Rethinking emerging markets for regulatory affairs with the creation of a Regulatory Authority Development Index

Abstract
This article discusses the concept of the "emerging market" and the associated terminology that has evolved historically to what is being currently used. Countries or regions can be classified as "emerging" or "developing" according to a raft of different criteria such as economic status, industrial development, relative level of per capita income, human development index, etc. From the perspective of the biopharmaceutical industry, most of the major companies have either created or reorganised their groups to focus on emerging markets based on the market size or commercial potential of a region rather than by its regulatory systems. From a regulatory science perspective, historically, market sizes are classified as "primary" or "secondary" depending on the level of data submitted in the registration dossier. The "emerging markets" label may not be applicable for regulatory sciences. Thus, an initiative has begun to create a Regulatory Authority Development Index (RADI) as a measure of the "regulatory sophistication" of a regulatory authority. This index will be generated through the measurement of various factors such as transparency, review/approval efficiency, consistency, clarity, effectiveness, lack of barriers, etc. It is intended that the RADI will initially be compiled following responses from TOPRA members to a questionnaire which will be made available in the near future on the TOPRA website (www.topra.org).

The terms "emerging markets", "emerging economies" and "developing countries" are common in today's vocabulary. The term "emerging market economy" coined in the early 1980s, representing approximately 80% of the global population in reaction to the Group of Six (G6) created by France in 1975, for the governments of six major economies: France, Germany, Italy, Japan, the UK and the US. Subsequently, Canada and then Russia were added to the group to become what is known as the G8.3 Over the past three decades, terms such as emerging countries, emerging economies, developing countries, BRICs, G8+5, G-20, least developed countries (LDC), more economically developed countries (MEDC), newly industrialised countries (NIC), advanced emerging markets and even terms such as pre-emerging markets and failed states have all been used to describe the "status" of a country. These terms have been crafted by various global agencies, including the United Nations (UN), World Bank, International Monetary Fund (IMF), investment banks (Goldman Sachs, Morgan Stanley) and academics. It is clear there is no single definition that describes emerging markets, and statistics on emerging market countries contradict each other from report to report, sometimes within the same organisation.16

The terms emerging market, developing market and developed country introduce a quite bit of confusion. Does a country's classification as emerging, developed or developing refer to its actual economy or to the extent to which it has financial liquidity; a modern, developed securities market or industrial infrastructure; or the human development index? For example, while Russia is part of the advanced economies of G8, it is part of the BRIC group of emerging countries. Nevertheless, a few general definitions are appearing. For example, based on a report by Forbes,17 an emerging market country can be defined as a society transitioning from a dictatorship to a free market-oriented economy, with increasing economic freedom, gradual integration within the global marketplace, an expanding middle class, improving standards of living and social stability and tolerance, as well as an increase in cooperation with multilateral institutions. By this definition, an analysis of all 192 country-members of the UN leads to the selection of 81 countries that can be categorised as emerging markets. The role of emerging market countries in the world is now difficult to overestimate.

Similarly, World Bank19 has a methodology for classifying markets as developed or developing. To arrive at a country's classification, World Bank focuses on a country's economy and, in particular, its relative level of wealth per capita. Countries with high levels of per capita income are classified as developed. Meanwhile, those countries with low, middle, and upper-middle incomes per capita, relative to incomes in other countries around the globe, are classed as developing, or emerging. For the most part, the output of this classification system synchronises with what is expected. The UK, the US, Canada, Western Europe, Australia, New Zealand and Japan all count as developed markets, as do rapidly growing and relatively wealthy countries such as Singapore, Saudi Arabia and South Korea. (Singapore and Saudi Arabia are still classified as emerging markets under some frameworks, while measures such as the Morgan Stanley Capital International (MSCI) Emerging Market Index classify these as developed countries.)19

"Pharmaemerging" countries
New definitions continue to arise such as, emerging, newly emerged, graduated developing countries, to-be emerged, and the list goes on. Despite the criticism and confusion of placing countries in any of these categories, our industry seems to have created a category based on its own criteria. The most common category for the biopharmaceutical industry is based on the market share and what is generally referred to as a "pharmaemerging" market is based on its sales and growth potential.20 There are 17 countries in this category ranked in three tiers – China in the first, the other three BRIC countries in the second and about a dozen in the third category from five continents. The list of "pharmaemerging" countries has grown from eight to 17 in past few years and the list continues to be dynamic, with more and more countries being added.

From the perspective of the biopharmaceutical industry, the definition of emerging markets also continues to evolve. Most major companies have either created or reorganised their groups to focus on emerging markets based on the market size or market potential rather than by regulatory systems. However, from a regulatory perspective, the definition and demarcation of "emerging markets" is rather straightforward. Generally, from the regulatory affairs perspective, the
The world is broken down into “primary markets” and “secondary markets”. The primary markets are those where the regulatory agencies conduct complete evaluation of safety, efficacy and quality of the product (usually the original ICH countries/regions). The secondary markets are the countries which depend on the approval of the “primary countries” and generally require a Certificate of Pharmaceutical Product (CPP).

From the content perspective, the primary countries would get the full content as per the ICH guidelines. For the “secondary countries”, which are also referred to as the “emerging countries” or “Rest of the World”, the dossier would be a stripped-down version of the full Common Technical Document (CTD). The rationale of stripping down the emerging markets dossier ranges from intellectual property (IP) concerns to the Drug Regulatory Authorities (DRAs) not requiring the expansive level of detail. Some DRAs focus their review on the some components of the marketing authorisation application (MAA) – safety, efficacy and quality – while some focus just on the quality section while referring to review/approval in a major ICH country as a basis for their approval. The past few years have seen an increasing trend towards a third or hybrid model where some countries have started requiring local clinical trials and the local clinical data become part of the MAA package. Historically, the countries that required local clinical trials were from Asia, but recently countries such as Russia have also started requiring data from Russian patients to be included in the registration dossier. With a focus on growth in emerging markets, this has meant requiring data from Russian patients to be included in the registration studies.*

The definition of emerging markets from a regulatory perspective continues to be muddled with various “regulatory harmonisation” activities. The first successful harmonisation effort was the setting up in 1995 of the European Medicines Agency (EMA), which was mainly

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Table 1: Comparison of clinical trial authorisation (CTA) requirements in selected emerging markets

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated number of patients for stand-alone registration studies*</th>
<th>Estimated number of patients if participated in Phase II to Phase III</th>
<th>CTA approval time (months)</th>
<th>Comments, special requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>300</td>
<td>Variable depending on number of Chinese in global studies</td>
<td>16–22</td>
<td>Extensive CMC section; CTA similar to full MAA; extensive quality testing upfront as part of CTA approval process (see Notes a–c, e, f)</td>
</tr>
<tr>
<td>India</td>
<td>200</td>
<td>0–100</td>
<td>6–9</td>
<td>New CMC regulations require more information than before (see Notes d–f)</td>
</tr>
<tr>
<td>S Korea</td>
<td>100</td>
<td>0–50</td>
<td>4–6</td>
<td>Straightforward CTA approval process</td>
</tr>
<tr>
<td>Taiwan</td>
<td>0–50</td>
<td>0–20</td>
<td>4–6</td>
<td>Straightforward CTA approval process</td>
</tr>
<tr>
<td>Russia</td>
<td>No guidance</td>
<td>No guidance</td>
<td>3–6</td>
<td>Inclusion Russian sites in global development programme exempt from mandatory local pre-registration inspection</td>
</tr>
</tbody>
</table>

*Patients on study drug
a. Number of patients can be negotiated depending on therapeutic area, medical need, etc.
b. Approval times can be reduced through special review mechanisms (eg, orphan drugs)
c. East-Asian countries may use data from other Asian countries (eg, Taiwan could use Japanese data)
d. Biologics approval may take a few months longer

e. Biological samples (eg, full blood, tissues) need special permission

f. First-in-human (FIH) studies not permitted unless molecule “discovered” in country.
made up of what we would today consider primary countries. However, in the past few years countries from “Emerging Europe” (eg, Romania, Bulgaria) have recently joined the EU and, while they come under the auspices of the EMA, as per the IMF definition, they are still considered to be “emerging countries” by biopharmaceutical companies from an economic and sales perspective, if not from a regulatory one.

Another recently observed trend is whether the countries have one-size-fit-all regulations for the development of biologics therapeutics. Historically, the regulatory framework for approval of safety, efficacy and quality of drugs has its roots in small molecules, or chemical entities. While only 20% of the drugs on the market today are biologics, it is expected that with 650 biotechnology medicines in development in 2010 for more than 100 diseases, one third to a half of the new drugs approved in 2015 will be biologics.21 Unlike the small-molecule drugs, biologics generally exhibit high molecular complexity, and may be quite sensitive to manufacturing process changes. To address these differences, over the past few years various new ICH guidelines have been developed specifically for biologics, and major regulatory bodies such as the US FDA and the EMA have developed separate regulations for these products. However, changes to the biologics regulations in key emerging markets are occurring at a varied pace. Some countries have taken a holistic approach to develop regulations for all biologics, while other countries have preferred to first develop the biosimilars regulatory system. For example, Mexico first generated a comprehensive biologics regulatory framework (which included the removal of local manufacturing requirements) and then followed up recently with biosimilars guidelines. Thus, there appear to be differences in how various health authorities in emerging markets approach biologic/biosimilars guidelines.

Tremendous efforts are being made by DRAs as gatekeepers to ensure availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. All DRAs strive to be viewed as science- and fact-based reviewers. Thus the “emerging market” label in regulatory sciences could be viewed as somewhat derogatory. Clearly, from a regulatory perspective, emerging countries cannot be force-fitted with the existing definitions. Instead of bundling countries into “primary”, “secondary”, “Rest of the World” or “emerging countries”, we believe there is a need to create a new definition for the biopharmaceutical industry. This is the thinking behind the initiative to establish a Regulatory Authority Development Index (RADI), which aims to measure the “sophistication” of a region’s regulatory system on a need-to-know basis for regulatory professionals. “Sophistication”, however, should not be confused with “complexity”. This would also apply to regulatory agencies that approve innovative medicines. The factors defining this index and the information sought will be as follows:

DRA transparency:
- Timely communication with sponsors
- Clear identification of the objective of regulation
- Defined avenues for consultation
- Sharing of assessment reports

Review/approval efficiency:
- Predictability based on guidelines/regulations
- Defined timelines
- Harmonisation with regional/ICH guidelines
- Referencing another agency’s review (eg, use of CPP)

Consistency:
- Minimisation or elimination of bureaucratic discretion
- Reliance on established processes and procedures of the regulatory system

Clarity:
- Objective regulatory decision making
- Clarity of questions

Effectiveness:
- Periodic review and update of regulations/guidelines

- Distinguish between regulations, standards and guidelines

Support of simultaneous global development:
- Acceptance of ICHES guidelines in lieu of local registration studies
- Acceptance of batch release data from the source country
- GMP inspections and mutual recognition of inspections based on PIC/S

Barriers:
- Lack of intellectual property protection
- Poor data protection and exclusivity
- Import/export of test drugs and biological samples
- Language barriers – translation, interpretation.

A step forward
There are close to 250 countries/autonomous regions in the world, and not all have regulatory agencies. Some of the countries can be combined under the ICH Regional Harmonisation Initiative (eg, Gulf Cooperation Council)22 or the evolving East Asia Harmonization initiative. The RADI will provide relative listings of the DRAs based on key measures. This table aims to be a “living document” which can be added to by regulatory professionals as and when new information becomes available. It is intended that the RADI will be updated annually. This measure will hopefully add clarity to the definition of “emerging markets” for regulatory affairs. Additional details will be made available in the near future on the TOPRA website.

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