Regulatory collaboration

IGDRP generic drug product regulatory gap analysis

The International Generic Drug Regulators Pilot (IGDRP) was launched in 2012 as an international collaborative initiative for information- and work-sharing activities for the regulation and registration of generic drug products. Initially operating as a three-year pilot (2011–2014) the IGDRP was renamed a Programme in 2014, recognizing the progress achieved during the pilot phase, the strong commitment from regulators and their continued interest and need to cooperate to facilitate the timely authorization and availability of safe, effective and high quality generic drug products.

A regulatory gap analysis survey was conducted to identify regulatory similarities amongst the IGDRP members as well as gaps that might create challenges for work-sharing and collaboration. The WHO Prequalification Team, the European Union (EU) and eleven regulatory authorities participated in the survey. The main gaps observed were: the definition of a generic drug product and what is considered to be the same active (or drug) substance; whether and when international reference products can be used in bioequivalence studies; the criteria for granting biowaivers; requirements to use national or regional pharmacopoeias; and the minimum stability data to be included in a generic drug product application at the time of submission.

Introduction
The International Generic Drug Regulator Programme (IGDRP), portrayed in an earlier issue of this journal (1), has the mission to promote collaboration and regulatory convergence in the area of generic drug products in order to strengthen the ability of health authorities to meet their respective mandates. Its goal is to facilitate the timely authorization and availability of safe, efficacious and quality generic drug products.

One of the enablers agreed among IGDRP participants to facilitate work-sharing was the conduct of a regulatory gap analysis survey to identify the similarities and differences in regulatory requirements and practices of participating IGDRP members regarding generic applications.

The gap analysis survey
The survey was led by the Brazilian Health Regulatory Agency (ANVISA). It was divided into four parts:
1. General issues/reference products;
2. Bioequivalence/biowaivers;
3. Quality and good manufacturing practices (GMP); and
4. Other issues.

The gap analysis survey described in this article was led by the medicines regulatory authority of Brazil, ANVISA. We thank Ana Carolina Moreira Marino Araujo and her team at ANVISA for contributing this article on behalf of IGDRP.
Participating organizations
The survey was answered by representatives of the WHO Prequalification Team (WHO-PQT)¹, the European Union regulatory system (referred to as “EU” in this article) and 11 regulatory authorities including: Australia’s Therapeutic Goods Administration (TGA), the Brazilian Health Regulatory Agency (ANVISA), Health Canada (HC), Japan’s Pharmaceuticals and Medical Devices Agency (PMDA), South Korea’s Ministry of Food and Drug Safety (MFDS), Mexico’s Federal Commission for Protection against Sanitary Risks (COFEPRIS), Singapore’s Health Sciences Authority (HSA), South Africa’s Medicines Control Council (MCC), the Swiss Agency for Therapeutic Products (Swissmedic), the Taiwan Food and Drug Administration (TFDA) and the United States Food and Drug Administration (U.S. FDA).

Timelines
The initial gap analysis survey tool was presented during the first IGDRP meeting held in Washington, DC, USA in April 2012. It was agreed that participants should review the tool and provide additional comments.

All organizations had the opportunity to comment on the questions and to update their answers. The data were further evaluated and validated during subsequent meetings and interactions. The results presented in this article reflect updated responses as of April 2016.

Findings
1. General issues/reference products

- Definition of “generic drug product”
All organizations answered that a generic product must fulfil the following criteria: same quantitative and qualitative composition in terms of active (or drug) substance, same (or comparable) dosage form, same route of administration, and bioequivalence with the reference product. However, there were differences in defining what is considered the same active (or drug) substance: The TGA, HC, HSA, MCC, U.S. FDA, EU, Swissmedic and WHO-PQT accept different salts as the same active (or drug) substance as the reference product and there are no safety and efficacy issues with the different form of the active (or drug) substance. ANVISA, COFEPRIS, MFDS, PMDA and TFDA do not consider a different salt to be the same active (or drug) substance.

- Requirements for reference product
The definition of a “reference product” was similar for all organizations: it is the innovator product that has proved its safety, efficacy and quality. However, not all organizations require that the reference product be marketed or registered in their country or region; some permit the use of foreign-sourced reference products (Table 1).

When the reference product is required to be sourced locally but the original reference product – usually the innovator product – is not available on the market in a country or region, it is necessary to identify a new reference product. The various organizations have different approaches for doing so: TGA, ANVISA,

¹ WHO Prequalification Team - Medicines; http://apps.who.int/prequal
Regulatory collaboration


HC, PMDA, COFEPRIS, MCC and MFDS use another registered product that has been demonstrated to be equivalent to the original reference product, but the acceptability of this approach is determined on a case-by-case basis and should be carefully justified. Similarly, HSA accepts the use of another registered product based on HSA’s assessment of the product characteristics and the applicant’s justification. In the EU the applicant needs to identify a reference product which is or has been authorized in the EU in accordance with EU legislation (i.e. a marketing authorization must have been granted, but it may have ceased to exist). MCC recommends that the reference product should be purchased from a well regulated market with a stringent regulatory authority participating in the International Council on Harmonization (ICH)². WHO-PQT, which operates supra-nationally, necessarily does not use national reference products. Instead it lists acceptable reference products that may be used in bioequivalence studies and requires that these are purchased from a well regulated market with a stringent regulatory authority participating in ICH, except in those cases where the reference product is not marketed in any ICH member or associated country.

Table 1: Requirements for use of national and international reference products

<table>
<thead>
<tr>
<th>Organizations that require that the reference product be registered in the country or region:</th>
<th>Organizations that allow the use of foreign-sourced reference products in bioequivalence studies</th>
</tr>
</thead>
</table>

* The organizations marked with an asterisk follow a regulation or policy that outlines the criteria for the use of a foreign-sourced reference product, such as proving similarity between domestic and foreign-sourced reference products.

2. Bioequivalence/biowaivers

- **Bioequivalence study sites**
  All organizations except TGA and HC stated that they require the site(s) conducting bioequivalence studies to meet good clinical practice (GCP) standards. TGA and HC responded that, although there is no formal requirement, the site is expected to be in compliance with GCP. It is important to mention that ANVISA, MFDS, COFEPRIS and TFDA require not only that GCP standards should be met, but also that the bioequivalence study site must be certified by the national regulatory authority.

- **Country and population**
  For the PMDA, MFDS and COFEPRIS the bioequivalence studies must be conducted in their country and in their own population (PMDA allows bioequivalence studies to be conducted in Japanese living overseas). The remaining organizations do not have this requirement.

- **Biowaivers**
  All organizations accept biowaivers for generic drug products, but the drug products and drug substances that are eligible vary among the organizations. Biopharmaceutics Classification System (BCS)-based biowaivers are accepted by most of the organizations, with the exception of PMDA. The TGA, HC, EU, COFEPRIS, MCC, U.S. FDA, Swissmedic

² [www.ich.org](http://www.ich.org)
and WHO-PQT accept BCS-based biowaivers for Class I and Class III drugs, whereas the MFDS, HSA, ANVISA and TFDA accept BCS-based biowaivers Class I drugs only. ANVISA and TFDA have positive lists of the medicines that are eligible for biowaivers.

All organizations accept biowaivers for additional proportional strengths of immediate-release solid oral drug products that are not included in the in vivo bioequivalence studies, with the appropriate scientific justification.

The IGDRP’s Biowaivers Working Group has conducted a specific and more detailed gap analysis on this topic as a mechanism to establish a common set of conditions for granting biowaivers as well as expanding the application of BCS-based waivers, additional strength biowaivers and biowaivers for certain dosage forms (e.g. oral and injectable solutions).

3. Quality and GMP

- **Active pharmaceutical ingredients (API)**

For a generic drug product application there is no limit to the number of API manufacturers that can be included in a single generic drug product application, provided all necessary information is submitted.

Procedures for API evaluation and GMP inspection of API manufacturing sites are summarized in Table 2. Most organizations require confirmation of GMP

### Table 2: Procedures for API evaluation and GMP inspection of API manufacturing sites

<table>
<thead>
<tr>
<th>Organization</th>
<th>API evaluated (a) separately from the drug product</th>
<th>API evaluated (b) with the drug product</th>
<th>GMP inspection must be conducted by the organization itself</th>
<th>GMP certification by another regulatory authority is recognized</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ANVISA</td>
<td>Yes (b)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HC</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (f)</td>
</tr>
<tr>
<td>EU</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PMID</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No (f)</td>
</tr>
<tr>
<td>MFDS</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>COFEPRIS</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (f)</td>
</tr>
<tr>
<td>HSA</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MCC</td>
<td>No</td>
<td>Yes</td>
<td>No (d)</td>
<td>No</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>TFDA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>WHO-PQT</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>U.S. FDA</td>
<td>Yes (c)</td>
<td>No</td>
<td>Yes (e)</td>
<td>Yes (g)</td>
</tr>
</tbody>
</table>

(a) In this context the word “evaluated” is used in the same sense as the word “registered” or “authorized”.

(b) Applies only to the 30 APIs on the positive list, other APIs are evaluated with the drug product.

(c) When the sites are separated

(d) GMP inspection not mandatory

(e) Yes, for domestic sites. For foreign sites, U.S. FDA relies on partnership arrangements with other regulatory authorities in limited cases.

(f) HC, EU and COFEPRIS accept GMP certification from countries with which mutual recognition agreements have been signed.

(g) U.S. FDA considers a full inspection report rather than a GMP certificate.
compliance for API manufacturing sites, and many require that the inspection must be conducted by their own inspectorate. Some IGDRP members recognize GMP certification by other authorities, such as stringent regulatory authorities (SRA) or regulatory authorities of countries with which mutual recognition agreements have been signed.

The organizations use different procedures to evaluate the quality information related to the manufacture and control of APIs. Some authorize APIs separately from the drug product, others do so in connection with the marketing authorization application for the drug product, and in some cases both procedures are possible.

The TGA, HC, EU, HSA, MCC, Swissmedic, TFDA and WHO-PQT recognize the European Directorate for the Quality of Medicines – EDQM’s certificate of suitability (CEP) and do not duplicate the assessment of the API information covered by the CEP.

**Stability studies**

In general, stability studies are conducted as per the requirements for the specific climatic zones (Zones I, II, III, IVa and IVb) that reflect a country’s climate (2). Most IGDRP members follow the recommendations of the ICH Q1A guideline (3). Three exceptions are HSA, ANVISA and WHO-PQT. These organizations require finished product stability studies conducted in Zone IVb; HSA follows the ASEAN Guideline on Drug Product Stability Data (4). ANVISA follows its national guidelines for stability studies (5), and WHO-PQT follows WHO stability guidelines (6).

All organizations require the stability study to be conducted with the drug substance or the drug product in its primary package. If the secondary package has a protective or functional effect, the study may be conducted in this package.

ANVISA and TGA require additional stability studies for the API in their own climatic zone if it is imported from a country in a milder climatic zone. HSA evaluates the stability impact of the API in the drug product stability studies and does not require additional stability studies for the API.

If there are multiple API or finished pharmaceutical product (FPP) manufacturing sites proposed for registration, TGA, WHO-PQT, ANVISA, COFEPRIS, HSA, TFDA and MCC require stability data from all API–FPP site combinations but TGA, WHO-PQT, HSA, MCC and TFDA accept science-based justification for not requiring all combinations of stability data. HC, EU, PMDA, MFDS and Swissmedic do not require the stability studies to be conducted with all API–FPP site combinations. For PMDA, stability data for the API-FPP combination prepared using the main manufacturing route must be presented, and the stability data for other manufacturing routes must be confirmed at the applicant’s own responsibility.

Information on the number of batches and minimum number of months of stability data to be presented for a general case in a generic drug product application is summarized in Table 3.
Imported drugs
The organizations have different requirements for imported drugs regarding responsibility for batch release analysis and mandatory marketing authorization in the country of origin (Table 4).

Acceptable standards and pharmacopoeias
All participants have specific guidelines related to quality and validation, and they also adopt international guidelines, such as those of ICH, officially or in principle. ANVISA is the only agency that does not officially adopt ICH guidelines, whilst the MCC generally accepts reference to ICH guidelines. Besides ICH guidelines, HSA also officially adopts the ASEAN guideline. The adoption of regional or national pharmacopoeias is mandatory for PMDA and COFEPRIS. For the other organizations it is not mandatory to use the national pharmacopoeia; they recognize other pharmacopoeias besides their own, for example the United States Pharmacopeia (USP), the British Pharmacopoeia (BP) and/or the European Pharmacopoeia (Ph Eur).

### Table 3: Minimum stability data required at the time of filing a generic product application

<table>
<thead>
<tr>
<th>Organization</th>
<th>Number of batches: API</th>
<th>Number of batches: drug product</th>
<th>Accelerated stability data</th>
<th>Long term stability data</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA</td>
<td>2 pilot or commercial scale</td>
<td>2 pilot or commercial scale</td>
<td>6 months</td>
<td>6 or 12 months depending on dosage form</td>
</tr>
<tr>
<td>ANVISA</td>
<td>3</td>
<td>3 pilot or commercial scale</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>HC</td>
<td>2 (a)</td>
<td>2 (a)</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>EMA</td>
<td>3 pilot or commercial scale</td>
<td>3 pilot or commercial scale</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>PMDA</td>
<td>0</td>
<td>3</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>MFDS</td>
<td>3</td>
<td>3</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>COFEPRIS</td>
<td>3</td>
<td>3</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>HSA</td>
<td>3</td>
<td>2 or 3 (c)</td>
<td>6 months</td>
<td>6 or 12 months (c)</td>
</tr>
<tr>
<td>MCC</td>
<td>2</td>
<td>2</td>
<td>3 months</td>
<td>9 months</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>3 pilot or commercial scale</td>
<td>2 pilot or commercial scale</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>TFDA</td>
<td>3</td>
<td>3</td>
<td>6 months</td>
<td>6 months at application + 12 prior to authorization</td>
</tr>
<tr>
<td>WHO-PQT</td>
<td>3</td>
<td>2</td>
<td>6 months</td>
<td>6 months (d)</td>
</tr>
<tr>
<td>U.S. FDA</td>
<td>3 pilot or 2 pilot + 1 small scale (b)</td>
<td>3 pilot or 2 pilot + 1 small scale</td>
<td>6 months</td>
<td>6 months at the time of submission (e)</td>
</tr>
</tbody>
</table>

(a) Reflects requirement at the time of the survey; this requirement was subsequently changed to 3 batches in an updated quality guidance document.
(b) If the size of the pilot scale batch does not follow ICH recommendations, the applicant should provide a justification.
(c) 2 batches of 6 months for stable API and conventional dosage form; 3 batches of 12 months for unstable API or critical dosage form
(d) For reproductive health products and second-line tuberculosis products an exception can be made to require only 3 months accelerated and long-term data at the time of submission.
(e) The Abbreviated New Drug Application (ANDA) should be updated with 12 months of long-term data during the review cycle.
Table 4: Requirements for imported drugs

<table>
<thead>
<tr>
<th>Organization</th>
<th>Quality control must be performed by the manufacturer</th>
<th>Quality control must be performed by the importer</th>
<th>The product must have marketing authorization in the country of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ANVISA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HC</td>
<td>No (a)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>EMA</td>
<td>No</td>
<td>Yes (d)</td>
<td>No</td>
</tr>
<tr>
<td>PMDA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MFDS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>COFEPRIS</td>
<td>Yes (b)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HSA</td>
<td>Yes (c)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MCC</td>
<td>Yes (b)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>No (a)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TFDA</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>WHO-PQT</td>
<td>Yes</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>U.S. FDA</td>
<td>Yes</td>
<td>No (e)</td>
<td>No</td>
</tr>
</tbody>
</table>

(a) Testing for release purposes can be performed by an alternate testing facility provided it is GMP-compliant.
(b) COFEPRIS and MCC allow testing exemption for the importer if the transport temperature and humidity is monitored.
(c) For import of only the first batch after approval, applicant must provide quality control of that batch for review.
(d) Medicinal products coming from third countries must undergo a full analysis in an EU Member State. This requirement may be waived where arrangements between EU and exporting country exist ensuring GMP standards at least equivalent to those in the EU.
(e) Unless the importer is finishing the processing of the API or drug product (in which case the importer becomes a manufacturer).

When compendial analytical procedures exist, their adoption is mandatory for PMDA and COFEPRIS; it is not mandatory for TGA, ANVISA, HC, EU, HSA, MCC, MFDS, Swissmedic, TFDA and WHO-PQT. However, HC, EU, MCC, Swissmedic and WHO-PQT require that the results of a comparison/equivalency study between the compendial and in-house analytical procedures are provided if a compendial standard is claimed but an in-house analytical method is used.

Regarding the use of primary standards, PMDA recommends their use if they are listed in the Japanese Pharmacopoeia. ANVISA requires their use in the validation procedure. TGA, HC, EU, TFDA, MFDS, COFEPRIS, HSA, MCC, WHO-PQT and Swissmedic accept the use of secondary reference standards with appropriate justification (e.g., standardized against a primary standard).

4. Other issues

- Work-sharing and cooperation
A few organizations have systems for work-sharing and cooperation in place. The EU has two procedures where authorizations are agreed by Member States: the decentralized procedure (simultaneously) and the mutual recognition procedure (sequentially). In addition, some generic drug products are authorized through the centralized procedure by the European Commission. Swissmedic, HC, TGA and HSA have
a cooperation procedure under the Australia-Canada-Singapore-Switzerland Consortium Generics Initiative (the ACSS Consortium), and HSA also has bilateral agreements for work-sharing on generic drug products with Malaysia. HC is engaged in a number of multi-lateral and bilateral international cooperation activities regarding generic products but does not have any mutual recognition agreements with any other regulatory authority for the assessment of generics.

- **Performance targets**
  All organizations have set performance targets or time limits for the assessment of generic drug product applications. It is important to identify these performance targets for the work-sharing process. One of the enablers of the IGDRP is the construction of a timeline with time limits and detailed milestones.

- **Common Technical Document (CTD)**
  The TGA, HC, EU, HSA, MCC, MFDS, Swissmedic, U.S. FDA, TFDA and WHO-PQT have officially adopted ICH’s Common Technical Document (CTD) format for generic drug product applications (7). PMDA, COFEPRIS and ANVISA have specific formats that are similar to the CTD.

- **Prioritization mechanisms**
  ANVISA, HC, PMDA, MFDS, COFEPRIS, HSA, MCC, U.S. FDA and WHO-PQT have mechanisms to prioritize generic drug product applications based on public health interests, considering factors such as drug shortages and governmental policies.

- **Intellectual property provisions**
  All IGDRP members have data protection and/or exclusivity periods before a generic drug product can be marketed. These periods vary from 5–20 years.

**Discussion**
While the participating organizations’ definitions of a “generic drug product” all appear similar, their definitions of “the same active (or drug) substance” differ. Some organizations accept different salts, esters and ethers as the same API as long as they have the same active moiety, while others do not. A product could therefore be considered a generic drug product in one country or region but not in another. This issue was identified as a gap. Solving it would enable greater information-sharing in the assessment of generic drug product applications.

The use of a foreign-sourced reference product is allowed by some organizations but not by others. Differences among IGDRP members in requirements for the reference product and documentation supporting the bioequivalence of a generic drug product were also identified as a gap. In this regard, the IGDRP concluded that it would be easier to start work-sharing activities with drug products that are eligible for a biowaiver, e.g., oral and injectable solutions.

All organizations accept biowaivers for generics, but the criteria for a drug product to be eligible for a biowaiver vary among them. This gap is being discussed in more detail in the IGDRP Biowaivers Working Group. A scientifically based discussion to work towards convergence and harmonization is in progress.

A further gap was identified regarding the minimum stability data – i.e., numbers of API and drug product batches to be tested, and the minimum number of months of accelerated and long-term stability data – that are required at the time of submitting the application. These
Regulatory collaboration

differences may delay the filing in certain countries, thus complicating the work-sharing among organizations.

The IGDRP members that participated in the survey are representative of the world’s regions and their different climatic zones. The conduct of stability testing according to the relevant climatic zone is indispensable, and the different requirements are scientifically based and justified. For applications filed globally, additional or complementary data must be provided by the applicant as appropriate.

Different procedures are used by the IGDRP members for the assessment of APIs. Some organizations authorize APIs separately from the drug product, others authorize them in conjunction with the drug product, and in some cases both pathways are possible. However, the differences observed in the survey were mostly related to organizational working procedures and do not hamper the work-sharing activities.

The requirement to use the national or regional pharmacopoeia of the country of application is a challenge for a globalized industry, since the use of different analytical procedures and acceptance criteria in different countries or regions will cause duplication of efforts. Differences in pharmacopoeial requirements complicate cooperation and collaboration.

Conclusion
The gaps observed in the survey warrant reflection on the reasons for the different requirements. If they are not scientifically justified, discussions on common practices should be stimulated within and among organizations.

References
5 ANVISA. Resolução - RE nº 1 de 29/07/2005.