Interview: Prof. Luca Pani â?? Director General, AIFA, Italy

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The Italian Medicines Agency, AIFA, sits at a crossroads. Its Director-General Prof. Luca Pani discusses the apparent contradiction in the agencyâ??s mission at a time of constricting budgets and expensive medicines, how the agencyâ??s role is evolving in response and in which ways the agency can collaborate with the industry.

AIFA occupies a delicate position in Italyâ??s regulatory environment, charged with promoting good health by granting market authorization to the latest treatments and also with negotiating the price of drugs. Today, at a time of severely constrained budgets coinciding with the introduction of new, more expensive medicines, how is AIFA dealing with the apparent conflict of interest here?

When the agency was founded, it was formed with the idea of weighing the risk-benefit and benefit-to-price ratios of new drugs in the same institution. This model is very rare; and you must combine this with the fact that Italy is perhaps the only G-20 nation which has full coverage and reimbursement under the national health system for everybody living in our country, even if that person is an illegal immigrant. Now, especially with the introduction of new costly drugs, the ability to fully negotiate the national registration for a drug â??under one roofâ?• has become an asset as a result of the fact that AIFA is the only negotiator who can decide over public reimbursement in the Italian NHS.

This model used to be far less efficient when we were evaluating only progression free survival. For instance, in oncology, where risk-benefit was a minor part of the picture, now we are now facing

significant changes in overall survival rate. Today, with new products starting to arrive â?? the anti-Hepatitis C drugs being good examples, but they are not alone â?? we must change our managed entry agreements methods. We need to move from classical payment for pills and vials to reimbursement of preventable cost and payment for measurable outcomes.

This is certainly the case for HCV, since we lack a comparator drug with the same efficacy and the new medicines will really give us the opportunity to eradicate the disease permanently. Our registry system makes Italy one of the few countries where we can look at the risk-benefit aspect of a drug and combine this with the resources saved by avoiding liver transplants for example, in order to estimate the drugâ??s actual value.

This type of analysis can only be performed rapidly when the same agency that does risk-to-benefit assessment can also access data on the savings generated in real life by using regulatory certified registries on hard endpoints. This is the way we understand and interpret the concept of early Health Technology Assessment (HTA) evaluation and on which we base our managed entry agreements and all the consequent reimbursement decisions.

You have spoken about HTA before, and the important role it plays in the Agencyâ??s assessment of new treatments, can you elaborate on how you see HTA facilitating the market authorization decision?

My interpretation of HTA is that it is not a technological assessment of health, but rather a health assessment to give economic value to a drug or to a technology. This is not a case of semantics but is really pivotal to the approach AIFA has followed over the last years.

So besides the usual measurements such as overall survival rates, biomarkers, quality of life and drug risk profiling, we would also like to know if and when, after a certain treatment, patients are able to go back to work. This has a huge impact not just from an economic point of view, but also from a psychological standpoint. So there are preventive costs, costs recuperated through a reduction in hospital visits, and even income generated by productive days gained. That is why the economic side, measured through and beyond HTA, is important to us, and why this represents an asset for an agency which is required to promote health and to manage the price of new medicines. We have made real progress in this area. Had you asked the same question on these apparently conflicting roles five years ago, I would have had to answer it in a different way, but today with such effective drugs being developed, I can say it has become an asset.

How do you see this new model of a combined role within a single agency evolving on a wider scale, do you see it helping regulatory agencies outside of Italy surviving the new reality of expensive drugs with constricting budgets?

I think that the next step is to bring the economic evaluation to the European level. We need to put together a number of fierce negotiators from national bodies and sit them in front of a panel of top industry representatives. Then we have the power of numbers, and we can say â??look, we have a combined market of six hundred million people, this will have a huge impact on your business. The drug has received approval from CHMP (European Committee for Medicinal Products for Human use), the bracket within which your product could be reimbursed in the European community is between, for example, 80 and 120. Providing that companies can demonstrate solid results on outcomes, then 80 would be for countries with lesser means, 120 for countries with more resources. This is only a provocative example that stems from a vision we should move towards. But there is a caveat. Under this common negotiation model, countries would need to surrender sovereign power in this area in order to get a better price and faster approval. If we can accomplish this, we could survive the new reality you described but it will not be easy.

Can you describe how AIFA collaborates with the industry in Italy today to ensure fair pricing for drugs?

First, letâ??s not forget that we have very different roles and we need to keep it that way. A price that is considered fair for us as a national health system may not be considered fair for the industry, and rightly so, as they need to look at the highest margin of profit for their shareholders. Having said that, we wrote a very important conflict of interest regulation in order to clearly define our separate roles, and in that sense we are very much in line with what the EMA has done. We also negotiate in full transparency. We state the problem clearly to begin with and describe where we would like to have the budget allocated.

It should also be remembered that once a drug enters the Italian reimbursement system, it stays there for its lifetime. Every once in a while reports appear stating that Italy is lagging behind other European countries such as the UK and Germany in approval times. It would be very easy for us to approve the registration of drugs nationwide. It is the reimbursement of drugs which is the issue. In Italy we do not back out of the reimbursement after a number of years, once a drug is in it, stays in. So in that regard we have a very different situation here. In our system we take more time to implement new drugs because we need to assess whether we can cover the drug over the long term calculating the prevalence of a certain disease five to ten years in advance. I hope everybody realizes how challenging this exercise could be. Right now it is becoming clear that the pharmaceutical budget may not be enough, despite all the savings that were recently ensured by renegotiating with companies and applying reference pricing. Anti Hepatitis-C drugs are already projected to reach 800 million for the Italian market before the discounts in the year 2015 alone, drugs like Nivolumab and Pembrolizumab are coming, the immunotherapies are coming as well and they will be expensive.

The positive side is that these are effective drugs, and they will offset other costs which we would otherwise incur by not treating the diseases they target. Our challenge lies in demonstrating that the drug allows a certain saving, which needs to be certified by the Ministry of Health or other Institutional bodies so that those resources are reallocated between the pharmaceutical and hospital budgets. Without such mechanisms, funding the reimbursement of new drugs will become increasingly difficult.

It is clear that AIFAâ??s role is evolving with the changing needs of the system. How would you describe this evolution?

The regulators, not only AIFA, need to get down in the trenches with companies, patients, prescribers and payers to account for the survival rate gained, as well as the additional peripheral costs these drugs entail, such as MRIâ??s or biomarkers. So the short answer is that we need to be involved in sharing part of the cultural risk and responsibility inherent in the development of any truly innovative drug.

We are discussing an idea that the EMA has launched, called progressive patients access scheme, where companies come to regulators early, with an initial data-set. If the results are reasonably positive they could be granted initial authorization more quickly than usual, which means patients in urgent need can get treatment earlier and companies can start marketing the drug earlier. This will allow us to gather more comprehensive data, applying the Post Authorization studies both for efficacy and safety as required by the new European pharmacovigilance legislation. In a totally opposite scenario, if regulators are not convinced by the risk/benefit profile of a new drug they should be able to tell the marketing authorization holder immediately. Any drug development which is not delivering what it is supposed to should be halted as early as possible so that funds can be better invested for the sake of patients awaiting effective treatments. This approach helps companies

as well as regulators, and saves time and money on both ends.

Moving forward, what can the industry expect from AIFA over the next few years?

As you know, we have gone through one of the most extensive revitalization processes among any regulatory agency in Europe. We have 240 people to hire over the next few years, so we are moving from a force of around 400 to 630. For us it is a big leap and a lot of responsibility. With the new workforce we will firstly, but not only, implement and fortify our inspection teams. We would like to make our inspections better, faster and we would like to certify the â??Made in Italyâ?? brand in pharmaceuticals as well.

Is there a final message you would like to give the international pharmaceutical community reading this report?

As I said there is a â??Made in Italyâ?• element in pharmaceuticals which is just as significant as it is in cars for Ferrari, or in leather for Gucci. We are incredibly good at using numerically controlled machines, such as those used in pharmaceuticals, and there is a very strong SME network in the country. The quality of the drugs these companies make is outstanding, accurate up to 99% and passing every external test. We also have most probably the highest concentration of doctor-to-patient points of contact in the world. We have now been investing in our national health system for 40 years, in an amount exceeding, in todayâ??s terms, 100 billion euros per year. As a result, the clinical network is extremely robust and outstanding in its capabilities.

In that respect we are an ideal country in which to conduct clinical trials, and that is why few months ago AIFA proposed the establishment of a sole national ethical committee. At the end of 2011 when I took office, there were 290 ethical committees, then we brought it down to 96, and now we need to move further, in order to make Italy a pharmaceutical hub for clinical trials which reflects the ability and the quality that we feel this country possesses and deserves.

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