

Regulatory harmonization

The International Generic Drug Regulators Pilot

The pre-market review of generic medicines puts mounting pressures on health regulatory authorities around the world due to increasing workloads and risks associated with complex global supply chains. This has led a group of regulators to launch the International Generic Drug Regulators Pilot (IGDRP), aimed at regulatory convergence and cooperation. The three-year pilot entails a series of concrete measures to facilitate the timely authorization and availability of safe, effective and quality generic medicines.

Results of the pilot will inform decisions on establishing a more permanent information and work-sharing arrangement as part of broader international efforts related to regulation of medicines. The success of the initiative will require the support of industry as well as other stakeholders interested in promoting access to affordable, quality generic medicines.

Introduction

The availability of quality generic drugs, also known as multi-source medicines or pharmaceuticals, plays an increasingly important role in helping to address rising health care costs and in promoting access to essential medicines worldwide. This, however, has led to significant pressures on medicines regulatory authorities (RAs) charged with the review and approval of these products. In addition to an increased workload associated with the growing number of generic drug applications, RAs must now also contend with more sophisticated generic drug products and complex global production and distribution chains.

Given these challenges, the need for regulatory cooperation and convergence has long been recognized. "Regulatory convergence" represents a process whereby the regulatory requirements and approaches across countries and

regions become aligned over time as the same harmonized technical guidance documents, standards and scientific principles are adopted and similar regulatory practices and procedures are introduced. Regulatory convergence in turn makes possible additional, enhanced forms of cooperation and collaboration between regulatory authorities.

Exploratory meeting

In an effort to address the challenges associated with the increasingly demanding review of generic drug applications, regulatory authorities from Australia, Brazil, Canada, the European Union, the Republic of Korea, Singapore, Switzerland and the United States as well as the World Health Organization (WHO) met in Ottawa in October 2011 to explore opportunities for collaboration. A number of positive developments and precedents were identified that favour a collaborative drug review model, including:

- a common set of quality requirements and application format provided by ICH

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Quality guidelines (1) and the Common Technical Document (CTD);

- the increasing number of multi-national generic companies, including the generic arm of innovator companies, with a potential for common products, ingredients and manufacturing sites across markets;
- the success of existing collaborative models, including the WHO's Prequalification Programme as well as the EU's Centralised and Decentralised Procedures (and the EU's Mutual Recognition Procedure, wherein a marketing authorization has already been granted by an EU Member State); and
- the restricted set of scientific disciplines involved in generic drug reviews, compared with reviews of first market entry drugs ("new drugs").

Preliminary surveys

The meeting in Ottawa was preceded by surveys, commissioned by Health Canada, with a number of multi-national generic drug manufacturers and with the participating RAs. Regulatory frameworks, data exclusivity, patent rules, submission management and other pertinent issues were also compared to help inform discussions.

RAs were asked about the potential advantages and disadvantages of a collaborative review process, when and what form of collaboration might be most beneficial and achievable, and desirable short, medium and longer term outcomes.

The survey of generic drug manufacturers was designed to establish current business practices and to solicit views on whether a business case existed for establishing a collaborative review programme if certain enablers were in place.

Findings from the surveys and views expressed in the exploratory meeting confirmed strong support in principle for regulatory collaboration in the pre-market review of generic drugs, although the degree of support was conditional for some RAs on the scope and form of collaborative model chosen. In general, there was also agreement on the main advantages, challenges and enablers to international collaboration (Table 1). Although important challenges were identified, they were not felt to be insurmountable.

The path forward

Recommendations from the exploratory meeting helped to shape the path forward. Key among these was the need to be pragmatic and to adopt a step-wise approach, starting with selected areas of collaboration, a mapping of regulatory programmes and information-sharing between authorities.

It was also recognized that many of the prerequisites for collaborative generic drug review – such as secure electronic platforms for sharing of documents, and mechanisms to treat and exchange confidential business information – also apply to other areas of potential cooperation. Finding solutions to these issues, together with the building of greater knowledge and trust between regulatory authorities, will facilitate additional areas of inter-agency cooperation in the future.

Participants further recognized the importance of industry support in realizing the full benefits of regulatory collaboration. Any work-sharing arrangement would clearly require the filing of common marketing applications to a consortium of RAs.

At the exploratory meeting, participants agreed on high level goals and objectives, on the general parameters of an operating model and on areas of initial focus based

Table 1. Benefits, challenges and enablers to a collaborative generic review process

<p>Benefits:</p> <p>Improved operational efficiencies Potentially faster and more consistent review and approval process Greater availability of generics that may otherwise not be registered in certain markets Regulatory convergence, promotion of regulatory science and the strengthening of RAs Greater regulatory oversight and peer review Reduction in overall regulatory burden and less duplication of effort Lower regulatory and product development costs/times Greater alignment of industry submission practices Fewer parallel registrations More affordable generic medicines Mutual learning and consistency in applying international guidelines such as ICH Q8(R2)</p>
<p>Challenges:</p> <p>Unfamiliarity with regulatory systems of other RAs Differences in:</p> <ul style="list-style-type: none"> • Legal frameworks: definitions of terms (“generic”, “reference product”, “data exclusivity”, “pharmacopoeia”, “variations”, etc.) • Treatment guidelines/therapeutic traditions between countries, both in terms of the medicines acceptable for market authorizations by RAs and acceptable indications • Technical requirements, e.g. bioequivalence (BE) requirements for complex products • Product and active pharmaceutical ingredients (API) differences – source, method of manufacture, packaging, etc. • Assessment timelines, which may be anchored in regulations • Timing of applications due to differences in data exclusivity/patent rules <p>Divergence following joint approval due to separate handling of post-approval changes Culture change Potential reduction in number of manufacturing sites, impacting on supply Complexity of setting up and maintaining a collaborative review system</p>
<p>Enablers:</p> <p>Regulatory gap analysis Secure electronic platform for sharing of reports/comments Confidentiality arrangements between RAs and/or consent of applicants Common technical requirements and definitions Practices to enable filing of common dossiers:</p> <ul style="list-style-type: none"> • Identify sections of CTD where content is identical or consolidated (e.g. multiple pharmacopoeial references) • Allow different BE studies within a single application where use of different reference products is unavoidable <p>Staff exchange, workshops and training Pilot programme, guided by policies, procedures to manage the pilot Leveraging the experience of jurisdictions and models such as EU and WHO</p>

on both perceived value and the likelihood of success. Most importantly, participants undertook a commitment to pursue discussions towards the achievement of concrete deliverables.

Meeting participants further learned of the formation of the Heads of Agency Consortium involving the RAs of Australia, Canada, Singapore and Switzerland, as well as the advanced degree of

collaboration and work-sharing efforts that are already taking place in generic drug review. These experiences could help facilitate discussions with the larger grouping of RAs.

Launch of the International Generic Drug Regulators Pilot

A second meeting of regulators, co-chaired by the US Food and Drug Administration (FDA) and Health Canada, took place in Washington in April 2012, marking the official launch of the International Generic Drug Regulators Pilot (IGDRP), with the addition of regulators from China, Chinese Taipei, Japan and Mexico.

Participants reached consensus on a three-year duration and on interim operating procedures for the pilot. A formal governance structure and terms of reference would be adopted on the basis of experience gained during the pilot and broader regulatory cooperation discussions concurrently taking place at the international level.

Operating procedures

Interim operating procedures defining the mission, goal, objectives and operating arrangements are outlined in Table 2. Agreement was also reached on the following working definition of a generic drug, recognizing that precise regulatory definitions across the IGDRP jurisdictions may differ:

“A generic drug is generally defined as a drug product that is equivalent to a reference product in active pharmaceutical ingredient, dosage form, strength, route of administration, quality and performance characteristics and intended use.”

At the same time, IGDRP participants confirmed that biosimilars – also known as subsequent entry biologics – would not be included within the scope of the pilot. They

acknowledged the need to make progress in the area of generic drugs before considering an expansion of activities.

Participants recognized the diversity of requirements and capacity of IGDRP regulators, as well as the importance of selecting activities that would complement and not duplicate work undertaken elsewhere. The diversity issue was addressed by acknowledging the right of participants to “opt-out” from work plan activities. “Opting-out” could occur due to constraints presented by existing regulatory systems, or decisions to delay involvement until the conclusion of the pilot.

Together with the participants’ commitment to promote regulatory convergence, these realistic key operating principles position the new consortium to make tangible short and medium term progress with a long term vision in mind: to facilitate the timely authorization and availability of safe, effective and quality generic drugs. Participants felt that IGDRP has the potential to achieve this goal by changing the international business and regulatory model for generic drugs.

Progress to date

To date, five meetings have taken place hosted respectively by the RAs of Canada (Ottawa, October 2011), United States (Washington, April 2012), China (Nanchang, December 2012), Australia (Canberra, May 2013) and Switzerland in conjunction with WHO (Geneva, October 2013). The next meeting is scheduled for May 2014 in Chinese Taipei.

Considerable progress has been made in identifying priorities and mechanisms for promoting convergence of regulatory approaches:

- Working groups and proposals have been established related to active substance master files (ASMF)/drug

Table 2. Interim IGDRP operating procedures

<p>Mission: To promote collaboration and convergence in the area of generic drug regulation in order to strengthen the ability of health authorities to meet their respective mandates</p> <p>Goal: To facilitate the timely authorization and availability of safe, effective and quality generic drugs</p> <p>Objectives:</p> <ul style="list-style-type: none"> • Faster review and greater availability of generics • More efficient use of resources through mutual reliance and work-sharing • Strengthen review process and international regulatory oversight while reducing regulatory burden • Promote adoption of modern, science and risk-based approaches • Rapid exchange of safety and quality information on marketed products • Enhance development of human resources <p>Scope: Activities that best meet needs of participants with a focus on the premarket review of generic drugs. Does not include biosimilars</p> <p>Key Operating Principles:</p> <ul style="list-style-type: none"> • Decision-making: by consensus on matters related to the operation of the pilot. Participating regulators may however “opt-out” from any work plan activities. • Activities will complement and not duplicate work undertaken elsewhere. <p>Governance, Structure and Meetings:</p> <ul style="list-style-type: none"> • IGDRP is composed of a Steering Committee (SC), Working Groups (WG) and Secretariat. • SC is composed of one representative from each participating RA and an Observer from WHO. • Observers from RAs or international organizations may be designated by SC on perceived value to IGDRP. • External experts may be consulted or invited to participate on WGs depending on perceived value and SC endorsement. • Chair and host rotate with each meeting, with two in-person meetings per year. • Chair becomes co-chair of the next meeting. • Location of meetings will rotate among RAs/regions and WHO (Geneva). <p>Transparency: Information on IGDRP will be provided using WHO information-sharing tools.</p>

- master files (DMF), biowaivers and work-sharing models (see Table 3).
- ANVISA (Brazil) has conducted a survey to identify similarities and differences in regulatory requirements and approaches. The results, together with findings from the preliminary 2011 comparative study and a comprehensive analysis of international BE guidelines authored by current and former scientists from the US FDA (2), should provide a solid baseline for regulatory convergence activities. It is anticipated that the most recent survey results will be published as one or more articles in WHO Drug Information.
 - Health Canada has launched an initial survey on laws, policies and procedures related to the management and sharing of non-public regulatory information,

Table 3. IGDRP working groups

Working Group	Objective	Scope
Active substance master files/ drug master files	Establish a framework for information-sharing and potential mutual reliance in the assessment of ASMFs/DMFs	APIs for human use that are the subject of Master File assessments
Biowaivers	Establish a common set of conditions for granting biowaivers as well as the possible expanded application of waivers	Biopharmaceutical Classification System (BCS)-based waivers Non-biostudy strengths of solid dosage form product line
Work-sharing model	Explore various work-sharing models with a view to piloting (an) appropriate model(s) for the premarket review of generic drugs	To include the model of the European Decentralised Procedure and possibly other models

including confidential business and trade secret information.

- Swissmedic has created an electronic platform for the sharing of non-confidential information and documents between IGDRP members.
- The IGDRP operating procedures have been refined to clarify interim governance and work arrangements, with measures to improve transparency and outreach (as an example, information on IGDRP will be provided using WHO information-sharing tools).
- Participants are committed to assist WHO in implementing proposed changes to the WHO Prequalification of Medicines Programme as it moves to a new operating model, and to encourage generic drug applicants in respective IGDRP jurisdictions to apply for prequalification of medicines of interest.
- WHO will serve as secretariat for the IGDRP for the remainder of the pilot (until end of 2014).
- IGDRP has been granted observer status to the ASMF Work-Sharing Working Group of the Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh), and conversely the latter's Chair will participate in the IGDRP ASMF/DMF working group, thereby

allowing for the sharing of best practices and possible opportunities to leverage ASMF/DMF reviews.

- New members from New Zealand, Russia and South Africa have joined the IGDRP, with the European Directorate for the Quality of Medicines and Healthcare (EDQM) joining as an observer organization. While the IGDRP steering committee recently agreed that membership should not be greatly expanded during the pilot in order to ensure efficiency of operations, members also agreed that increased communication and transparency of operations were important. Towards this goal, read-only access to the secure electronic platform could be granted on request to other RAs not actively participating in the IGDRP.

Decentralised Procedure as a model for cooperation

One of the most significant work-sharing developments relates to the possible use of the EU's Decentralised Procedure (DCP) as a policy model for information-sharing with third-party RAs external to the EU /European Economic Area (EEA) during the scientific assessment phases of the DCP (Figure 1).

The model would be operationalized based on the following conditions:

- The process is restricted to the DCP.
- Integrity of the DCP is respected (e.g. structure, technical standards, timelines, etc.), with minimal impact on resources.
- The process is initiated at request of the generic drug applicant.
- The applicant gives consent to share confidential business information.
- No legal impediments exist on the part of the respective third party RA to participate in such an arrangement.

At the 5th IGDRP meeting in Geneva, members agreed that a logical first step would be to test the model through a limited pilot involving one or two non-EU RAs. This requires the willingness of a few generic drug manufacturers to participate in the pilot.

Interested regulatory authorities are currently consulting with the generic industry to identify suitable candidates with a view to launching the pilot in 2014. Further discussions are planned to elucidate the details of how the pilot would operate.

IGDRP members agreed that other models should also be considered, taking into account the availability and use of existing review reports as well as WHO's experience with various regulatory work-sharing initiatives.

Some observations

As the IGDR initiative enters its third and final year as a pilot, some observations may be made regarding the necessary prerequisites to successful outcomes.

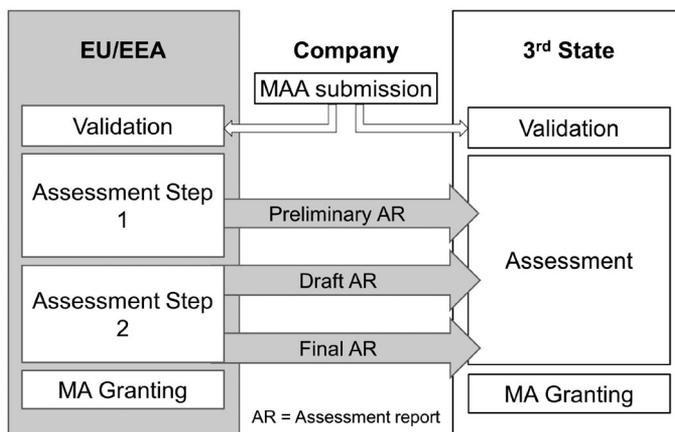
The first and foremost prerequisite is the strong and continued commitment of participants to IGDRP goals and objectives.

Secondly, regulatory authorities must get to know one another, for example through rotating meetings which expose staff from host agencies to different points of view, serving in turn to promote change and convergence.

Thirdly, key enablers such as secure IT platforms, mechanisms for the exchange of confidential information and common technical requirements play a crucial role.

Fourth, relationships should be established with other international

Figure 1. Decentralised Procedures as a model for regulatory cooperation



Source: (3)

initiatives to leverage resources and avoid duplication of work.

Finally, the critical need for industry support for regulatory work-sharing efforts must be emphasized. Success of the IGDRP will require productive engagement with generic drug applicants as well as other stakeholders interested in promoting timely access to affordable, quality generic drugs.

Conclusion

Considerable progress has been made since the start of the IGDRP in establishing the necessary conditions for enhanced regulatory cooperation. It is expected that work underway should lead to advancing regulatory convergence and the piloting of new models of cooperation prior to the end of 2014.

Results of the pilot phase will inform decisions on whether and how the initiative should transition to a more permanent information- and work-sharing arrangement as part of broader international efforts

aimed at the effective and timely regulation of medicines within an increasingly challenging global environment.

References

- 1 International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Quality Guidelines [website], at www.ich.org/products/guidelines/quality/article/quality-guidelines.html.
- 2 Davit B, Braddy A, Conner D, Yu L. International Guidelines for Bioequivalence of Systemically Available Orally Administered Generic Drug Products: A Survey of Similarities and Differences. *The AAPS Journal* 2013; 15(4): 974-90.
- 3 Bachmann P. Global Generic Dossier and Evaluation: an EU Regulators' Perspective. Presentation made to the 16th Annual International Generic Pharmaceutical Alliance (IGPA) Conference, Brussels, Belgium; 9-11 December 2013.