Interview: Kristin Raudsepp – Director General, State Agency of Medicines, Estonia

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Kristin Raudsepp, director general of Estonia's drug regulator – the State Agency of Medicines – discusses her organization's mandate, current priorities, and reactiveness to the pervading trends in international regulation.

Can you introduce the State Agency of Medicines of Estonia and its mandate to our international readers?

The mission of the State Agency of Medicines is to protect human and animal health through the supervision of medicines and biological medicinal products used in Estonia, to support the rational use of medicines and to contribute to the development of pharmaceutical research and entrepreneurship.

The State Agency of Medicines (SAM) is a governmental body with the aim of:

- ensuring that medicines approved for use in Estonia for the prevention, treatment and diagnosis of human and animal diseases are proven to be efficacious, of high quality and safe;
- promoting the rational use of medicines;
- ensuring the protection of the safety and rights of the clinical trial participants in Estonia;
- ensuring that cells, tissues and organs used in the treatment of humans in Estonia are proven to be safe and of high quality;

- ensuring that narcotic and psychotropic substances and their precursors are used appropriately and in accordance with international conventions.

All the necessary information can be found on the webpage http://www.ravimiamet.ee/en

What would you identify as your proudest achievements and the main important results during your 16 years as director general?

The Estonian Agency is 27 years old, and I have been at the helm for more than 16 of those. I can say that it has been a very challenging time which included building up all new procedures and practices, joining the EU, finding the place for the agency in the EU network, setting priorities (we are one of the smallest agencies in the EU) and being active within the frame of our possibilities and available resources.

We work hard to be an open and trusted organization which values the maintenance and development of professional competence and capability and we do more and more co-operation inside the agency as well as nationally and internationally to ensure the necessary information, optimal use of resources and an efficient distribution of duties and competence.

The Estonian State Agency of Medicines is a flexible, modern and cooperative organisation in the European Union. Over the 27 years of development, the agency has become a stable organisation with all the possibilities to meet the developments in science, pharmaceutical industry and legislation. Maintaining and improving the professional competence of the agency is a very important goal for us.

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One of our aims is to improve the access to medicines through the optimisation of the administrative burden relating to marketing authorisations, and through providing better information to the pharmaceutical manufacturers.

In spite of our smallness we have earned recognition in the comparative measurements of European agencies of medicines – the professionalism of our employees and experts is valued in the European Union drug regulatory network, European Medicines Agency, the World Health Organisation, the European Medicines Agency, the European Directorate for the Quality of Medicines & HealthCare, International Narcotics Control Board and many others.

What would you say are your main priorities right now?

We hope that in the future the network of EU Medicines Agencies will strengthen and more IT solutions will be developed together, with the needs of smaller agencies considered as well. We are going to contribute to the regulatory optimization – less national requirements, optimised and simple processes and more work-sharing.

One of the main tasks for the next 5 years is the data standardization – ISO developed new standards for the identification of medicinal products (IDMP) which should be used worldwide. The five ISO IDMP standards should simplify the exchange of information between all stakeholders, enhancing interoperability of systems at the European Union (EU) level and internationally. Estonia represents small agencies at the EU Data Network Board which is taking part of the ISO/IDMP Task Force. For our agency, electronical data exchange is very important – we have to maintain everyday work with limited resources and our goal is to make our business processes as compact as possible and avoid any manual input of the data. The precondition for data exchange is standardised data and all the databases should speak the same language.

A big challenge for the coming years will be the implementation of the new clinical trials regulation and safety features regulation.

Nobody knows exactly all the details in connection to the BREXIT, but it is important to maintain the sustainability of the Network and to mitigate the risk of increasing number of availability problems of medicinal products.

A 2016 WHO report highlights the limited selection of available medicines in Estonia – in terms of different formulations and number of generics on the market – in comparison with other EU countries. How does the state agency of medicines keep all the stakeholders informed of possible drug shortages? And how do you intend to minimize the effect?

The State Agency of Medicines makes the list of current shortages available on our website and we always put up a new shortage as a news thread. Our website also has an opportunity to order all the news to your own inbox and drug shortages is one classification that one can subscribe to. As a further development we are working towards a solution to add information about drug shortages to the register of medicines and through that on the interfaces of prescribing doctors and dispensing pharmacists.

As to minimizing the negative effects of drug shortages we have always stressed the importance of cooperation between different stakeholders who are impacted by drug shortages. We, as a regulatory agency, are in a good position to mediate information between the marketing

authorisation holders, the wholesalers, the pharmacists and the media. We can also suggest possible solutions or preventive measures but the drug still has to reach the patient through the wholesale system and the pharmacy which means all parties have to contribute. This is also perfectly natural as the whole healthcare system is impacted by drug shortages and everyone should try their best to avoid patients not getting the treatment they need because of it.

On a similar note, to what extent does parallel trade represent a threat in Estonia?

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As Estonia is a small country and a small market parallel trade imposes quite a real threat to us. The number of packages in stock for medicines that are used not very often are not that big and if these packages are exported for a bigger market we might be left with no medicine for our own patients. We have had some examples of this sort.

Given that Estonia is a very small pharmaceutical market (EUR 240 million), what measures are you taking to further incentivize innovation and incite international companies to bring their innovative products?

It is very difficult to provide access of Estonian patients to the very newest medicines given the pricing of these medicines is similar all over Europe. We do try to be flexible and work out solutions with companies that would satisfy both parties and would be affordable to Estonia. The promotion of generics is one instrument to free up assets for innovative medicines and careful deliberation on the cost-effectiveness of new medicines in order to ensure the most outcome for the Estonian patient is the other one.

What is the agency’s attitude towards generic medicines and what are you doing to enhance the uptake at national level?

Our opinion of generic medicines is, of course, that they are of the same quality and efficacy as originators. Generics give an opportunity to save on costs of medicines and through it invest more in innovative medicines. This is positive to all counterparts as more patients get access to the medicines they need.

In Estonia it is compulsory for the healthcare provider to prescribe using the INN unless there is a medically relevant reason to use brand name. Also in the pharmacy the patient has to be offered the cheapest alternative by the pharmacist. In the end it is the decision of the patient which product to prefer, but the use of generics has been increasing in Estonia – slowly but steadily.

The question here really is that the patient should not have to pay more than they need to, so they ought to choose the cheapest preparation within the class of active substances. This actually is not always a generic medicine, it could very well also be the originator. So, contradistinguishing generics and originators is sometimes artificial. The message is that all medicines with a marketing authorisation are of high quality and it is reasonable to go for the cheapest option. This has also been stressed by the Estonian Health Insurance Fund through their advertising campaign.

How do you compare to the other Baltic states in terms of the time it takes to process approvals and costs?

The State Agency of Medicines is an active member of the EU drug regulatory network. The approval times as foreseen by the Directive 2001/83/EC are respected, i.e it takes 210 days to process the initial marketing authorisation application in national and decentralised procedures and 90 days in mutual recognition procedures. It should be mentioned that there are no additional country-specific requirements for the submission of the marketing authorisation applications in Estonia.

The assessment fees for national applications and the applications when Estonia is a concerned member state is 1275 EUR (full application) 958 EUR (abridged application) and 511 EUR for any additional strength or pharmaceutical form. Additional assessment fee 14 000 EUR in case Estonia is acting as the reference member state in the MRP or DCP is applicable. More information on fees can be found here http://www.ravimiamet.ee/en/assessment-fees-2

The general position of Estonia in the EU regulatory network and the contribution as the RMS is indicated in the statistics published by the CMDh.

http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Statistics/2017_Annual_CMDh_statistics.p

There are a number of medicinal products which are not authorised in Estonia, but there is a medical need for them (oxacillin injectable, norepinephrine, metoclopramide injectable, benzylpenicillin injectable etc.). The companies are invited to contact the State Agency of Medicines to discuss the possible submissions.

What is your level of collaboration with the Lithuanian and Latvian agencies and to what extent, if at all, do you share best practices?

We work very close with the Latvian and Lithuanian agencies, as we all are the members of the EU regulatory network, we have lots of cooperational activities and common procedures to carry out. Cooperation is smooth. We have signed several agreements for international collaboration in the

area of medicinal products, which creates a framework for success in cooperation. Dedicated Baltic meetings of the medicines regulatory agencies take place yearly.

To save money and avoid availability problems, we strongly recommend the applicants to use the Baltic package for human and veterinary medicinal products and in cooperation with the agencies from the other Baltic States we have made this procedure quick and easy to use. The main idea at the core is that a company who wants to use all three languages on the package of medicines can just communicate with one of the agencies.

As the science is moving more towards biologics, regulatory agencies are really being pushed to the limit. How are you dealing with these changes in terms of enhancing your capabilities?

This is true, that one of the important trends that affects the agency's work is the rapid advances in biological medicinal products. Global development and the interest of local enterprises in the production of biologicals, also the widespread use of biological medicines require the Agency to increasingly provide scientific advice – for this purpose, there is a need for a very good field-specific knowledge and network of experts. The Estonian State Agency of Medicines realises the urgency of dealing with this and we have stated the target in the strategy document of the Agency.

The Agency's management board has approved a strategy to guide the Agency's work over the four year period. The Strategy for 2015-2018 sets out the strategic vision and actions and serves as the basis of the scheduling of our annual plan. One of the goals stated there, is to improve our competence in evaluating the quality of biological medicinal products. Attention is being paid also to the improving competence of the GMP inspectors to advise and inspect biologicals and advanced therapy medicinal products, as well as improvements concerning network of experts.

As the European regulatory system for medicines is based on a network of all national medicines regulatory authorities, it is also important to have permanent representation and contribute in various working groups, including in Biologics Working Party (BWP), which focuses on the quality aspects of biological medicinal products. During current strategy period, the Estonian expert has been nominated.

Participation in European scientific and regulatory initiatives is essential for innovative regulation. Since the EU enlargement, the Estonian Agency contributes to all common European marketing authorisation procedures. Despite being a small agency we have lot of experiences in decentralised marketing authorisation procedures, acting as a reference member state and also as a rapporteur and co-rapporteur in centralised procedures, but not yet in the area of biologicals. To achieve this

goal, the Agency has defined a concrete aim to start in multinational assessment teams.

Since a growing percentage of new medicines are authorised via common European procedures, rapporteurships are allocated according to capabilities and taking into account the influence of BREXIT, we are planning to increase the capacity of experts in the forthcoming period in addition to the improvement of competence.

Thus the Agency is working on these themes – we want to maintain and develop our present commitment.

With the aim of improving the quality and access to Estonian healthcare, the government has decided to increase healthcare funding by EUR 300 million over a period of five years. How will this impact the state agency of medicines?

The funding is directed towards increased and timely access of patients to the modern health-care services. Estonian healthcare system has been identified by many international analyses as extremely cost-effective but seriously underfinanced. The additional budget will increase access to new medicines – among other improvements in health services. The Agency has a role in comparative effectiveness assessment of medicines in context of the reimbursement decisions. We hope our work will support the best use of the additional funding for Estonian patients.

We heard that one of Estonia's competitive advantages for businesses is the opportunities of collaboration with universities and excellent centres and the excellence of Estonian scientists in the field of oncology and genomics. Do you think Estonia has the capability to emerge as an R&D hub in Europe and, if so, what can the agency do to help the process?

Estonia has a well-integrated medical science network of our major universities and the health care institutions. The country is indeed looking for the best ways to use its e-health infrastructure for the research purposes in addition to the day-to-day provision of services. The University of Tartu Estonian Genome Centre is developing application for precision medicine with pilot projects under way in oncology and cardiovascular prevention. It is also actively looking for industry collaboration for studies in drug development using its 50,000 person biobank which it is currently upscaling. The Agency has been eager to observe these developments and is looking forward to supporting these projects in respect of both regulatory and scientific advice.

As an agency, which tasks do you perform best, and where do you identify that there is still room for progress?

Despite of the Agency’s smallness we have earned the recognition in the comparative measurements of European agencies of medicines, and the professionalism of our employees and experts is valued in the European Medicines Agency (EMA) and other International organisations, e.g. World Health Organisation (WHO). We contribute to all of the common European marketing authorisation procedures as a reference member state or Rapporteur/Co- Rapporteur and also in the EU work sharing procedures for pharmacovigilance. In addition to the Committee for Medicinal Products for Human Use (CHMP) and The Pharmacovigilance Risk Assessment Committee (PRAC), we are active in Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and other committees and working groups. We take part in the European Medicines Agency coordinated supervision, checking the GMP and GCP compliance. The laboratory of the Agency regularly participates in the control of centrally authorised medicines.

Ensuring that medicines are used with minimum risks may be a challenge for those involved in prescribing and using medicines. Risk minimisation measures (routine and additional) help to support the safe and effective use of medicines. To evaluate the additional risk minimisation measures effectiveness and raise doctors’ awareness, several surveys based on Estonian Health Insurance Fund prescription databases (99% of prescriptions are digital) have been made and results published.

We are also proud about our drug statistics. The Agency has been consistently collecting drug utilisation data from wholesalers since 1994. Drug consumption studies and reports based on these data show trends in the country including the comparisons with other Baltic or Nordic countries. The data has contributed to important new knowledge for policymakers and researches, comprehensive and valid drug utilisation data are needed for professionals as a tool to optimise drug utilisation.

Important development for the benefit of patients, is our commitment to coordinate and manage the medicines shortages. The Agency works closely with all relevant stakeholders to limit the impact of human medicines shortages on the Estonian market and is actively involved in co-chairing the Steering Committee of the Task Force on Availability of authorised medicines.

Concerning the room for progress I can say we want to strengthen our influence in the EU. We are planning to increase and expand the expertise area in centralised procedures to be involved in more rapporteurships. Additionally, we are preparing for the role of the reporting member state to be ready for the new clinical trial regulation. There is a willingness to contribute more in other areas as well and provide the best possible assessment. Of course, there is always room for improvement in thorough communication to the public.

What would you like to tell all your industry peers that will be reading this interview?

We are working hard to make the life of applicants easier, e-solutions are highly recommended and accepted in Estonia. The assessment fees are reasonable, including the assessment fee in MRP and DCP as Reference Member State. We use common EU systems where possible as it is not reasonable to create different systems/portals in all Member States. There are no country-specific requirements in Estonia for marketing authorization applications, these being harmonized with EU rules. We have a Client Portal for local users, for example Estonian representatives can send notifications about shortages and withdrawal of the MA via our portal.

Changes of rules are quick and smooth – in the small agency we have less bureaucracy, proposals and good ideas from our specialist and clients go live quickly. Estonia is an e-country, the agency offers more than 30 e-services. Our agency is involved in the development and maintenance of the national e-prescription system, which has been in operation since 2010. Today more than 90% of prescriptions in Estonia are digital prescriptions.

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* In connection with this article, I would like to express my gratitude to my colleagues from the Estonian State Agency of Medicines – Katrin Kiisk, Margit Plakso, Ott Laius and Alar Irs.

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