

Regulating Medicines in Croatia: Five-year Experience of Agency for Medicinal Products and Medical Devices

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Aim To present the activities of the Agency for Medicinal Products and Medical Devices in the first 5 years of its existence and to define its future challenges.

Methods Main activities within the scope of the Agency as a regulatory authority were retrospectively analyzed for the period from 2004-2008. Data were collected from the Agency's database and analyzed by descriptive statistics.

Results The number of issued medicine authorizations rose from 240 in 2004 to 580 in 2008. The greatest number of new chemical and biological entities was approved in 2005. The greatest number of regular quality controls (n=5833) and special quality controls was performed in 2008 (n=589), while the greatest number of off-shelf quality controls (n=132) was performed in 2007. The greatest number of medicine labeling irregularities was found in 2007 (n=19) and of quality irregularities in 2004 (n=9). The greatest number of adverse reactions was reported in 2008 (n=1393). The number of registered medical devices rose from 213 in 2004 to 565 in 2008.

Conclusion Over its 5 years of existence, the Agency has successfully coped with the constant increase in workload. In the future, as Croatia enters the European Union, the Agency will have to face the challenge of joining the integrated European regulatory framework.

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The harmonization of Croatian legislation on medicinal products with the EU regulations started in 1997, when the first Act on Medicinal Products and Medical Devices was adopted (1). It was followed by a new Act on Medicinal Products and Medical Devices (2) in 2003, which provided a legal framework for the establishment of the Agency for Medicinal Products and Medical Devices as a regulatory authority. Today, the medicinal products in Croatia are regulated by the Act on Medicinal Products (3) from 2007 and its Amendments from 2009 (4), which were adopted during the process of harmonization with the EU medicines legislation (5-8).

The agency was formed in the fall 2003 from the Croatian Institute for the Control of Medicinal Products and the Croatian Institute for the Control of Immunobiologicals, from which it inherited the expertise in the control and testing of medicinal products, vaccines, and blood products and the evaluation of their pharmaceutical quality. The Agency also took over a part of the duties of the Ministry of Health such as granting marketing authorizations for medicinal products, listing medical devices into their register, issuing of import/export licenses and manufacturing licenses, withdrawing of medicinal products and medical devices from the market, monitoring drug consumption, and promoting rational use of medicines. In 2005, the Agency took over the adverse drug reactions monitoring from the Zagreb Clinical Hospital Center. It also assumed a greater role in the area of medicinal products, immunological medicinal products, homeopathic products, and medical devices. This required new staff recruitment, additional training for the existing staff, and administrative capacity building. Over the first 5 years of its existence, the Agency has had to deal with the inherited backlog and, at the same time, organize administrative processes accompanying legislative reforms and adoption of European regulatory practices. The Agency's vision of the safety of health care products includes technological and scientific development, globalization in the area of the production and distribution of medicinal products, and increasing the expectations of health care professionals and the wider public (9,10). Moreover, the Agency is continuously assessing the benefit/risk ratio for the patient (11-14), checking the quality of medicinal products from the Croatian market, and defining terms and conditions for the production and distribution of medicinal products of legal entities based in Croatia. These activities are similar to those of most medicines regulatory authorities in Europe (15-18).

The aim of this study is to present the results of the Agency's work in the first 5 years of its existence and to define

the Agency's future challenges. The key data on Agency's work in the area of medicines authorization, quality control, adverse reactions monitoring, and regulation of medical devices were analyzed.

METHODS

Study design, setting, and period

The main activities within the scope of the Agency as a regulatory authority – authorization and quality control of medicinal products, monitoring of adverse reactions, and regulation of medical devices – were retrospectively analyzed for the 5-year period (2004-2008). Data were collected from the Agency's database.

Agency for Medicinal Products and Medical Devices: activities and principles

Marketing authorization for medicinal products. Applications seeking authorization for new finished medicinal products have to be submitted to the Agency along with the valid registration documentation. The assessment is followed by the technical evaluation of quality, safety, and efficacy of a medicinal product, which involves a network of experts from the Agency, plus external experts. Upon successful completion of this procedure, marketing authorization for the medicinal product concerned is granted. Statutory period for the authorization procedure is 210 days. Authorization validity must be renewed every 5 years, so the data in this analysis include renewal data as well. During the life cycle of a medicinal product, any modification in its documentation is considered as the variation of the marketing authorization and must be reported to the Agency for its approval. Variations are also entered in the Agency's database and thus included in this study.

There are two authorization procedures covered by the Agency: national and simplified procedure for EU products. In the national procedure, which is conducted according to the relevant Ordinance (19), the Agency performs a complete assessment (evaluation) of medicinal product documentation. The simplified procedures are conducted according to the special Ordinance (20) and refer to the medicines already authorized in the EU by the centralized procedure with the European Medicines Agency (EMA from December 2009, prior to that EMEA) (21-25) or to the medicines authorized in the Member States by the decentralized procedure or the mutual recognition procedure. These simplified procedures

are based on the New Collaboration Agreement between Drug Regulatory Authorities in Central and Eastern European Countries (nCADREAC) (26). They are subject to shorter statutory terms – 150 days for the centralized procedure and 180 days for the decentralized and mutual recognition procedures.

Medicines quality control. The Agency conducts laboratory quality tests for the first batch of medicinal products, following the granting or renewal of the marketing authorization. This is termed special quality control. Products are also sampled out of the distribution network once in every 5 years and their quality is controlled within the Agency. This off-shelf quality control is based on the annual sampling plan for marketed medicinal products. Laboratory quality control is conducted according to the manufacturer's specification accepted within the approval procedure of the medicinal product.

Along with the special quality controls and off-shelf quality controls from the supply chains, the Agency controls every imported batch of medicinal products in the process of regular quality control. For the EU products, the regular control is based on the reviews of the manufacturers' certificates of analysis and the reviews of the packaging of the presented finished product. For all other medicines, the regular quality control is performed by the laboratory quality tests. After conducting regular quality control of the imported batches, the Agency issues an approval for the import of the controlled batch. The Agency can also perform an extraordinary quality control in the case of urgency (in the event of contingencies). Irregularities can be singled out from the laboratory quality control findings or they can be related to inadequate product packaging, harmonization of patient information leaflet, or outer and inner labeling with the current updated product registration documentation.

The Agency is also required to withdraw batches of medicinal products based on the evaluation of field reports on quality defects and/or adverse reactions from the country or abroad (27). For prompt field-reporting on adverse reactions and quality defects of medicinal products and medical devices, the Agency has made available a 24-hour telephone line.

Pharmacovigilance and adverse reactions monitoring.

Pharmacovigilance activities in the Agency can be defined as the control and prevention of the risks caused by the adverse reactions and includes data from

spontaneous reports on adverse reactions, registration documentation, and laboratories performing quality control on distributed medicinal products. The pharmacovigilance system is based on the legal obligation of health care professionals to spontaneously report to the Agency any adverse reaction on medicinal products and the obligation of the Agency to examine and follow up the reported case. Adverse reactions to vaccines must be reported to both the Agency and the Croatian National Institute of Public Health. For each reported adverse reaction, the notifying party is given a personalized expert opinion by the Agency. The Agency is a member of the World Health Organization (WHO) Programme for International Drug Monitoring (28), and reports of adverse reactions in the Republic of Croatia are regularly forwarded to the adverse reactions database of the WHO.

Regulation of medical devices. The notified body provides an assessment of the product compliance, on the basis of which the product receives the CE label of conformity (French: *conformité européenne*). The compliance assessment procedure for medical devices is not carried out by agencies for medical devices; instead, they are delegated to the private sector, ie, to notified bodies, registered by the European Commission for such procedures (29-34). Once a medical device has received its CE label (35,36), it can freely be circulated within the whole European market, while agencies for medical devices supervise the market and the vigilance of medical devices (37,38), as well as the private companies. Pursuant to the European legislation, medicinal products have been separated from medical devices in Croatia, and the new Act on Medical Devices (39) was passed by the Croatian Parliament on October 1, 2008. After the death of 23 dialysis patients in October 2001 due to irregularities in the quality of a dialysis equipment (40,41), Croatia assumed the obligation to officially register all medical devices prior to their arrival on the market. The registration is supervised by a special commission.

Data extraction

We collected the information from the Agency's medicinal products and medical devices databases. Information related to medicines approvals includes marketing authorizations for finished medicinal products as the Agency's output documents. Absolute numbers are shown for the authorizations for new medicinal products, renewals, and variations of finished medicinal products in the five-year period 2004-2008, as well as transfers of authorizations in 2008, which include administrative transfers of autho-

rization from one entity to another and which were earlier treated as variations. During the analyzed period, each pharmaceutical form, potency, or packaging of one active substance received a separate marketing authorization for a finished medicinal product. Also, the number of new chemical and biological entities licensed in Croatia for the first time in the form of finished medicinal products was taken from databases for each year.

Data concerning medicines quality control are expressed as the number of findings in the laboratory quality control or approvals for the import of finished products based on the regular quality control reports. The study also used the information from the Agency's databases on adverse reactions reported by health care professionals, physicians, and pharmacists. We analyzed the information over the four-year period 2005-2008 because the Agency has been responsible for monitoring the safety of medicines since March 2005. The number of adverse reactions to conventional medicinal products, especially vaccines, was singled out. The number of medical devices registered in the Medical Devices Register of the Agency (2004-2008) was also obtained from the Agency's medical device database. Data were analyzed by descriptive statistics.

RESULTS

Marketing authorization for medicinal products

In the period from 2004 to 2008, a steady increase in the number of authorization and renewal issuances was observed. Also, a continuous increase in resolved variation cases was recorded. The number of resolved transfers of authorizations was first recorded in 2008 (n = 112), because they were previously treated as variations. The number of newly authorized active substances licensed in Croatia for

the first time in the form of finished medicinal products increased with the total increase in authorizations issued for finished medicinal products, a tendency particularly noticeable in 2005. The number of marketing authorizations for medicinal products in the period 2004-2008 is summarized in Table 1. In 2008, 76.1% of marketing authorizations were granted on the basis of national procedure, and 23.9% according to a simplified authorization procedure for EU products depending on the procedure conducted in the EU (mutual recognition procedure, decentralized procedure, centralized procedure). This analysis was made for the first time in 2008 because that was the year when the Ordinance regulating simplified procedures (20) came into force.

Medicines quality control

Special quality control was carried out on every first batch of manufactured medicinal products and 51 findings were issued in 2004. The number of findings increased in 2005 and 2006, followed by a slight decrease in 2007 and a new increase in 2008 (n = 589). In 2005, the Agency started performing off-shelf quality control, and that year 41 medicines were sampled out of the market by pharmaceutical inspectors. In 2006, there was slight increase in these controls, while in 2007 and 2008 the number of quality controls out of the pharmacies and wholesalers increased to 132 and 120, respectively, pursuant to the annual sampling plan (Figure 1).

Over the years, the number of approvals for the import of medicine batches from the EU to Croatia was rising, and so was the number of newly authorized medicinal products. Therefore, there was an increase in the number of regular quality controls conducted by the Agency (from 3327 in 2004 to 5833 in 2008) (Figure 2). During the issuance of ap-

TABLE 1. The number of marketing authorizations issued by the Agency for Medicinal Products and Medical Devices, Croatia, in the period 2004-2008

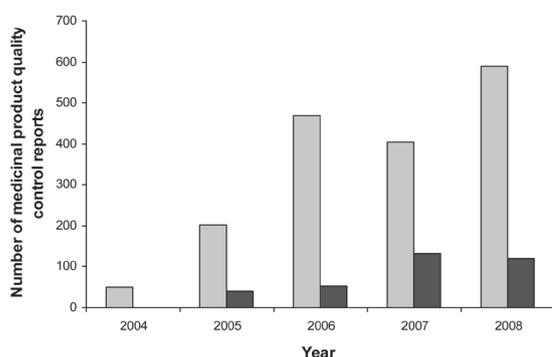
		2004	2005	2006	2007	2008
Marketing authorizations		248	452	254	510	598
Classification of marketing authorization by the type of authorization procedure*	CP	–	–	–	–	33
	DCP	–	–	–	–	59
	MRP	–	–	–	–	51
	National procedure	–	–	–	–	455
Renewals		177	270	197	267	367
Variations		56	352	450	651	624
Transfers		–	–	–	–	112
Number of authorized new chemical and biological entities		24	44	35	41	40

*Abbreviations: CP – simplified procedure for products authorized in the EU by centralized procedure; DCP – simplified procedure for products authorized in the EU by decentralized procedure; MRP – simplified procedure for products authorized in the EU by mutual recognition procedure.

provals for the import and the findings of laboratory quality controls performed on first batch products and medicines sampled from the market, quality defects and defects in inner and outer packaging and instructions for patients were also documented. There were 9 findings of substantial quality defects in 2004, 5 quality defects in 2005 and 2007, 6 quality defects in 2006, while in 2008 no irregularity in the quality was found. Eleven medicine labeling irregularities were detected in 2004, 5 labeling irregularities each in 2005 and 2006, followed by an increase of 19 irregularities in 2007 and 18 in 2008 (Figure 3).

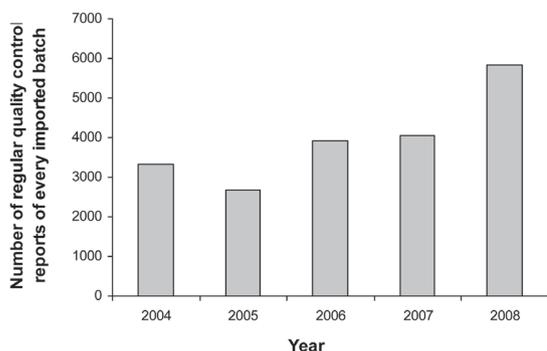
Adverse reactions monitoring

Figure 1.



Medicinal product quality control reports issued by the Agency for Medicinal Products and Medical Devices, Croatia, in the period 2004-2008. Gray bars – special quality control of the first batch; closed bars – off-shelf quality control.

Figure 2.



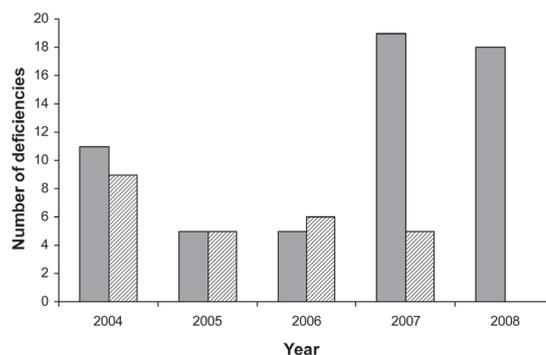
Agency for Medicinal Products and Medical Devices, Croatia, in the period 2004-2008: regular medicinal product quality control reports of every imported batch in Croatia.

The role of the National Pharmacovigilance Center was taken over by the Agency in 2005, when 498 adverse reactions were reported and documented. In 2006 and 2007, the number of reported adverse reactions constantly increased and in 2008 rose to 1393 (Figure 4). The total number of notified adverse reactions increased by 180% in 2008 compared with 2005.

Regulation of medical devices

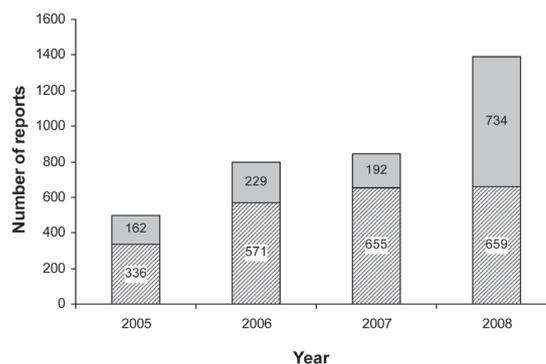
At the start of the Agency's work in 2004, a total of 213 medical devices were registered in the official Register of Medical Devices. In the following years, the number of reg-

Figure 3.



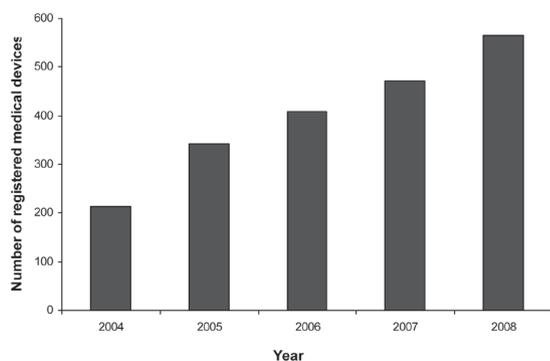
Agency for Medicinal Products and Medical Devices, Croatia, in the period 2004-2008: deficiencies of medicinal products. Gray bars – non-compliance in labeling and patient information leaflet; striped bars – substantial quality defects.

Figure 4.



Number of spontaneous adverse reactions reported to the Croatian Agency for Medicinal Products and Medical Devices in the period from 2005-2008. Striped bars – number of spontaneous adverse reactions reported for medicinal products; gray bars – number of spontaneous adverse reactions reported for vaccines.

Figure 5.



Number of medical devices registered in the Medical Devices Register of the Agency for Medicinal Products and Medical Devices, Croatia, in the period 2004-2008

Number of registered medical devices constantly increased (from 342 in 2005 to 565 in 2008) (Figure 5).

DISCUSSION

In the first 5 years of its existence (from 2004-2008), the Agency issued 2062 marketing authorizations, 1278 renewals, and 2133 variations to the authorizations for finished medicinal products. According to the statistical data available on the Web site of the German medicines regulatory agency, the Federal Institute for Drugs and Medical Devices (BfArM), in the same period issued 12 096 authorizations (42). Greater number of issued marketing authorization in Germany from 2004-2008 could be explained by the difference in market size (number of patients using medicines) and the fact that in the first 5 years of its existence Croatian Agency had to develop a number of different internal procedures along with all the other duties. On the other hand, European Medicines Agency in the first 5 years of its activity (1995-2000) issued 126 marketing authorizations and 856 variations (18). Smaller number of medicines authorized by EMA in comparison with the Croatian Agency can be explained by the fact that EMA conducts more complex centralized authorization procedure for all EU member states, which is based on a specific evaluation of medicinal products and provision of scientific advice (43). Also, the Croatian Agency had had a sizeable backlog of applications for marketing authorizations, variations, and renewals already upon its establishment. At the same time, it had had to cope with the inflow of new applications for which the statutory term of 210 days had to be strictly observed (19). The EMA did not

have any backlog because it was a completely new institution, which is why there were no renewals in the EMA during its first 5 years.

In the first year after its establishment (2004), the Agency issued 248 marketing authorizations, while the Montenegrin Agency for Medicines and Medical Devices issued 147 authorizations in the first year of its existence (2009) (44). This could be explained by the differences in market size and level of expertise/experience of these two agencies. The Croatian Agency was created from two national health institutes and inherited a considerable amount of expertise, while the Montenegrin Agency started without previous experience. This presumption leads to the conclusion that one of the most important factors in the performance of medicines agencies is professional experience and expertise in specific regulatory issues. For this reason, co-operation between medicines agencies through the exchange of the best practices and regulatory knowledge is crucial for developing their expert and administrative capacity.

The number of resolved cases in the Croatian Agency was growing each year (as was the influx of new molecules), being the greatest in 2005, which can be explained by the improving work routine of the Agency, notably its Experts Committee's endeavor to solve the backlog as soon as possible. In the recent years, the number of finished product authorizations has risen, but this increase is no longer necessarily accompanied by an increase in new molecules on the Croatian market, but rather by a greater number of generic medicines that have appeared after the expiry of patent protection for a certain number of proprietary medicinal products. In the last analyzed year (2008), the Agency issued 598 marketing authorizations, similarly to 695 authorizations issued by the Serbian national agency (45).

In 2008, the overwhelming majority of cases were resolved by the "national procedure" (19,46), with only a minor number of cases resolved by the simplified European procedures (nCADREAC). The simplified authorization procedures for the EU products brought several advantages: the summary of product characteristics, the patient information leaflet, and its labeling on the outer and inner packaging are harmonized between the EU member states and Croatia; the registration procedure is shorter; and the patient can get a new medicinal product, whether innovative or generic, without unnecessary delay. This is why in the following years the Agency expects a considerable increase in applications for simplified authorization procedure, which will shorten the authorization

process and lead to an increased availability of medicines in Croatia.

In the first 5 years of its existence, the Agency performed 1716 special quality controls of the first batch of medicinal products after granting the authorization, 345 off-shelf quality controls, and 19802 regular quality controls of imported batches. On the other hand, the Medicines and Healthcare products Regulatory Agency as a national Agency of the United Kingdom performed 11 269 quality controls in the five-year period from 2002-2006 (47). The main difference between these two quality controls systems is that Croatian system is more oriented on the pre-authorization control and the UK system on the market surveillance (with sampling and testing of strictly selected medicinal products at, or destined for, the UK market).

The quality defects found with the manufactured product batches are largely related to the discrepancies in product labeling and patient information leaflet. This has been a growing tendency in the past two years, whereas the number of quality defects among medicinal products from the distribution network and first batch has been on decline. These discrepancies in the product information of new medicines are associated with the manufacturers' inability to furnish the manufactured batch in accordance with approved variations in due time.

The number of spontaneously reported adverse reactions in 2008 rose by 180% compared with 2005. Although in 2006 and 2007 an approximately equal rate of adverse reactions to conventional medicinal products was recorded, in 2008 there was a difference in that rate due to an increase in the number of adverse reactions to vaccines ($n=734$). This can be attributed to the introduction of newly authorized vaccines in the prophylactic practice and a sudden increase in the number of adverse reactions to the mumps component of the combination vaccine (MMR – measles, mumps, and rubella), the consequence of which was the exclusion of this vaccine from primo vaccination in the mandatory vaccination calendar. However, the overall increase in spontaneous reporting is certainly a result of the Agency's developing partnership with health care professionals in the area of spontaneous reporting. For this purpose, in 2005 the Agency started to organize workshops for health care professionals, hitherto more than 60, on spontaneous reporting.

WHO Programme for International Drug Monitoring
(28) coordinated from the Uppsala Monitoring Cen-

tre in Sweden has compared the number of spontaneous reports between 96 countries in the five-year period from 2004 to 2009. Croatia ranked 19th, with about 150 adverse reactions per million inhabitants per year. New Zealand ranked first, with more than 1100 reported spontaneous adverse reactions per million inhabitants per year (28). This indicates low awareness of the importance of reporting in Croatia in comparison with some other countries. This is also one of the reasons why the Agency must continue with the education of Croatian health care professionals.

Evaluation of medicines safety profile is crucial because the Agency is also required to withdraw medicinal products due to safety reasons. Nevertheless, in most cases a medicinal product is recalled at the request of the marketing authorization holder, as it happened in September 2004 with rofecoxib (Vioxx), where the manufacturer, due to severe cardiovascular adverse reactions detected during the post-marketing studies, globally recalled the medicinal product and requested a repeal of its authorization in all countries (48,49).

From its establishment, the Agency has registered 2001 medical devices in total. Over the five-year period, a steady increase in the number of medical devices in the Medical Devices Register has been recorded, and we can conclude that these products are well controlled on the Croatian market. Registration of medical devices prior to marketing is a specific feature of Croatian legislation that is going to be changed in the process of harmonization with the EU legislation because it is not in accordance with the free movement of goods (although it enables stricter market control of these products).

Looking at the future challenges and considering the fact that the regulatory framework for medicinal products in Croatia is well aligned with the *acquis communautaire*, it is reasonable to expect that upon Croatia's accession to the EU, the Agency will join the integrated European regulatory framework without major difficulties. However, the Agency faces several challenges – one of them is that the Croatian representatives in EMA committees will have to actively participate in the evaluation of new medicinal products authorized via the centralized procedure, for which Agency experts must still gain some specialized knowledge. Croatia will thus be expected to participate in the "work sharing," which is one of the basic principles underlying the functioning of the European regulatory system and to take an active role in inter-governmental work on new legislation for medicinal products and medical de-

vices. In order to achieve this, the Agency will have to maximize its international co-operation and reorganize its activities. As part of the preparations for EU membership, the Agency has already established international cooperation with various European institutions, notably the EMA within the European Commission's Instrument for Pre-Accession Program through which the Agency's experts have the observer status in certain EMA committees.

It can be concluded that due to its expert capacity, after the 5 years of experience, the Agency is able to process all requests for its services for the Croatian market. The current challenge is the massive inflow of new applications concerning variations in the existing marketing authorizations for the finished medicinal products. It should also be noted that the Agency is preparing to reorganize its activities due to the Croatian accession to the EU, which is a major challenge for its future work.

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