of generic medicines accounted for 55% of all submitted applications. More than five generic medicines were approved for the following active compounds: amlodipine, lisinopril, atorvastatin, tamsulosin and omeprazole. In the following years, the number of applications from international manufacturers stagnated, while the number of applications by local manufacturers is on a steady climb, with the exception of 2008. From 2005–2009, an almost continual increase in the number of applications for the approval of generic medicines is evident. The largest number of generic medicines was approved for generic medicines intended for the treatment of cardiovascular disease (amlodipine, lisinopril, atorvastatin). A continual increase of applications from local manufacturers has been recorded. In the approval of these medicines, it is very important to develop a uniform approach to assessing the quality of each medicine, in order to guarantee a high quality product for the patient.

Key words: generic medicines in Croatia, quality of generic medicines, bioequivalence, marketing authorization

Introduction

Definition and price of generic medicine

Generic medicine is a medicinal product having the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence is proven to correspond with that of the reference medicine through bioavailability testing^{1,2}. The same active substance is considered to be different salts, esters, ethers, isomers, mixtures of isomer, complexes or derivatives of the active substance, unless there are significant differences in their properties with regard to the safety and/or efficacy^{3–5}. Various immediate-release oral pharmaceutical forms are considered to be the same pharmaceutical form.

At the time of expiry of patent protection for a given originator (reference) medicine, any manufacturer is free to market the said medicine as a generic medicine, under the conditions that it abides by Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP)^{6–8} bearing in mind that adequate pharmaceutical and preclinical tests are provided and that bioequivalence of the generic medicine to the original medicine is proven by the manufacturer. Alongside the manufacturer marketing authorization holder also has an important role in the authorization procedure and post-marketing period of the medicine concerned. Some applicants, who don't have appropriate bioequivalence studies for their generics, try to submit well-establish use application for the medicines concerned. This malpractice may raise important public health con-

cerns, especially in the new Member States of EU which have to be particularly aware of this problem.

The reason why the price of generic medicines is less than the price of the originator medicine lies in the fact that generic medicines contain an active substance whose efficacy and safety have already been established, not only in clinical trials prior to approval, but also in the many years of use in patients once it is marketed. Proven bioequivalence implies, at the present state of science, the same therapeutic value, so consequently, repetition of human trials is both scientifically unnecessary and unethical. The requirement for repeating experiments in humans for the purpose of proving facts that are already well known is contrary to the Helsinki Declaration on ethical principles in medical research conducted on humans^{9,10}. Consequently, the procedure of approving generic medicines is substantially shorter, and also requires substantially less financial investment by the manufacturer.

In all developed countries of the world, the legal regulations are being amended in order to take better advantage of generic medicines, which by definition should be less expensive than the originator medicine. In line with the above, the European Generic Medicines Association (EGA) lists a price reduction for generic medicines of 20–90% in comparison with the originator medicines¹¹.

Data exclusivity period

Data Exclusivity Period is a period of time during which the applicant is restricted from applying to the medicines authorities for generic marketing authorization route, e.g. referring to the originator's dossier and submitting only bioequivalence study results. Consequently generic medicines can only be evaluated and approved by the medicines authorities after the data exclusivity period has expired. Data exclusivity guarantees additional market protection for originator pharmaceuticals by preventing health authorities from accepting applications for generic medicines during the exclusivity period.

The New EU Pharmaceutical Legislation adopted in 2004 has created a harmonized EU eight-year data exclusivity provision with an additional two-year market exclusivity provision. This effective 10-year market exclusivity can be extended by an additional one year maximum if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorizations, are held to bring a significant clinical benefit in comparison with existing therapies. This is so called 8+2+1 formula which means that a generic application for marketing authorization can be submitted after year 8, but that the product cannot be marketed until after year 10 or 11^{12–14}.

U.S. law provides five years of data exclusivity for new chemical entities, and three years for other pharmaceutical products^{13–15}.

In Croatia, the data exclusivity period for a generic medicine is six years which is stipulated by the Act on

Medicinal products; however, Amendments to the Act of 2009¹⁶, which regulate the period following the accession of Croatia to the EU, adopted the 8 + 2 + 1 formula¹⁷.

Approval of the generic medicine – necessary documentation for granting authorization

The application for marketing authorization of a generic medicine is accompanied by the documentation on the medicinal product in the form of the Common Technical Document (CTD). This documentation consists of five basic parts (Modules), as depicted in Figure 1.

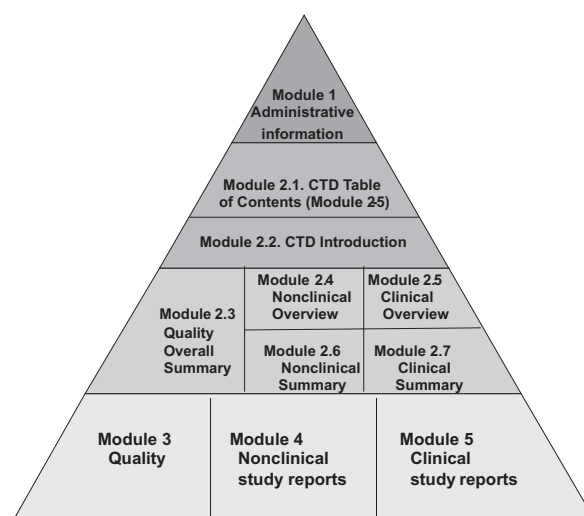


Fig. 1. Documentation on the medicinal product in the form of the common technical document (schematic overview of the Common Technical Document (CTD) format).

Given the known efficacy and safety of the active substances, it is not necessary to append the results of conducted non-clinical (Module 4) and clinical (Module 5) trial to the application for marketing authorization for a generic medicine. Instead of the complete Module 4 and 5 documentation (Figure 1), for the majority of generic medicines, primarily those in solid oral forms, it is necessary to submit the results of *in vivo* bioavailability testing that confirms the bioequivalence with the originator product (Module 5.3.1).

The quality of each medicine, including generic medicines, must be specifically proven through comprehensive documentation which is assessed in detail by the regulatory authority prior to granting marketing authorization.

Assessment of the documentation on medicine quality

Medicine quality is a group of acceptable physicochemical and biological properties of a medicine that is proposed by the medicine manufacturer according to internationally accepted standards (European Pharmacopoeia¹⁸,

European Directive¹⁹ and Scientific Guidelines on medicine quality²⁰ and guidelines of the International Conference on Harmonization (ICH)²¹.

Medicine quality is directly related to the quality of the starting materials (active substance, excipients, type of container), the production procedure that must be carried out in line with the rules of Good Manufacturing Practice (GMP) and the stability of the active substance and drug product that is ready for marketing.

The form and content of the documentation on medicine quality (Module 3 – Quality) is precisely prescribed (in both Croatia and the European Union) and does not differ for originator and generic medicines. This documentation consists of two main parts: data on active substance (Section 3.2.S) and data on the drug product (Section 3.2.P). Each of these sections contains the stipulated chapters with information that defines the quality of the active substances or the quality of the drug product.

With the previously stated differences in the documentation necessary for marketing generic medicines, originator and generic medicines differ in the manufacturer of the active compounds, excipients, production procedure (technology) and selected container that is in direct contact with the medicine (blister package, glass bottle, etc.). In the majority of cases, the manufacturer of the reference medicinal product is also the manufacturer of the active substance, while this is not the case with generic medicines. Considering that different active substance manufacturers use different synthesis procedures, there are then differences in the quality requirements of generic medicines having the same active substances, and any assessment of quality thus requires a uniform approach with the application of the valid regulatory and scientific guidelines on medicine quality²⁰.

The Croatian Agency for Medicinal Products and Medical Devices (hereinafter: Agency) issues marketing authorization for medicinal products pursuant to the Medicinal Products Act^{2,16} and the accompanying Ordinance²². The Medicinal Products Act prescribes the basic requirements for granting marketing authorization for a medicinal product, the conditions for the production and sale of medicinal products, assessments of medicine quality, advertising and information about medicines, and the role and obligations of the Agency, while the accompanying Ordinance describes in detail the procedure of granting marketing authorization for medicinal products and the documentation required for granting authorization. In the marketing authorization procedure, the documents with important information on the medicine intended for health care workers (Summary of Product Characteristics) and patients (Patient Information Leaflet) and the medicine labeling are also approved.

Quality of active substances

For the purpose of determining the acceptability of the quality of active substances, the Agency for Medicinal

Products and Medical Devices (hereinafter: Agency) is permitted further insight into the section of the documentation on the active substance, with detailed information on the starting materials in the synthesis of active substances, and the production procedures in the synthesis of active substances. In the majority of cases, the manufacturer of the generic medicine does not have insight into these “restricted” data, except in cases when the manufacturer of the active compound is also the manufacturer of the drug product.

In assessing the quality of active substances, it is important to differentiate the active substances described in the European Pharmacopoeia (Ph.Eur.) or other world Pharmacopoeia from those not described in the European Pharmacopoeia. Considering that Pharmacopoeia monographs define a certain standard of quality, the use of these substances ensures the same/equivalent quality of active substances, thereby greatly facilitating the quality assessment. Also, certificate of suitability (CEP) issued by EDQM (European Directorate for the Quality of Medicines & HealthCare) is usually used by the manufacturers of pharmaceutical products in their marketing authorization applications to demonstrate the compliance of the active substance used with the monograph of the European Pharmacopoeia. This CEP procedure is aimed at facilitating and simplifying exchanges between all partners (drug substance manufacturer, drug product manufacturer and authorities) to ensure that the quality of substances is guaranteed. On the other hand, in the quality assessment of active substances not described in the Pharmacopoeia, it is necessary to use the more general Guidelines that are valid in the European Union²⁰ with instructions on acceptable criteria for the quality of active substances. Therefore, conducting an assessment on the quality of such active substances is much more complex and requires more experience and time.

Quality of drug products

The assessment of data on the quality of drug products is even more complex, as in addition to the shown properties of the active substance, it is necessary to also consider other factors that can directly influence drug quality. Special attention is directed at the selection of excipients and their compatibility with the active substances, appropriateness of the selected and implemented the production procedures and stability of the drug product in the selected container. Considering that the European Pharmacopoeia lists only the general requirements that certain pharmaceutical forms of drug product must comply with, and does not prescribe monographs for individual medicines, the valid Guidelines in the European Union²¹ are applied in the assessment of drug product quality. The monographs of individual drug product described in other Pharmacopoeia (United States Pharmacopoeia/USP²³, British Pharmacopoeia/BP²⁴) can also be used; however, they serve only as an aid in forming the opinion on the quality of the drug product.

Methods

Data were collected from the Agency’s medicinal products databases. Absolute numbers are shown for the applications for marketing authorizations for medicinal products in total as well as for generic medicinal products in particular for the period from 2005–2009. Data were analyzed using descriptive statistics. Additionally, we analyzed the Anatomical Therapeutic Chemical (ATC) Classification of medicines whose applications were submitted to the Agency in 2009.

Results

Applications for marketing authorization for medicinal products in the Republic of Croatia

Figure 2 shows the number of applications for marketing authorizations for medicinal products in Croatia submitted to the Agency in the period 2005–2009. The shown number of applications includes the number of received applications for granting marketing authorization, including all doses and pharmaceutical forms of the same medicine.

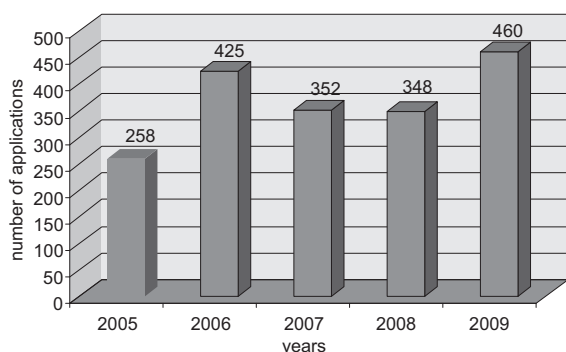


Fig. 2. Annual number of applications for marketing authorization for medicinal products in Croatia from 2005 to 2009.

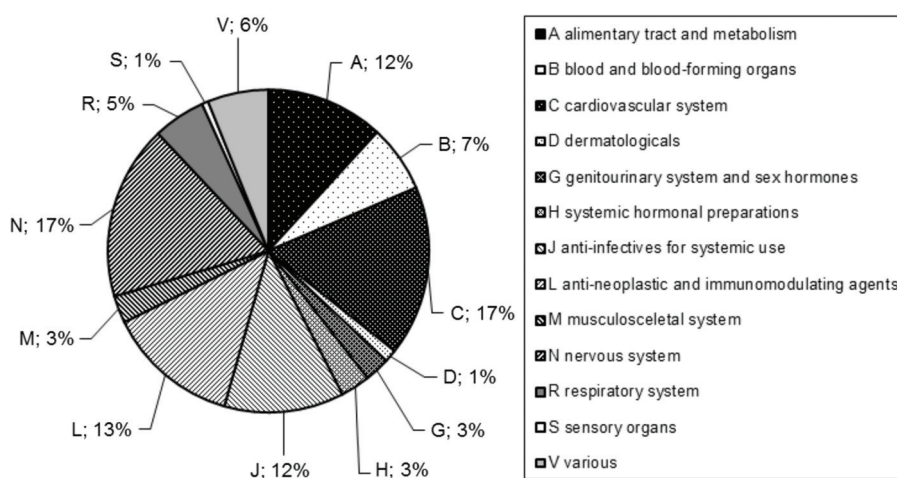


Fig. 3. Share of applications for marketing authorization in Croatia in 2009 according to the Anatomical Therapeutic Chemical (ATC) classification.

From the above, it is clear that the total number of applications for marketing authorizations in 2009 was almost twice the number of applications submitted in 2005.

Figure 3 shows the number of applications for marketing authorization in 2009 by individual organic systems (from A to V) according to the Anatomical Therapeutic Chemical (ATC) Classification of Medicines. The number of applications shown includes the total number of received applications for marketing authorization, including all doses and pharmaceutical forms of the same medicine. From the above, it is clear that the number of applications for approval submitted in 2009, the majority pertain to medicines acting on the cardiovascular system (C/17%) and nervous system (N/17%). These are followed by anti-neoplastic and immunomodulating agents (L/13%), anti-infectives for systematic use (J/12%) and medicines acting on the alimentary tract and metabolism (A/12%). This division by organic system largely corresponds to the division within the EU Member States²⁵.

Figure 4 shows the share of applications for marketing authorization for generic medicines in comparison to the originator medicine, and all other applications that can further be divided into medicines with well established use, over-the-counter medicines, herbal medicines, homeopathic products, etc. in the period from 2005 to 2009. From the figure, it is evident that the number of marketing authorization applications for generic medicines accounts for 55% of all submitted applications in this period.

Figure 5 shows the annual number of applications for marketing authorization of generic medicines from 2005 to 2009. A continual increase of the total number of marketing authorizations for generic medicines was recorded in this period, with the highest increase in 2006. The reason why 2006 does not follow this trend is that in 2006, the accelerated application procedure was introduced for medicines approved in the EU (through the Ordinance on special conditions for marketing medicinal products in the Republic of Croatia having marketing authorization in the European Union Member States²⁶). Therefore, in that year

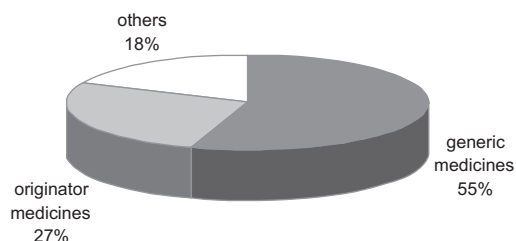


Fig. 4. Share of applications for authorizations for generic medicines in comparison to other applications in Croatia from 2005 to 2009.

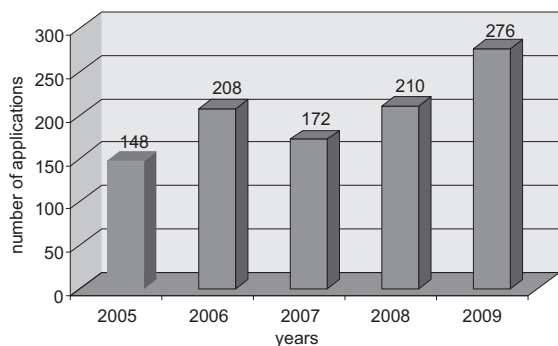


Fig. 5. Annual number of marketing authorization applications for generic medicines in the Republic of Croatia in the period from 2005 to 2009.

a significant jump in the number of applications received for medicinal product approvals were recorded (Figure 2). The same trend was noted also for the approval of generic medicines (Figure 5).

Figure 6 shows the marketing authorization application for generic medicines submitted by manufacturers seated in Croatia (hereinafter: local manufacturers) and those seated outside of Croatia (hereinafter: international manufacturers). Manufacturers seated in Croatia carry out the comprehensive product procedure or individual phases of medicine production pursuant to the Medicinal Products Act. These are most often the phases of packing and quality control of a medicinal product from another manufacturer, with the obligation of releasing individual

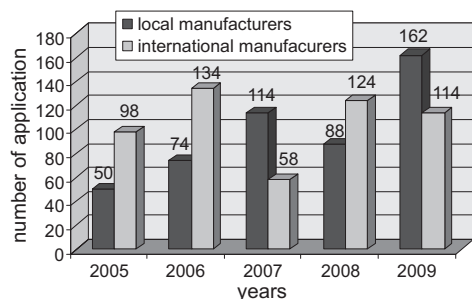


Fig. 6. Annual number of marketing authorization applications for generic medicines by local manufacturers in comparison with international manufacturers.

batches of medicines onto the Croatian market. The figure indicates virtually continuous growth in the number of marketing authorization applications for generic medicines by local manufacturers (with the exception of 2008). The number of applications by international manufacturers generally stagnated (with the exception of 2006 and 2007).

In an overview of the authorizations granted for generic medicines by local manufacturers and international manufacturers, it is evident that more than five generic medicines have thus far been approved for certain active substances in the Republic of Croatia (amlodipine, lisinopril, atorvastatin, tamsulosin, omeprazole, clopidogrel and pantoprazole), as shown in Table 1.

TABLE 1
OVERVIEW OF SEVERAL APPROVED GENERIC MEDICINES WITH THE SAME ACTIVE SUBSTANCE, FROM 2005 TO 2009

Active substance	Local manufacturers	International manufacturers	Total	ATC
Amlodipine	5	3	8	C08CA
Lisinopril	5	2	7	C09AA
Omeprazole	5	2	7	A02BC
Tamsulosin	2	4	6	G04CA
Atorvastatin	4	2	6	C10AA
Clopidogrel	4	1	5	B01AC
Pantoprazole	4	1	5	A02BC

The table shows that there are a large number of medicines by local manufacturers for the said active compounds that are most prescribed in Croatia (with the exception of tamsulosin as a newer active substance). Namely, the business policy of local manufacturers is based on the need for offering as many of the most commonly prescribed medicines as possible, in order to ensure regular supply of these medicines to the local market through the health care system. On the other hand, each newly approved medicine with the same active substance lowers the price on the Croatian market, which in turn reduces the interest of international manufacturers for submitting applications for active compounds which are already in use in large numbers in the Republic of Croatia. For that reason, the interest of international manufacturers is more directed at obtaining authorization for newer generic medicines which have not yet been represented on the Croatian market, or have been represented in fewer numbers.

Specificities in the approval of generic medicines with regard to assessments of their quality documentation (shown on the example of atorvastatin)

Finally, we analyzed examples of approved quality applications for impurities/degradation products for three

generic medicines containing atorvastatin from different manufacturers. The active compound atorvastatin is not described in the European Pharmacopoeia. As previously mentioned, several medicines with atorvastatin have already been approved for use in Croatia, of which one is the originator medicine, six are generic medicines and one is a combination of atorvastatin and other active substances (total of eight medicines). These medicines are produced by seven manufacturers (including three from Croatia) using atorvastatin as active substance from five manufacturers with different synthesis procedures in their production. Therefore, the active substance used differs in possible impurities, physicochemical properties (polymorphism, solubility, and release from the solid pharmaceutical form) and stability. This is the reason why for these medicines, the manufacturers propose significantly different quality requirements, especially with regard to impurities, as shown in Table 2. In examples A and C, there are clear differences in the permitted levels for individual/group impurities that the medicine must comply with prior to marketing (at release) or during the proposed validity period of the medicine (shelf life).

TABLE 2
EXAMPLES OF PERMITTED LIMITS FOR IMPURITIES/
DEGRADATION PRODUCTS IN MEDICINAL PRODUCTS
CONTAINING ATORVASTATIN

Example A	Release	Shelf life
Impurities/degradation products:		
– impurity 1	max. 0.2%	max. 0.3%
– impurity 2	max. 0.5%	max. 0.7%
– impurity 3	max. 0.6%	max. 2.0%
– impurity 4 and impurity 5	max. 0.9%	max. 2.5%
– impurity 6	max. 0.4%	max. 0.6%
– greatest unknown impurity	max. 0.2%	max. 0.2%
– total impurities	max. 3.0%	max. 5.0%
Example B	Release	Shelf life
Impurities/degradation products:		
– impurity 1	max. 0.3%	max. 0.3%
– impurity 3	max. 0.25%	max. 0.25%
– impurity 7	max. 0.3%	max. 0.3%
– impurity 8	max. 0.5%	max. 0.5%
– impurity 9	max. 0.7%	max. 0.7%
– impurity 10	max. 0.3%	max. 0.3%
– other individual impurities	max. 0.2%	max. 0.2%
– total impurities	max. 2.0%	max. 2.0%
Example C	Release	Shelf life
Impurities/degradation products:		
– individual impurity	max. 0.5%	
– known individual impurity		max. 1.5%
– other individual impurity		max. 1.0%
– total impurities	max. 2.0%	max. 5.0%

Discussion

Applications for marketing authorization for medicinal products in the Republic of Croatia

Following establishment of the Agency in late 2003, the marketing authorization granting procedure was unified, thereby greatly simplifying and accelerating the authorization procedure in Croatia. Previously, the assessment of the pharmaceutical documentations on medicine quality was carried out by the Croatian Institute for Medicine Control and the Croatian Institute for the Control of Immunobiological Medicines, while the Ministry of Health and Social Welfare conducted assessments of non-clinical and clinical documentation on medicines for the granting of marketing authorization. In addition to this change to the authorization procedure, the further development of the pharmaceutical industry in the new global economic and regional political circumstances fostered a significant increase in applications.

According to available information, the significant increase in the number of applications for granting marketing authorization for generic medicines in the period from 2005 to 2009 is tied to the expiry of patent protection of a large number of reference medicine products. According to the submitted marketing authorization applications, it was also observed that a large number of applications was submitted by multiple applicants for the same medicine, under a different name, but based on the same medicinal product documentation, which lead to a further increase in the number of applications submitted for the same medicines. In this way, the majority of generic medicine manufacturers also use, in addition to their own development, the possibility of submitting marketing authorization applications based on the medicinal product documentation of another owner or manufacturer that developed the medicine.

The growing trend in the number of applications for the approval of generic medicines observed in this period resulted in the fact that the share of applications for generic medicines surpassed the number of requests for originator and other medicines. This share was 55%, and it is expected that it will continue to grow in line with the growing trend of the number of generic medicines available in Europe and the world^{27–29}.

While examining the seat of the manufacturers of generic medicines, during the observed period, the number of applications by international manufacturers stagnated (with the exception of 2006 and 2007). As previously mentioned, 2006 differed from all other years due to the introduction of the accelerated application and approval procedure for medicines already approved in the EU (made possible with the coming into effect of the Ordinance on special conditions for marketing medicinal products in the Republic of Croatia having marketing authorization in the European Union Member States²⁶), which benefited international manufacturers. Therefore, a significant jump in the number of applications submitted for all medicine approvals (Figure 2) and a jump in the number of applications for the approval of generic medicines (Figure 5) have

been seen. Of these, the majority were those produced by international manufacturers, as the said Ordinance shortened the approval procedure for medicinal products already approved in the EU. After this jump in the number of applications for the approval of generic medicines by international manufacturers in 2006, a logical drop in the number of applications followed in 2007.

On the other hand, the number of applications of local manufacturers has been on a constant climb in the observed period, with the exception of 2008. In 2007 and 2009, the number of applications submitted by local manufacturers exceeded the number submitted by international manufacturers. The increasing number of applications from local manufacturers lies in the fact that new manufacturers of generic medicines are constantly being established in the territory of the Republic of Croatia.

It was also observed that more than five generic medicines were approved for the following active compounds: amlodipine, lisinopril, atorvastatin, tamsulosin and omeprazole. These are primarily medicines for the cardiovascular system (amlodipine, lisinopril atorvastatin), as the largest number of applications are submitted for these medicines in general (Figure 3).

Specificities in the approval of generic medicines with regard to assessments of their quality documentation

In the examination of the medicine quality documentation, it was noted that several shortcomings commonly occur. The most common is the non-compliance of the data in individual sections of the documentation, non-compliance with the valid quality guidelines, improperly conducted and documented development of the medicine formulation, and lack of data on the active substance.

In accordance with the Ordinance in effect in Croatia, the quality of the active substance must comply with the requirements of the Ph.Eur. and the manufacturer is obliged to declare according to this Pharmacopoeia. Only in the case if the active substance is not described in the Ph.Eur. the requirements of other Pharmacopoeia may be accepted as quality standards, and thus the most common shortcoming in the documentation is the declaration of the quality of the active substance according to another Pharmacopoeia (USP, JP) despite also being described in the Ph.Eur. while referring to BP is acceptable because BP follows the EP for active substance.

Another common deviation was seen in the general quality requirements for individual pharmaceutical forms prescribed in the Ph.Eur. (i.e. requirement for the release of active substance, uniformity of dosage units) and the lack of testing important for individual pharmaceutical forms (i.e. testing the sub-visible particles in parenteral solutions). It is also common that the manufacturer did not conduct stability testing of the medicine in line with the valid ICH guidelines (testing protocol, number of tested series, availability of results, etc.), or did not prescribe the validity period of the medicine and storage conditions, in line with the valid ICH guidelines.

To present an example of differences in medicine quality specifications we showed possible impurities/degradation products in three medicines products with atorvastatin (Table 2). Two presented examples (A and B) illustrate requirements in line with the valid quality guidelines²⁰ that stipulate the criteria for setting and accepting permitted limits for possible impurities/degradation products in the medicinal product. Differences in impurity requirements in examples A, B and C are due to different polymorphic form of active substance that show different stability which consequently affect the stability of drug product. Specification of drug product with more stable polymorphic form of drug substance (example B) is confirmed with stability results. Differences in the specifications for release and shelf life in examples A and C are caused by less stable polymorphic form of active substance (it is evident from the stability results). In order to accept the requirement from example A, the manufacturer must conduct further qualification and toxicological testing of such an atorvastatin due to the greater quantity of individual and total impurities, in order to confirm the safety (which is in line with ICH Guideline Q3B(R2) Impurities in New Drug Products which describe the principle of the requirements to indicate, identify or toxicologically qualify the contaminants). Considering the quality requirements, example C does not meet the valid quality guidelines, and pertains to a medicine that has long been marketed, this application needs to be renewed / harmonized through upgrade documentation.

Table 2 also clearly shows that there are significant differences in the quality documentation of generic medicines, which could additionally suggest the differences in the quality of these medicines. Only those medicines with proven quality are allowed to be marketed. Their quality can be proven in the comprehensive medicinal product documentation, based on laboratory testing.

Conclusions

From 2005 to 2009, a growing trend was evident in the number of applications for the approval of generic medicines, and among the active substance for which the majority of generic medicines were approved; most were intended for the treatment of cardiovascular diseases (amlodipine, lisinopril, atorvastatin). This is in line with the Western European trends, as the consumption of these medicines for the treatment of chronic cardiovascular diseases is significant, making these medicines interesting for medicine manufacturers. In general, it can be concluded that the production of generic medicines is interesting to manufacturers, as they take a high share on the market owing to their lower prices.

Virtually constant growth has been recorded in the applications of local manufacturers, and these have surpassed the number of applications by international manufacturers in recent years. The growth in the number of applications from local manufacturers lies in the fact that new generic medicine manufacturers are continuously being established in Croatian territory. The continuation of this trend is also expected in the future, due to the an-

nouncement of new generic medicine manufacturers in Croatia.

In the approval of generic medicines, special attention must be paid to the quality of generic medicines, and to ensure that only those medicines whose quality is guaranteed pursuant to comprehensive medicinal product

documentation and laboratory testing can be marketed. It is important to develop a uniform, systematic and comprehensive approach to assessing medicine quality, in order to guarantee high quality products for patients. Therefore, the regulatory body has an important task in the assessment and approval of these medicines.

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GENERIČKI LIJEKOVI U HRVATSKOJ – REGULATORNI ASPEKTI I STATISTIKA

SAŽETAK

Generički lijek je lijek ekvivalentan referentnom lijeku. Sadrži istu djelatnu tvar kao referentni lijek, »esencijalno je sličan« referentnom lijeku te stoga može zamijeniti referentni lijek. Svrha ovog istraživanja je odrediti koliki se udio od ukupno zaprimljenih zahtjeva za odobravanje lijekova u RH odnosi na generičke lijekove, kao i specifičnosti u odobravanju generičkih lijekova vezane uz ocjenu dokumentacije o njegovoj kakvoći. Također proučeno je dolaze li proizvođači generičkih lijekova prvenstveno iz Hrvatske ili inozemstva te za koje djelatne tvari postoji više od 5 odobrenih generičkih paralela (lijekova) u Hrvatskoj. Prikupljeni su podaci iz baze lijekova Agencije za lijekove i medicinske proizvode. Prikazani su absolutni brojevi zaprimljenih zahtjeva za dobivanje odobrenja za lijekove općenito te posebno za generičke lijekove u periodu od 2005.–2009. godine. Podaci su analizirani deskriptivnom statistikom. Godišnji broj zahtjeva za odobravanje generičkih lijekova u RH je narastao sa 148 u 2005. godini na 276 zahtjeva u 2009.g. Odnosno, u razdoblju od 2005. do 2009. godine, broj zahtjeva za odobravanje generičkih lijekova čini 55% ukupno podnesenih zahtjeva. Za sljedeće djelatne tvari je odobreno više od 5 generičkih lijekova: amlodipin, lizinopril, atorvastatin, tamsulozin i omeprazol. U narednim godinama broj zahtjeva stranih proizvođača u pravilu stagnira dok je broj zahtjeva domaćih proizvođača u stalnom porastu (uz izuzetak 2008.g.). Od 2005.g. do 2009.g. vidljiv je gotovo kontinuiran porast ukupnog broja zahtjeva za odobravanje generičkih lijekova, a među djelatnim tvarima za koje je odobren najveći broj generičkih lijekova prevladavaju one koje su namijenjene liječenju kardiovaskularnih bolesti (amlodipin, lizinopril, atorvastatin). Zabilježen je gotovo stalan porast zahtjeva domaćih proizvođača što se očekuje i u budućnosti zbog najave novih proizvođači generičkih lijekova u Hrvatskoj. Kod odobravanja ovih lijekova važno je razviti jedinstven pristup ocjene kakvoće svakog lijeka kako bi se jamčio kvalitetan proizvod za pacijenta.