Interview: Marius Savu â?? Director, NAMMD, Romania

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The director of Romaniaâ??s national pharmaceuticals regulator outlines how his institution is embracing health technology assessment (HTA) capabilities and the transformative changes this will have on the local industry. He also speaks frankly about hot topics sweeping the sector: among them the pressing need for increased regulation of medical devices and the logic behind a financing model based on cost-volume agreements.

Could you please outline the functions and scope of the agency?

We have 3 core areas of responsibility. Firstly, we are responsible for the safety of pharmaceutical products that are getting to the Romanian consumer. This covers the entire value chain from production to distribution to ensuring the right product is correctly delivered up from the pharmacies and the hospitals to the very patients who need them most.

Secondly, there is the medical device domain which is coming to the fore in terms of needing to be properly regulated. This is because medical devices constitute a step system compared to pharmaceuticals. When you scrutinize new devices entering the Europe market they are becoming more and more intrusive in nature and thus the need to verify their proper usage and safety is increasing. Far greater oversight is required for echographs and implantable devices that could be hazardous to public health if not up to specification or improperly handled. One only need look at the unfortunate incident in France where, in the under-regulated domain of cosmetic surgery, the materials used for breast implants were discovered to be deteriorating subsequent to implantation.

Our third and final role, that we assumed only in June last year, is to do with the reimbursement of pharmaceuticals on the Romanian market. We have extended our activities into the area of health technology assessment (HTA) which represents an entirely new capability that the agency had never previously possessed.

Two of these three functions are more established whereas, with the third one, we are actually breaking new ground. In pharmacovigilance and medical devices we adhere strictly to longstanding

routines. We donâ??t have to reinvent the wheel. In the health technology area, however, we are one of the pioneering countries. Like some of the other newer EU member states, we are struggling to balance the access of patients to the sorts of quality pharmaceuticals they need with attentiveness to the cost to the social system to the extent that that system remains sustainable and viable. We are at the cutting edge of identifying new pathways in public health that can ensure stable and prolonged provision.

How have the recent changes to your mandate affected public perceptions of the agency?

They have certainly increased the visibility of the national drug agency because the classic activities are quite technical when talking about pharmaco-vigilance. Not too many people, outside of the industry, understand what itâ??s all about when we set in motion processes to combat falsified medicines or the negative by-products of parallel trade. Nor are members of the public aware of all the work going on behind the scenes on our part to ensure only quality, efficacious, safe products make their way into the pharmacy and hospital supply chains and are distributed amongst the population.

Today we have managed to achieve decently controlled delivery of the system. Romaniaâ??s factories strictly adhere to the GMP rules and the distribution side of the market is increasingly tending towards regularity. Falsified medicine networks were uncovered in certain instances, but we have been doing an effective job in dismantling them: other member states such as Italy struggle with far greater problems in this sphere. With a few exceptions, we have proved truly efficient and capable in controlling the quality of the products found on the market.

Now that we are branching into conducting health technology assessment, people are beginning to associate us with the decision making process as to which treatments are awarded reimbursement status. There is no way of getting away from the fact that difficult trade-offs will have to be made and that it will be impossible to keep absolutely everyone happy. When you have an atypical medication for schizophrenia becoming genericized and then a modified release formulation which is still has exclusivity and costs 100 times more, wouldnâ??t it be better to place this financing instead behind a new cancer therapy that is demonstrating high performance? There is no easy answer. Here we face an eternal challenge between the real needs of patients, pressure from industry and the absolute amount of cash remaining in the health budget.

It is important that the public fully understands that when the state apparatus exercises price cuts and starts the delisting process, none of the money recuperated will move outside of financing pharmaceuticals. Instead, it will all get reinvested and channeled towards bringing in real innovation.

What, to your mind, constitutes â??realâ?? innovation?

Real innovation versus â??me tooâ?? innovation must be taken into account. There is often a logical friction between the industry and the payer, but it is possible to engineer win-win outcomes. We fully understand private industryâ??s right to patents and exclusivity for the value added research behind a particular product that has been invented. R&D for breakthrough medicines does cost a lot and it is entirely right that there should be channels for recuperating those expenses. When a firm starts to move into line extensions that no longer constitute real innovation, then you start testing the limits of what is acceptable because these loopholes deprive patients from gaining access to real innovation. Because state public budgets are finite, having the state finance me-too innovations comes at the direct cost of being able to finance real innovations and this is when the patient is the one that loses out. This is a scenario that is simply not acceptable.

There are cost-efficiency implications for the clinical trials sphere as well. A lot of trials are versus placebo whereas in the future there will be greater need to demonstrate that you are better than a

specific existing treatment. You might, of course, be better than placebo but it doesnâ??t necessarily signify that there is a real need for your product in the patient category. If you are only marginally better then you shouldnâ??t claim you are real innovation. These are the sorts of elements that need weeding out so that we can refocus the money we have on where it will deliver the biggest impact. We basically require a rationalization exercise.

For many years the reimbursement list has appeared frozen with originator companies experiencing difficulty in getting innovative products placed on the list. Change now seems imminent. Can you please update us as to the latest developments and the specific role the NAMMD is playing with regard to this?

The NAMMD has been working very hard to clear the backlog of medicines to be assessed for reimbursement. Decisions of this nature have to be conducted with upmost seriousness and care so take time. They cannot just be realized overnight. Up to now, we had to cope with a historical accumulation of dossiers requiring the analysis of a great number of products. We are making headway with this and hopefully by autumn there will no longer be piles of outstanding requests. We had to amend the law and ministerial orders. All of this entails remaining transparent in discussions, conducting consultations and engaging public debate. It has been a difficult and long-winded process.

Already we have witnessed some openings to the reimbursement list. We started in May 2014 with orphan drugs which answered some urgent unmet needs more or less totally. We then updated the list with a range of products that were uncontestably cost efficient. The third reevaluation of the list is imminent and is currently undergoing consideration.

The idea is to transition to a much more continuous and permanent evaluation where we can foresee updates occurring perhaps on even a biannual basis. To facilitate this we are introducing three new concepts: new molecules that will make the list without restriction, those that will secure their place through managed entry agreements, and those that will be de-listed. These constitute the three pillars by which products will enter and leave the list and our aspiration is this will become more or less the definitive model for the years to come that future political groupings and generations of government will automatically embrace.

What are the actual mechanics of assessing which medicines can make the list or not?

We will try to be as objective end transparent as possible. This is why we are looking towards the decisions of the French, British and German agencies when calculating our own listings and de-listings. We are explicitly taking into consideration the number of countries where the product is available and if there is an obvious saving to budget on an existing product then there should be a release without restriction. On the other hand, if there is a clear efficacy upside, but costs are higher than whatever is already on the list for a specific therapeutic area then that is when we look into cost-value agreements as a compromise solution. That way we can hopefully secure that product with a better end cost for the national healthcare system.

The law has changed 3 times because we were generating feedback from the patients and industry and reworking and improving the legislation accordingly. Moreover letâ??s not forget some of our successes. We are among the first European countries to adopt such a clear policy on orphan drugs. If an orphan drug is reimbursed in a minimum of 3 countries then we are trying to bring it in on cost volume agreements.

Then for infectious agreements such as HIV/AIDS, TB and hepatitis C, we donâ??t want to wait for a full 6 to 12 months when these are reaching epidemic proportions. There is thus urgency for having these new products here as soon as possible providing we can financially afford them. Meanwhile

we are introducing a new reimbursement level of 20 percent for non-lifesaving products that we nevertheless still want to make affordable for patients. Itâ??s a halfway house.

Cost-volume agreements with each pharmaceutical manufacturer donâ??t sound especially transparent. Whatâ??s the rational behind this new arrangement?

Managed entry agreements arenâ??t needed so much for us as for the industry itself. Itâ??s something weâ??ve embraced after considering the demands of the private sector. In the absence of a single European pharmaceutical pricing system, practically the only way an economically small member state like Romania can obtain an affordable price is by keeping agreements non-transparent. This is because, so long as there are massive price deviations between member states, the industry will worry about hemorrhaging profits due to parallel exports from poorer members states such as Greece or Romania. From a profitability perspective, large multinationals can afford to go to very low prices if the sales volumes are guaranteed, but from a transparency perspective they canâ??t afford to disclose low prices to the most powerful economies where customers demonstrate willingness to pay more for the same product.

During EU discussions in Milan, I personally argued that cost volume agreements fail to respect the EUâ??s own transparency directives. Ideally, there should be a transparent price on the conditions under which a state is buying its medicines because, as a small state where purchasing power is low, you donâ??t have the same negotiating capacity as your more influential counterparts. Joint efforts to combat Hepatitis C opened the door to these discussions and there was even talk of European member states banding together to purchase the patent for the most effective therapy as a more cost-effective solution to paying premium prices individually.

Itâ??s a brainstorming exercise because new molecules are never cheap. No one wants to return to the South Africa example of the 1990s where treatment for AIDS/HIV existed but drug companies wouldnâ??t sell it because the country didnâ??t display an attractive enough purchasing power capability.

Meanwhile I think itâ??s a legitimate request that Romanian drug prices should be at the lowest level within the EU because we are not the richest country even if that creates parallel exports and produces some profitability losses.

How can the Romanian healthcare system become simultaneously more effective and more sustainable in terms of expenditure?

Its difficult to balance all the competing needs given that healthcare has become one of the most expensive areas of government in recent years with costs exploding in line with advancements in high end technology. The paradigm has changed dramatically compared with merely a decade ago when you could fine pharmaceutical treatments costing only 100 euros per month for diabetes and schizophrenia. Nowadays, with advanced in technology and radical breakthroughs on the R&D side, high quality hepatitis C therapies can cost a full 60,000 euros per patient. Considering that this is a disease that afflicts somewhere up to 5 percent of the population in Romania, when you start to do the basic arithmetic, then you realize the public healthcare system is not sustainable in its current form.

This is partly because there is little linkage between the payer (the state), the prescriber (the physician) and the end customer (the patient) in terms of economics. Neither the physician nor patient take any real interest in the cost of the treatments they are prescribing or consuming: their only concern is to secure the most medically effective therapeutic solution for a given illness. From an economic standpoint the incentive structures are simply not there to produce cost-effective outcomes. Nowadays with increasingly targeted therapies appearing on the market for oncology and

radical breakthroughs on the horizon for treating diseases like Alzheimerâ??s, we can expect the cost of healthcare to soar even higher.

The impetus is on the state to strike the right balance between bringing innovative and highly effective products into the market and being able to pay for them. I am not sure Romania is in a position where the country can practically handle this dilemma. Outside of the box solutions have to be found. A real radical rethink is needed about how we go about delivering public healthcare. Though we are far from alone in grappling with this problem we are one of those countries, at least within the EU, where these issues are played out more sharply.

How does the NAMMD interlock with what is going on in terms of pharmaceutical regulation, reimbursement and technical assessment at the EU-wide level?

We are recognized in the EU and integrated with the European Medicines Agency (EMA) which is a decentralized agency of the European Union and essentially responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. One of our priorities is to integrate at the national level what the Europe Union is saying on pharmaceutical regulation at the supranational with a view to unifying the approaches as much as possible.

Right now, we can witness a sort of transition phase across the EU where member states are retaining part of their independence in decision-making. There are still two pillars between nationalized competent authorities and centralized competent authorities. Sometimes responsibilities remain blurred and would ideally be much more clearly defined. According to the European treaties, reimbursement and pricing is a national competency which creates quite an imbalance because, on the once side, you have a cross border directive where every EU citizen is expected to receive analogous treatment and standard of care and yet on the other side you have vast differences of national wealth. This becomes more evident in the case of Romania which finds itself at the bottom of the spectrum in terms of national wealth and the level of public financing that can be allocated for healthcare.

Historically, local commissions have played an influential role in determining which particular products make it onto the reimbursement list. Nowadays we are striving to align much more with EU norms while at the same time not losing sight of characteristics and features that are unique to the Romanian context. Already amongst the EU member states there are some well established agencies such as Britainâ??s National Institute for Health and Care Excellence (NICE), Franceâ??s Haute AutoritelÌ• de SantelÌ• (HAS) and Germanyâ??s Institute for Quality and Efficiency in Health Care (IQWIG) that have a combined staff of hundreds of experts looking into the cost efficiency of products. These three agencies can be considered the backbone of expertise within Europe for health technology assessment and it makes rational sense that we should consider their advice and embrace the bulk of their decisions.

In the future, it is entirely predictable that the EMA will eventually seek to centralize health technology assessment for the EU and, in doing so, it is highly likely that these three agencies will be considered the reference point and standard for a harmonized approach. In this sense, by adopting much of their learning, we are demonstrating considerable foresight and aligning ourselves with emerging tendencies and trends.

You nevertheless mentioned the need to adapt your choices to Romanian characteristics. Can you please elaborate further on that?

If we apply only the criteria of NICE and other counterpart agencies, then we will risk skipping important products that Romania specifically needs. That explains why we have been placing so much emphasis on countering infectious disease when this is not considered such a priority in much

of the rest of the EU. Other European member states generally doesnâ??t care about reimbursing and evaluating multiple drug resistant TB, because they donâ??t encounter anything like as much incidence of this disease as we do. Only Romania, Lithuania and Holland (due to prevalence amongst their immigrant minorities) consider this an important public health issue to be dealing with. Therefore, in this instance, we canâ??t just copy and paste NICEâ??s criteria because we will miss out on an element that is highly important for our population.

How do you evaluate NAMMDâ??s capabilities for fulfilling its current mandate and functions?

Itâ??s difficult, especially in the beginning, because we donâ??t have people with previous experiences in areas such as health technology assessment which never previously existed in Romania. Therefore we find ourselves having to build them up right from scratch which takes time. We have been enlisting World Bank support to help train up our existing staff in some of these new areas. We also try to emulate what the big European state member agencies are analyzing. Once we have enough knowledge in-house we will take more decisions on our own. At the moment we are in a process of growing ourselves: developing our wings, so to speak, so as ultimately to be able to take flight and fly on our own.

One area where I could do with more staff is relates to the clinical trials approval process. We hired additional personnel for this function only to find the industry enticing them away with higher salaries and perks. On one side, the CROs claim that we donâ??t give them sufficient support and then we discover that they are taking away our staff. Subsequent to a rigorous training program, I had 4 members of staff leaving within the last 6 months alone because we cannot compete with private sector salaries. Itâ??s ironic that industry is pressurizing us to condense the approval timeframes, but it is actually the very same people who are slowing us down!

You mentioned the difficulties of retaining staff due to private sector wages outcompeting the NAAMD. Is there any way the agency could tap alternative revenue sources?

Actually this is a dimension I am actively working on. My goal is to transition the agency away from being reliant on state funding to having its own for-profit component. I want the NAMMD to become a self-financed institution much like the EMA because the fact remains that we generate a lot of added value. This would enable us to attract the highest caliber of personnel, as our wages would be competitive.

Moreover, presently I cannot participate in the EU network as much as I would like precisely because we are a state budget agency. The EMA makes many referrals that are carried out by national agencies. The EU will propose investigating a product then national drug agencies can offer to conduct that analysis using their own apparatus and the EMA will grant considerable funds precisely for that purpose. Literally millions and tens of millions of euros are dispersed and can be attracted by a performing national drug agency if it is empowered to take on for-profit activities. Under its current mandate the NAMMD cannot do this. My vision is that the NAMMD will ultimately be able to engage in these sorts of activities and will be less reliant on state funding.

You mentioned that regulation is becoming more necessary for the device market. What are the NAMMDâ??s priorities in this domain?

Our most important role is guaranteeing that the devices operating on the market are functioning and delivering the results they should be. Itâ??s a control exercise. There needs to be assurances in place so you donâ??t risk obtaining false positive results on echographs. Unreliability in this area needs to be stamped out. Itâ??s about mainstreaming a day-to-day control function. We will follow European guidance here because we donâ??t have the internal expertise to start innovating in this

area.

We actually withdrew from awarding the CE mark because we recognize that we donâ??t have the competencies and resources in house. In medical devices, a European member state authority can give out the CE mark and then it can be commercialized to the entire EU and this is something that should be urgently addressed in my opinion. Not every country should be allowed to do this. We were happy to let thie capability go because we calculated we didnâ??t have the engineers and technicians to competently fulfill this function when there are perfectly adequate authorities in France and Germany much better versed in performing that task. My question is who is controlling the authorities that are awarding the CE mark? Our thinking is that this function should be restricted to a handful of the most performing national agencies or alternatively rendered the prerogative of the EMA alone.

For pharmaceutical products, when the EU discovered raw materials of dubious quality coming in from India and China, there was a common decision to devise a community wide policy on APIs. Exactly the same rigor should be applied to medical devices. This is especially relevant for implantable devices. This is no longer just about mild inaccuracies with a oxygen device, but about pieces of equipment that are being put in peoples heads and hearts. If they malfunction, patients can die. We have to be sure that these products are of the very highest quality.

What will be the next steps for enhancing the efficiency and sustainability of Romanian healthcare?

There is an advantage to being a latecomer in that we can take the biggest strides forward in the shortest space of time. We have resolved upon criteria for introducing and delisting molecules and the legislation now exists for the managed entry agreements. Most of the basic building blocks are now in place. The next stepping stone will be to set about seeking out additional efficiencies. There should be a step-wise approach in which we gather the low hanging fruit first before moving on to other smart forms of healthcare provision. Future sustainability will ultimately hinge upon preventative healthcare, greater patient autonomy and ensuring the product being prescribed is the optimum one. We should even start channeling money towards genotyping in order to verify that prescribed therapies will generate the desired effect on a specific patient. The idea is not to wait to utilize smart technologies, but rather to position ourselves right at the frontline of these sorts of game-changing developments.

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