Promoting Regulatory Collaboration and Convergence in Asia

Regulatory reliance is increasingly being used by National Regulatory Authorities (NRAs) with different regulatory systems and is actively promoted by the World Health Organization (WHO) as a mechanism to better manage resource capacity issues and strengthen regulatory systems. NRAs in Asia remain key in spearheading efforts and offer opportunities for all stakeholders.

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In 2016 the WHO published an article in its Drug Information Bulletin titled *Collaboration, not competition: developing new reliance models*[1] The article´s authors argued that modern medicines manufacture and distribution were becoming more and more globalized and that as a consequence the manufacturing processes and supply chains of pharmaceutical products, including generics, were increasingly complex´. They went on to say that the same medicinal product was often distributed in several countries or world regions and used by patients all over the world, pointing out too that it was also common that different manufacturing phases for the same product takes place in different countries, often separated by long distances.

The authors highlighted the fact that new medicines coming onto the market such as biotechnology, gene therapy or cell therapy products were complex products and that some National Regulatory Authorities (NRAs) may lack the resources or specific competences to carry out assessments of these products before they are put on their markets. They argued that collaboration among NRAs was vital to avoid duplication of work, release scarce resources for more critical areas and speed up patient access to both new and existing medicines and vaccines.

The article was prescient in its analysis and the ideas behind it are even truer today. The growing awareness of the need for regulators to work together has led to

1 https://3zb9gz1us4bxkdpdb1n79pv3-wpengine.netdna-ssl.com/wp-content/uploads/2018/01/Mental-Capital.png

the emergence of new models of cooperation, such as regulatory reliance.

Reliance is a broad concept and can be achieved in real life in different ways.

The WHO defines regulatory reliance as `the act whereby the regulatory authority in one jurisdiction may take into account and give significant weight to – i.e. totally or partially rely upon – evaluations performed by another regulatory authority or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others. '

For example, when an assessment report for a medicine authorised in the EU is shared with an NRA in Africa, the receiving authority might still need to consider differences in conditions of use, patient population and other parameters. In many cases reliance on the assessment or inspection work carried out by another trusted NRA can be the best way to cooperate effectively. Reliance can be unilateral, bilateral (mutual) or multilateral.

Regulatory reliance is a concept whose time has come.

Strengthening regulatory systems and increasing their efficiency is something all players in the biopharma sector wish for and ultimately benefit from. Momentum for the move towards regulatory reliance is being driven by various bodies such as the WHO , the Pan American Health Organization (PAHO) and the European Medicines Agency as a mechanism for NRAs to better manage resource capacity issues whilst simultaneously strengthening regulatory systems. This allows them to focus on core national activities and is a key exemplar of a risk-based review system.

More recently, the International Conference of Drug Regulatory Authorities announced recommendations to NRAs that included `exploring approaches to utilise concept of reliance and collaborative decision-making to increase timely access to safe and effective medical products.'

Over the last decade we have seen the growing emergence of regulatory reliance

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in the sphere of infectious diseases: vaccines or medicines used to prevent or treat public health priority diseases are a case in point. Examples of this include the WHO Expanded Programme on Immunisation, medicines for protections against diseases such as HIV/AIDS, tuberculosis and malaria and products of global health interest (innovative small molecule and biologicals, biosimilars, vaccines and generic medicines).

There are numerous other examples.

Switzerland has in place a system that legislates for its regulatory authority Swissmedic to approve medical products that have been approved in other countries provided that the applicant approaches it do so.

Singapore and Mexico have similar agreements with the latter having revised agreements with the European Union as well as the U.S., Canada, Australia and Switzerland.

But regulatory reliance is becoming increasingly important in regions like Asia where efforts are being spearheaded both by influential bodies like APEC and countries like Singapore.

APEC established a Regulatory Harmonization Steering Committee (RHSC) in 2010 to advocate for regulatory convergence in pharmaceuticals for improved public health and economic development among its 21 economies (APEC Member Economies 2017[2]). Convergence will focus on the process of aligning multiple countries' regulations for greater regulatory cooperation and does not necessarily require the regulations to be "harmonized". The ultimate aim would be for APEC economies to achieve the maximum level of regulatory convergence feasible by 2020 and would focus on four key areas: Certificate of Pharmaceutical Product (CPP); the Pharmaceutical Inspection Co-operation Scheme (PIC/S) membership; managing multiple sites in one license; and risk-based reliance evaluation system.

Huge progress has been made, but in some countries it has been uneven.

Singapore, for example, has led the way on both CPP and risk reliance evaluation.

The CPP was developed by the WHO as a tool to support product registration among national regulatory authorities, especially in developing countries. It serves as evidence that a product has been approved by the national regulatory authority that issued the CPP. Previously, Singapore (a member of both APEC and ICH) used to request for CPPs but as its regulatory system matured, the requirement for the CPP has been removed from both its pre- and post-marketing control requirements[3].

On risk reliance Singapore signed an agreement with Australia nearly two decades ago, which has treaty status and includes the sector on Medicinal Product GMP Inspection. Under the MRA, the Therapeutic Goods Administration (TGA) of Australia accepts the conclusions of inspections of manufacturers carried out by GMP Auditors of (Singapore) and vice-versa[4]. In 2011, two of Singapore's Reference Agencies, Health Canada and the Swissmedic, invited Singapore to begin sharing work

2 https://link.springer.com/article/10.1186/s41120-018-0024-2#CR4

3 https://link.springer.com/article/10.1186/s41120-018-0024-2

4 https://link.springer.com/article/10.1186/s41120-018-0024-2

on generics evaluation. This cooperation led to a four-member regulatory consortium (ACSS) established in 2007.

Elsewhere though there is room for improvement. Several NRAs in Asia still dictate on cumbersome and duplicative regulations that continue to stifle efficiency and the development of regulatory partnerships.

What then are the conditions needed for the effective implementation of regulatory reliance?

First of all, regulatory reliance should be considered by NRAs regardless of their resource or capacity level and independent of their maturity. In fact, streamlined processes for handling regulatory reliance can be seen as an exemplar of maturity. All agencies in future will need to engage in reliance whether this is through information sharing, work sharing, collaborative evaluations, targeted assessments or full mutual recognition.

Second, clear public health priorities based on medical needs and regulatory capacity should guide NRAs' approaches to regulatory reliance.

Third, the timeline from reference country approval to submission of dossiers in a reliance-based regulatory procedure should be flexible. Country filing decisions are based on multiple factors - not only regulatory considerations. Reliance-based regulatory procedures that require submissions within a defined time of reference country approval may limit the usefulness of the procedure.

Fourth, pilot programs for reliance-based regulatory procedures will provide initial practical experience for NRAs and applicants. Robust evaluation of results from these programs, including feedback and dialogue between NRA and Industry users, could swiftly capture opportunities to improve processes and procedures leading to increased trust and acceptability by all stakeholders.

Fifth, reliance-based regulatory procedures can be implemented at many stages in the product life-cycle.

Sixth, when products are approved through reliance-based regulatory procedures, then post-approval changes should also be managed through reliance-based procedures.

Lastly, the key to effective implementation will be getting the simple practicalities right- publishing a list of accepted reference NRA countries; providing guidance on what documents are required and how they are used for the assessment; clarity on who is providing which documents (e.g. reference NRA vs applicant) should also be given and confidentiality should be assured; assessments ought to be based from one reference NRA, and not upon two or more reference NRA countries.

There will of course be challenges along the way.

Regulatory reliance cannot happen in a vacuum so there will inevitably be a need to map out implications of increasing reliance globally within existing regulatory networks/schemes. It also means that administrative requirements for existing reliance schemes need to be taken into account going forward.

The misalignment over the source (NRA or manufacturer) and volume of information is a potential problem as would be the lack of advance agreement between NRAs on the information to be relied upon. The lack of safeguards of confidentiality also need to be addressed.

BREAKOUT BOX

With the recognition by the US Food and Drug Administration (FDA) of Slovakia, the European Union and the United States have now fully implemented the mutual recognition agreement (MRA) for inspections of manufacturing sites for certain human medicines in their respective territories.

Each year, EU national authorities and the FDA inspect many production sites of medicinal products in the EU, the US and elsewhere in the world, to ensure that these sites operate in compliance with good manufacturing practice (GMP). Under the MRA, EU and US regulators will now rely on each other's inspections for human medicines in their own territories and hence avoid duplicative work. As a result of the MRA, both the EU and the US will be able to free up resources to inspect facilities in other countries.

The MRA is underpinned by robust evidence on both sides of the Atlantic that the EU and the US have comparable procedures to carry out GMP inspections for human medicines. Since May 2014, teams from the European Commission, the EU national competent authorities, EMA and the FDA have been auditing and assessing the respective supervisory systems. With the positive assessment of Slovakia, this process has now concluded for GMP inspectorates covering human medicines.

From now on, a batch testing waiver will also start to apply. This means that the qualified persons in EU pharmaceutical companies will no longer have to carry out quality controls for products manufactured in and imported from the US when these controls have already been carried out in the US.

The MRA implementation work will continue with a view to expanding the operational scope to veterinary medicines, human vaccines and plasma-derived medicinal products .

Source: European Medicines Agency

But the reward and opportunities of buying into regulatory reliance are enormous and still very much untapped - implementing regulatory reliance provides stakeholders with opportunities that go beyond regulatory processes.

Harmonisation will foster regulatory reliance and implementing WHO and ICH guidance can facilitate the implementation of regulatory reliance mechanisms. At the same time changes to regulatory and legal frameworks should aim to leverage the benefits of regulatory reliance.

Regulatory reliance supports capability building - the learning and experience-sharing aspect of regulatory reliance will allow NRAs to address potential capability gaps in the longer term.

Collaboration and dialogue will help to create and build trust between stakeholders, which is the foundation of regulatory reliance.

So, who are the winners in a system of regulatory reliance?

Certainly, patients and healthcare providers are huge beneficiaries - regulatory reliance can improve timely access to safe, effective and quality medical products.

The NRAs also gain enormously by efficiently utilising resources that avoid duplication of work and providing opportunities to strengthen the regulatory system, while maintaining sovereignty over decision-making. As does industry with streamlined management of regulatory submissions and global supply systems as well as predictable, timely approvals.

References are available at www.pharmafocusasia.com

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