Interview: Jarbas Barbosa da Silva – Director-President, Brazilian Health Regulatory Agency (ANVISA), Brazil

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In an exclusive interview, Jarbas Barbosa da Silva, Director-President of the Brazilian Health Regulatory Agency (ANVISA), discusses some of the key specificities of the Brazilian market and highlights some of the main regulatory updates implemented by ANVISA over the past two years, while providing insights into the collaboration opportunities he envisions for international regulatory agencies, a few months after ANVISA officially became a regulatory member of the prestigious International Conference on Harmonization (ICH).

What are some of the unique specificities of the Brazilian market that you take into account when strengthening the country's regulatory framework?

Very few of the world's largest pharmaceutical markets have been growing at a sustained pace over the past years, and Brazil proudly stands as one of the best performing markets. Furthermore, the Brazilian pharmaceutical landscape has been characterized by a significant level of consolidation across the board, although the number of M&A deals occurring over the last two years has maybe slightly decreased in comparison to a few years ago.

In this regard, regulating a fast-growing and rapidly evolving pharmaceutical ecosystem stands as a completely different endeavor than addressing a stagnating market. Therefore, ANVISA's objective is to ensure that Brazil's regulatory landscape meets the highest standards globally, while integrating the specificities that come with our market's rapid growth and its ongoing

consolidation.

In this context, what have been some of key regulatory updates implemented by ANVISA since you took over the helm of the agency in July 2015?

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We have conducted a comprehensive review of ANVISA's process, holding the twofold objective of strengthening our registration processes and making Brazil a more transparent and predictable ecosystem for all stakeholders.

Overall, ANVISA's timelines for the registration of innovative medicines are already aligned with those of other leading regulatory agencies around the world, such as the EMA and the US FDA. Nevertheless, the entry of a large number of generic products into the Brazilian market over the past decade has generated a backlog of around 780 generics and branded generics, which are still waiting to receive market registration. In this regard, we have been working with international institutions such as the Center for Innovation in Regulatory Sciences (CIRS) to implement standardized risk assessment models that would speed up the registration process for generics. Leveraging this regulatory update, we expect to have reviewed the very last registration files of this backlog before April 2018.

We have also taken steps to reduce the huge gap between the total number of pharmaceutical products approved by ANVISA (over 60,000) and the number of medicines actually commercialized in Brazil (around 16,000 in 2016). The main reason behind this discrepancy goes back to a decade ago, when the Brazilian government decided to set up particularly low registration fees for generic products – between USD 2,000 and 4,000 per dossier – in order to incentivize pharmaceutical manufacturers to develop and bring more generics onto the Brazilian market. Nevertheless, the total number of registered products held by a given pharmaceutical manufacturer also has a deep influence on the company's value, which – in a country marked by a high number of M&A deals – prompted manufacturers to register products years before the latter actually enter the market. As a result, in 2016 we implemented a mandatory deadline between product registration and commercialization.

Furthermore, we recently reached a long-awaited agreement with the National Institute of Industrial Property (INPI) that clarifies the respective responsibilities of the two organizations for the handling of patent applications of pharmaceutical and healthcare products, which should in turn further accelerate the overall patenting process in Brazil as well as bolster the entry of generics products when patents expire.

In November 2016, ANVISA became a regulatory member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), whose founding regulatory members are the US FDA, the EU EMA and Japan's PMDA. Why is this membership important for ANVISA and for the Brazilian pharmaceutical ecosystem in general?

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Being accepted as a regulatory member of the ICH stands as a great recognition of the level of maturity that ANVISA has already been able to reach, only eighteen years after its establishment. This membership also highlights the quality of our regulatory processes, while providing us with a heightened influence in the global discussion for regulatory harmonization. On the other hand, becoming a regulatory member of the ICH also means that ANVISA will have to comply with a new set of guidelines framing pharmacovigilance, clinical research, Common Technical Document (CTD) and the implementation of a Medical Dictionary for Regulatory Activities (MedDRA), but I am absolutely confident that we will be able to meet these requirements even before the stipulated deadlines.

I also consider that this ICH membership in particular and the continuous strengthening of ANVISA's recognition in general are instrumental in fostering the internationalization of our domestic manufacturers. When we first set up ANIVSA, many observers believed that implementing world-class standards in Brazil would hinder the development of local players; however, now, most local companies see ANVISA's reputation and the stringent nature of our country's regulatory framework as a true competitive advantage when it comes to entering new markets and exporting locally manufactured products.

International harmonization is a topic that has been continuously gaining in importance among leading regulatory authorities. As a new regulatory member of the ICH, what do you consider as the main issues at stake in this regard?

International harmonization is a challenge for all regulatory agencies around the world, as patients do not understand why regulatory requirements – and ultimately registration timelines and product access – still vary substantially from one country to another. In this regard, the social pressure weighing on regulatory agencies' shoulders has never been so intense, and it becomes particularly acute every time new, very innovative products are ready to enter the global market.

As a regulatory member of the ICH, we will work on addressing two of the main challenges that lie ahead for national regulatory bodies: first, ensuring a greater similarity between the frameworks of

different pharmaceutical markets around the world, and, second, building up mutual trust among regulatory authorities in order to favor multiple country processes and authorizations – rather than individual, national requirements. In this regard, we recently saw that the US FDA and the EMA jointly assessed the market approval of a new pharmaceutical product – these kind of eye catching initiatives clearly needs to be replicated and expanded in the future.

As you mentioned the necessity to reduce processes duplication, which next steps should be concretely targeted in terms of international collaboration?

ANVISA is part of the International Coalition of Medicines Regulatory Authorities (ICMRA), a voluntary, executive level leadership entity that provides direction for a range of areas that are common to many regulatory authorities' missions. One of the key priorities identified by ICMRA members is putting an end to the requirement for pharmaceutical companies to replicate similar certifications and regulatory processes for each and every country in which they want to bring their products.

The current system will not be sustainable in the long term, both in terms of clinical data and auditing process – for GMP certification for example. The latter is extremely resource consuming for the regulators, which have to audit facilities all around the world, as well as for manufacturers, which have to wait for and welcome each regulatory agency one after the other.

In this regard, we should take inspiration from what has already been implemented in the medtech field with the Medical Device Single Audit Program (MDSAP), which has four national regulators as its members *[from Australia, Japan, Canada, and Brazil, e.d.]*, while the World Health Organization (WHO) and the European Union are official observers of the program. The Medical Device Single Audit Program allows an MDSAP recognized auditing organization to conduct a single regulatory audit of a medical device manufacturer that satisfies the relevant requirements of the regulatory authorities participating in the program – and I believe that this kind of program also stands as the way forward for the certification of pharmaceutical plants.

Another aspect to assess at the international level relates to the registration pathway of very specific products, such as orphan drugs. In this specific case, it is normal that patients refuse to wait for several years before accessing life-changing treatments that do not have any existing alternatives, while the extremely small patient population targeted usually means than extended timelines are needed to collect clinical data and register the product in a given market. In this context, we need to collaboratively design innovative mechanisms that would enable provisory market approvals. For example, we could grant orphan drugs a provisory license at the phase III

stage of clinical trials and then use post-marketing surveillance in order to guarantee access while regulators are still gathering efficacy data.

Finally, it becomes critical for regulatory bodies to join forces and build tangible, collaborative tools dedicated to horizon scanning, especially given the technology revolution entailed by the rapid generalization of biologicals.

You took over the helm of ANVISA in the midst of the Zika outbreak, which started in Brazil and was deemed a Public Health Emergency of International Concern by the WHO in February 2016. What do you see as the role and contribution of regulatory agencies when such a public health emergency occurs?

Public health emergencies are also a topic discussed among ICRMA members and I am the representative of the Crisis Management Group of the association. I believe that regulatory authorities can provide a key support to health ministries in addressing public health crises, as they can ensure swift access to new and life-changing diagnostic tools, vaccines or treatments while guaranteeing their quality, safety and efficacy. Looking at ANVISA’s experience in tackling the Zika outbreak, we notably leveraged a specificity of the Brazilian regulation that enables fast-track registration of critical products in the case of public emergency of national and/or international concern. As a result, the first laboratory kits for the Zika virus received market approval within less than six weeks.

Another important aspect relates to information sharing between regulatory authorities: during the Zika outbreak, we notably held several videoconferences gathering ANVISA and some of its international counterparts. In times of crisis, it is also absolutely critical to foster collaboration between the industry and regulators, as, by closely guiding pharmaceutical companies, we can ensure that regulatory requirements are well understood and integrated before critical, new products are ready to enter the market.

What would be your final message to our international readership?

Brazil is the sixth largest pharmaceutical market in the world and we are steadily moving toward the fifth position, which we will probably reach within the upcoming years. The sustained growth of the Brazilian market is being nurtured by many different factors, which notably includes particularly rapid demographic and epidemiological transitions. In the meantime, our population indisputably benefits from a broader and faster access to quality healthcare products and services than 20 years ago, despite structural issues faced by our public health system and particularly with regards to its financing. In the meantime, government initiatives implemented at the beginning of

the millennium, which notably aimed to ease the market entry of generics products, will continue to bear fruit and propel the growth of the Brazilian market in the years to come, while generics already stand as the main growth driver of the Brazilian market.

As per ANVISA, our fundamental mission will be to further implement global standards into our local ecosystem while respecting the specificities of the Brazilian market; in the meantime, we want to play an active role in fostering international harmonization and convergence of regulatory standards and provide the Brazilian population with greater and faster access to quality, safe and effective medicines.

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