# Croatia ready for action on EU medicines regulation front

Croatia joins the EU on 1 July. ***Viola Macolić Šarinić***, the head of the country's healthcare products regulatory agency, HALMED, tells ***Neena Brizmohun*** that while challenges remain, early preparations in key areas of drug regulation have paid off.

On 1 July Croatia will become the 28th member state of the EU. In the Q&A below, Dr Viola Macolić Šarinić, head of the Croatian Agency for Medicinal Products and Medical Devices (HALMED), explains how the agency plans to be involved in – and contribute to – the regulation of pharmaceuticals at EU level.

***Scrip Regulatory Affairs*: In which areas of drug regulation does HALMED have strengths and expertise?**

**Viola Macolić Šarinić:** The areas of medicinal product regulation in which HALMED's special expertise based on long-lasting tradition should be emphasized are, primarily, medicinal product quality assessment, quality control and, finally, pharmacovigilance.

The tradition of medicinal product quality assessment and quality control, including quality assessment and control for medicinal products and biologicals, dates back to the early 1950s.

HALMED's pharmacovigilance system continues a long tradition of monitoring adverse events (yellow card scheme), which dates back to 1974. With the strong development of the pharmacovigilance regulatory component from 2005 onwards, HALMED today has significant experience in collecting spontaneously reported adverse drug reactions (ADRs) and signal management. The agency also has significant experience in the field of risk management, communicating safety information to the public, assessing risk management plans (RMPs), and adapting risk minimization activities on the national level.

Furthermore, HALMED's expertise at assessing the bioequivalence of generic medicines is increasingly strong.

***SRA*: How can HALMED drive and improve drug review and safety at the EU level?**

**VMS:** With its pharmacovigilance expertise, HALMED firmly believes it can contribute significantly on the European level by introducing good practice in post-market pharmacovigilance with regard to spontaneous ADR reporting not only by healthcare professionals, but also by patients, which is equally included in the benefit-risk assessment of medicines, ie signal generating. What is more, HALMED's experience in communicating risk can serve as one of the baselines in developing guidelines in this field.

HALMED will also actively transfuse its experience in the field of bioequivalence and medicinal product quality assessment through mutual work with other member states in developing the guidelines in these fields.

***SRA*: What is HALMED's agenda with regard to joining and contributing to the following scientific committees of the European Medicines Agency: the Committee for Medicinal Products for Human Use (CHMP), the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee for Orphan Medicinal Products, the Paediatric Committee and the Committee for Advanced Therapies?**

**VMS:** HALMED has been an active observer in EMA committees from the beginning of 2012 and has established contacts with the delegates of other member states, as well as said committees' secretariats representatives through its work, which makes HALMED technically ready for work in these committees in a full membership status. Immediately after the accession to the EU, HALMED plans to apply for rapporteurship at the PRAC.

Regarding the CHMP, HALMED intends to commence working as peer reviewer, and shortly apply for the first co-rapporteurship/rapporteurship for generic medicinal products.

Up until now, HALMED has been an active observer in the said bodies. From 1 July it will formally join all the EMA committees and working groups as a delegate.

***SRA*: What main challenges will Croatia's current regulatory framework for medicines face following the 1 July EU accession?**

**VMS:** European legislation and regulatory practice form the basis for Croatian legislation and have been used by HALMED from the very beginning of the agency's establishment [in October 2003].

Latest harmonization with the European legislation for Croatia in relation to marketing authorization procedures will include: mandatory participation in the common European procedures – centralized procedure, mutual recognition procedure (MRP) and decentralized procedure (DCP); application of data/market exclusivity "8+2+1" formula; performance of batch release and batch testing in the EU, mandatory introduction of braille and readability user test, submission of renewal submission at least nine months before marketing authorization ceases to be valid; and, finally, variation classification, timelines and workflow.

At the beginning of 2012, HALMED began an intensive campaign of publishing on its website useful information for marketing authorization holders to ensure that they are timely informed on all the expected Croatian regulatory amendments.

***SRA*: Which Croatian laws relating to medicines are you having to reconsider/change to keep in line with EU legislation and how will this impact drug companies that are already doing business in Croatia?**

**VMS:** Primarily, it is the Medicinal Products Act which is to be harmonized to the fullest with the European legislation, and which will enter into force on 1 July 2013, along with the accompanying bylaws on the types of granting marketing authorization and pharmacovigilance. Latest harmonization with the European legislation for the Republic of Croatia relating to the marketing authorization procedures will encompass the changes listed under the answer to the previous question.

***SRA*: What is HALMED's agenda with regard to joining and contributing to the Heads of Medicines Agencies (HMA)?**

**VMS:** HALMED already participates as an observer in the work of HMA, as well as in the HMA's Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) from the end of 2011, with its delegates being fully integrated in the working system of these bodies. HALMED will also actively participate in HMA task forces, and it already actively participates in IT projects, such as the CESP (Common European Submission Platform). Furthermore, it has been assisting in the organization of the meetings of the presiding member states, although it will not be able to organize all the required informal meetings in Croatia. HALMED is also joining activities dealing with all the other challenges in the regulatory field that are placed before HMA.

***SRA*: Applications for drug approval via the MRP or the DCP can be submitted to HALMED as of 1 July. What are your plans with regard to taking part in these procedures?**



 

**VMS:** With Croatia's accession to the EU, HALMED intends to play an active role in DCPs and MRPs as a reference member state (RMS) competent authority. HALMED will be receiving the applications for considering the possibility of starting MRPs or DCPs with Croatia as the RMS between 15 July and 1 August. At the moment, HALMED is open to applications for considering the possibility of starting the procedure for generic medicines. Over the course of the next year, we plan on being included in approximately 20 MRPs and DCPs as a RMS.

***SRA:*** **What pharmacovigilance activities does Croatia have under way in preparation for the 1 July accession?**

**VMS:** Croatia has already fully adopted the new European pharmacovigilance directive, and it awaits the accession to the EU in this field entirely prepared. Croatia started using the EudraVigilance Gateway for the submission of electronic individual case safety report (ICSR) by marketing authorization holders to HALMED in 2010; this will become mandatory from 1 July. Testing with marketing authorization holders is currently being carried out, and detailed instructions with regard to this have been published on HALMED's website. With the new Medicinal Products Act coming into force, it is expected that good manufacturing practice (GMP) and good pharmacovigilance practice (GVP) inspection will be put under the competence of HALMED (at the moment these inspections are within the competence of the Ministry of Health). A more active role of these inspections in the EU regulatory framework is expected, as well. As for the EMA's EudraVigilance medicinal product dictionary (XEVMPD), the timeframe for marketing authorization holders in Croatia to finalize their medicinal products submission is still being determined in co-ordination with the EMA. The timeframe will be known at the end of June 2013. HALMED will organize additional specific workshops for marketing authorization holders in order to facilitate their management of this issue.

***SRA:*** **What challenges does HALMED foresee with regard to its ability to meet the requirements of the new EU pharmacovigilance legislation?**

**VMS:** HALMED has been working intensely in the field of pharmacovigilance for many years now. ADR reporting has already been mandatory in Croatia regardless of the adverse reaction seriousness so this is not a novelty for us. Electronic ADR reporting has also been introduced, although it has not been mandatory in Croatia, while assessing RMPs and risk minimization measures have been previously implemented at HALMED. The challenges we are facing, on the other hand, include active participation in the PRAC's work, taking over referrals and the role of rapporteur, and signal management for each active substance put under HALMED's responsibility for the territory of EU. We have been preparing intensely for these tasks since 2006. We have been using the EudraVigilance database, and we understand the operating modes for work delegated to the member states. Therefore, we look forward to finally being able to participate in this work actively, not merely as observers.

***SRA:*** **To what extent will Croatia's accession to the EU result in drugs having to be taken off the market in Croatia after 1 July?**

**VMS:** This matter concerns a considerably small number of medicinal products whose marketing authorizations will need to be revoked prior to Croatia's EU accession due to the change in the data exclusivity rule for the original product manufacturer, or due to their dossiers not having been upgraded in accordance with the European legislation. This applies to approximately ten medicinal products. HALMED has been working extensively on preparing instructions and processing requests related to medicinal product dossier upgrading. By doing so, we have harmonized the dossiers for national marketing authorizations in our country with the European legislation, which enables the national approvals to remain valid after Croatia's EU accession. It should also be noted that more than 30% of medicinal products on the Croatian market have been granted marketing authorization through the New Collaboration Agreement between Drug Regulatory Authorities in Central and Eastern European Countries (nCADREAC) procedure with the same documentation they were authorized with through the MRP/DCP procedure in the EU, which signifies that these dossiers already fully correspond to those required in the EU.

***SRA:*** **For drugs approved by the European Commission under the centralized procedure (749 drugs as of July 2011), market authorization holders are legally obliged to provide translations of the product information in Croatian as of the date of accession. How is HALMED faring with the task of completing the translation procedures for the centrally approved human drugs by July 2013?**

**VMS:** So far, HALMED has managed to review the translations for more than 70% of the medicinal products and is still working on this task. The task needed to be prolonged, and the procedure of resolving it changed due to marketing authorization holders not supplying the EMA with their translations on time, which prevented the EMA from sending these applications to HALMED. Marketing authorization holders sent a significantly smaller amount of translations than planned (15 products per slot every 15 days) by Week 35 of the pre-accession product information linguistic review process (ie the PALC III procedure). In order to compensate for the delay, in the period from Week 35 more products per slot than planned were received, which greatly burdened HALMED's resources. Nevertheless, we've managed to resolve them successfully. Medicinal products that have undergone the PALC III procedure can be marketed in Croatia from the date of Croatia's accession to the EU, but only after they have requested the inclusion of these translations into commission's decision.

***SRA:*** **Approximately how many centrally-authorized drugs are there likely to be that will not have the necessary translation in place by 1 July? And what will happen to these drugs in Croatia?**

**VMS:** Currently, the reviews have been carried out for approximately 50 medicinal products that are nationally authorized and marketed in Croatia. We believe most of these reviews will be completed by 1 July. In case the reviews of all the texts are not carried out completely, there is a possibility of authorizing the imported series of medicinal products that have been authorized in a foreign language in order to prevent shortages.

***SRA:*** **After 1 July, how will you deal with those drugs that are approved under the centralized procedure but which have already received approval by Croatia under the national procedure?**

**VMS:** On the date of Croatia's EU accession, HALMED will initiate the procedures of revoking national marketing authorizations for centrally authorized medicinal products that were issued before the accession, and the commission's decisions on marketing authorization will automatically apply. This concerns approximately 250 products.

The series of medicinal products manufactured in accordance with national marketing authorizations can be launched and marketed in the Republic of Croatia until the relevant expiration date, or up to 12 months after the date of Croatia's EU accession.

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