Regulatory Strategy for the Emerging Markets – Far East, Africa, Middle East, Latin America

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Learning Outcomes

- Appreciation of growing commercial importance of Emerging Markets
- Broad understanding of the evolution of the regulatory model in these countries
- Contrast regulatory challenges and strategies with ICH/ICH-like countries
- Practical points of consideration when building and executing regulatory strategies for Emerging Markets
In this presentation we will cover

- Context and importance of Emerging Markets.
- Compare and contrast with ICH environment - outline of major regulatory procedures timelines and challenges
- How to build and execute successful strategies;
Emerging Markets

World population:
- 4.5% - USA
- 6.8% - EU
- 60% - Asia

In the next 10 minutes:
- 77 children will be born in the US
- 100 children will be born in EU
- 1000 children will be born in India + China.
Diverse.......and challenging
...with common features

LARGE POPULATIONS

FAST GROWING

PAY OUT OF POCKET

VOLATILE

BRAND DRIVEN

DYNAMIC
Global Pharma Industry Volume and Growth

North America
Size: $352-383 bn
Growth: 1-4%

Western Europe
Size: $ 148-161 bn
Growth: 0-3%

Central & East Europe
Size: $ 58-62 bn
Growth: -1-2%

China
Size: $ 170-185 bn
15% of global market

Japan
Size: US$ 102-111bn
9% of global market

Brazil, Russia, India
Size: US$91-99 bn
8% of global market

Pharmerging Markets
Size: US$113-123 bn
10% of global market

Other Markets
Size: US$91-99 bn
8% of global market

IMS Regional Pharmaceutical Outlook for 2017
(Global Market US$ 1135-1235 Billion/3-6% growth in period 2013-17)
## Emerging markets – IMS definitions

<table>
<thead>
<tr>
<th>Tier</th>
<th>Markets</th>
<th>Global share % (2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>China, Japan</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>Brazil, Russia, India</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Algeria, Egypt, Nigeria, Saudi Arabia, South Africa</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Indonesia, Pakistan, Thailand, Vietnam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poland, Romania, Turkey, Ukraine</td>
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<tr>
<td></td>
<td>Argentina, Colombia, Mexico, Venezuela</td>
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Compare and contrast with ICH environment - outline of major regulatory procedures timelines and challenges
ICH/ICH-aligned countries: common characteristics

- Adoption of ICH guidelines
- Independent review
- Information sharing
- Harmonisation
- Strong IPR and regulatory framework
- Transparent and accountable authorities
- Priority review
- Rx-OTC separation
- R&D facilitated
## Considerations for Regulatory Strategic Development in Emerging Markets

### Regulatory requirements
- Clinical Development
- File format and content
- Label
- Source
- CPP
- Samples
- Clinical trials
- Life cycle
- TIMINGS

### Other considerations
- Medical practice/epidemiology
- Medical/commercial need
- Cost/logistics
- Intellectual Property Protection
- Capacity and capability
- Local/generic vs R&D/MNC
- Language and culture
- Caution/suspicion
- TIMINGS
The Emerging Markets Regulatory Challenge

Across a wide number of countries and internal/external systems:

- Drive consistency of approach (efficiency/compliance)

While

- Giving top quality support to key business drivers

Very BROAD range of reqts/systems across many 50-100 countries

DEEPENING technical, clinical, regulatory expertise in key countries
Challenges at Agency Level

- Getting smarter
- Access to more info than ever before
- Resources generally not keeping up
- Under HIGH pressure
- Flexible: good & bad
- Reliance on others
- Focus on initial approval – life cycle capabilities generally not well-developed
USA FDA cf China SFDA

USA - FDA
- Around 12000 total employees
- 400 pharma companies, 300 biotech companies
- Excellent infrastructure,
- Progressive, innovative,
- PDUFA - set standards for review timelines
- IND review fast

China - CFDA
- Staff strength: 180 at SFDA (19 for registration and administration); 120 in CDE for drug review), 400 at the different centres working for SFDA and 1500 in 30 provinces
- Approx. 5000 pharma manufacturers, including biotech companies
- 6409 applications received in 2013; 37.8% are generics
- Need to improve technical knowledge and better understand international review practices (FDA/EMA)
### Local Clinical Data Requirements

<table>
<thead>
<tr>
<th>Country</th>
<th>Local Clinical data requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>Phase I and Phase III (at least 100 patients each arm is part of global trial). Major impact on dev/reg time.</td>
</tr>
<tr>
<td>S. Korea</td>
<td>Phase III in Korean patients if not qualified for bridging waiver.</td>
</tr>
<tr>
<td>Taiwan</td>
<td>Could accept other Asian data. Local study is bridging study evaluation failed.</td>
</tr>
<tr>
<td>Vietnam</td>
<td>Data in local patients required. Lifted 5 years after approval in reference country.</td>
</tr>
<tr>
<td>India</td>
<td>Local study with pivotal design. Could be qualified for waiver in case of unmet medical need.</td>
</tr>
<tr>
<td>Mexico</td>
<td>Local studies are not mandatory for MAA purposes. It’s highly recommended, though, especially if Mexico is the first place to have it registered (i.e. New Molecule Committee may request local clinical data).</td>
</tr>
<tr>
<td>Russia</td>
<td>Russian patients in phase III or local trial. Local BE study for generics is required.</td>
</tr>
</tbody>
</table>
China/Japan/Korea/Taiwan: require a level of local (or Asian) supporting data

**CHINA**: Most common registration route is Class III registration – chemical drugs
- Phase I PK data in Chinese patients
- Phase III data in at least 100 Chinese patients per arm for global clinical trials

**JAPAN**: Full Japanese ‘bridging’ clinical development (Phase I-III) required, per ICH E5
- PMDA will accept Asian data provided “significant number” of Japanese patients

**KOREA**: Require local bridging data to global clinical data package, per ICH E5
- Phase III Safety/efficacy data in Korean patients and no official patient numbers stated

**TAIWAN**: Require ‘bridging data’ to global clinical data package, per ICH E5
- No minimum patient numbers stated, but flexible in accepting Asian, non-local Phase III data
- Incentives in terms of speed, help with study and reimbursement outcome
ASEAN Harmonization

Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam

- ASEAN Economic Integration by Dec 2015
- ASEAN Common Technical Document Implementation by January 2015. All pharmaceutical submissions should be in ACTD format.
- ASEAN Adoption of ICH guidelines on Safety & Efficacy in 2014.
- Discussions ongoing – RA Capacity Building, Biological guideline, MRA on Bioequivalence, GMP inspections, Stability and ASEAN Variation Guidelines
LA Market Overview

LA market historically constituted 5-7% of the global market share ($62.9 billion in sales in 2011) and registered a growth of 8.9% in 2012.

Clinical research mostly established and centered in Mexico, Argentina and Brazil, with Chile, Colombia and Peru rapidly evolving.

Market expected to grow at 10-13% by 2016 in Brazil, Argentina, Colombia, Chile, Peru and Venezuela.
LA Regulatory Overview

- No regional guidelines or regulations...
  
  - No regional “CTD-like” type application.
  
  - Substantial efforts towards harmonization (past 15 years): Pan American Health Organization (PAHO) via Pan American Network for Drug Regulatory Harmonization (PANDRH).
  
  - PANDRH releases recommendation – including PVG and pharmacopoeias.
  
  - 5 national reference authorities in the region recognized by PAHO: Argentina, Brazil, Colombia, Cuba and Mexico.

- MAA needs to be planned per country requirements

  - Demanding challenges to pharmas seeking marketing penetration.
  
  - Same set of regulations: regulated all types of pharma products (for most LA countries). Exceptions are:
    
    - Brazil: that has a different set of regulations per type of drug (i.e. biologics, synthetics, devices)
    
    - Colombia: even if standard framework, there are specific regulations for each product (including a recent one for biologics)
  
  - Recent attempt of homologation: El Salvador and Ecuador if Mexico approval is granted. Under implementation process.
  
  - Biologic/Biotech and Orphan drugs: recent wave of regulations
Dossier: most can be obtained from ICH-CTD, but most countries require additional and substantial information.

Local infrastructure for filing
- Entity legally allowed to file a MAA (such as authorization or certification to become a MA holder). For instance:
  - Argentina: only a locally authorized lab with licensed pharmacist
  - Brazil: only a locally authorized commercial importer, distributor or manufacturer (local QC facility)
  - Some Central America countries: country native expert with valid Power of attorney is enough
  - Partner with local distributor, labs, etc.: an option, but to be noted activities prior to MAA (i.e. due diligence and agreements) and potential issues if as per local requirements the partner becomes the drug MAA owner & may be resistant later to transfer the MAA (therefore, contractual details are important)
LA: Overall Drug Registration Requirements

Reference Agency Approvals (FDA/EMA)
Quality Review
Local Labelling
Samples
**LA: Overall Drug Registration Requirements**

**Compilation, Translation, Submission**
- **E-submission:**
  - Chile mandates.
  - Argentina starting.
  - Brazil and Colombia – but not mandatory

- **Mandatory RA meeting for MAA: Venezuela, Costa Rica**

- **Pre-submission meeting in Mexico: for new molecules, applicant to present the product to “New Molecules Committee” – RA agreement on strategy, including PVG plan**

**Review Process**
- **Timelines:** vary a lot between countries and type of product (more details next section)
  - 3 months (Paraguay, Ecuador) to 2-3 years (Venezuela, Brazil)
  - Predictability is challenging
  - Brazil has announced measures, such as e-submissions, to expedite
MEA Market Overview

- > 1 billion inhabitants
- > 15% of world’s population
- Pharmaceutical market ~ US$ 40 Billions
- ~ 4% of the world’s market
- < 1% of worldwide clinical trials (excluding Israel which is a developed CT market)
- Predicted to increase exponentially in next decade.
MEA Regulatory Overview

Regulatory Characteristics

- Guidelines and procedures are not up to international standards and rather administrative
- Many sectors are still not sufficiently regulated i.e. variations, Biologicals, Biosimilars, Pharmacovigilance, Orphan drugs ... where requirements mainly depend on experience and direct approach to Health Authorities
- Inadequate resources. However, no full reliance on decisions made by other recognized authorities
- Trend to shift regulatory responsibilities from MoHs to independent authorities e.g. SFDA (Saudi), FDO (Iran), MCC (South Africa),
- Company/Site registration is a separate process in many countries (Saudi) and should sometimes precede product registration
- Inspection required by many authorities. PICs recognized by few ones (Iran)
- Pricing is part of the registration procedure
- Francophone countries are very much connected to France regulation and approvals
- Turkey taken major steps towards harmonizing its legislation with EU
MEA Regulatory Overview
Harmonization

• Independent regulations per country
  • ~ 60 different national regulatory authorities working independently to register medicines across Middle East and Africa
  • MAA and license maintenance should be handled country by country
  • Different administrative and technical requirements, process and procedures for medicines registration

• Harmonization and co-operation initiatives in Africa
  • Several attempts in Africa
  • AMRH Africa Medicine Regulatory Harmonization
  • Objective: to achieve a harmonized medicines registration process in RECs (countries belonging to the Regional Economic Communities) based on common documents, processes and shared information systems
  • East African Community progressing in the implementation of EAC MRH
MEA Regulatory Overview
Harmonization

- Harmonization and co-operation initiatives - GCC-DR
  - Gulf Central Committee for Drug Registration
  - Approved in May 1999.
  - Seven Member countries: KSA, UAE, Kuwait, Qatar, Bahrain, Oman and Yemen
  - Population ~ 70 million
  - Total pharmaceutical market size: US$ 8.5 Billion (2012 estimate) ≈ 1% of global world
  - Grant company and product approvals that cover the seven member states
  - A national procedure in each country should follow - which is not well defined – in order to obtain a final approval per country
  - Recommended for Generics and Biosimilars
  - Clinical trials not yet centrally regulated
MEA: Overall Drug Registration Requirements

- CTD format mandatory – with few exceptions
- Local entity legally allowed to apply for a MAA:
  - Most countries require CPP by Reference Agency - however, Reference Country is defined differently (MAH, bulk manufacturer, batch releasing country)
- Stability studies (CZ IV in many countries
- Samples
- Labelling
MEA: Overall Drug Registration Requirements

Compilation, Translation, Submission

- Country-specific local forms
- Technical documents accepted in English or French
- Insert leaflet in English/Arabic + local language
- Declaration & certificates (CMP/CPP, GMP, contracts): must be legalized notarized or apostilled
- E-submission/eCTD is emerging:
  - South Africa mandates.
  - Saudi and other GCC countries starting (Jan. 2015)
- Pre-submission meeting not required

Review Process

- No clear indication of/abidance by time for review
- Timelines: vary a lot between countries
  - 6 months in Bahrain
  - 3-4 years in South Africa
At the Starting Line

- USA and EU regulatory strategies
- Commercial priority globally and regionally
- Global development plan and timelines
- Key emerging countries
- Competition
- Manufacturing strategy
- Any 3rd party commitments
- Resources to deliver
- Plan B, C…..
Four Pillars for Operational Success

ALIGNMENT
- Mutual understanding HQ↔Region↔Country↔[agency]
- Clarity on roles and responsibilities
- Senior management awareness, planning and reporting
- Key stakeholders internally in manufacturing, labelling etc.
- If using a 3rd party – ensure no less clarity there

PEOPLE
- Hiring, training, coaching, retention. Differentiating roles: leader, strategist, writer, compiler, publisher, expert

INTELLIGENCE
- Capture, harness, interpret and exploit. Map the future and use that intelligence as influencing lever.

PROCESSES
- Routine where at all possible. Appropriate standard while achieving compliance. Simple limited KPIs/measures.
Present/Future: Global Development Regulatory Programme

Pre-submission, submission and Q&A activities in narrower time-windows: concentrated global effort required.
People

• Profile
  – Committed to Quality
  – Business oriented
  – Process-minded

• Need re-fillable pool
• Central/virtual location for global support: off-shore/outsource?
• Cost-effective
• Effective and fast on-boarding/training
• Opportunities for growth and development
People

• PLANNING
  – Build and manage work plans – master and detail
  – Able to tailor plan to match internal resources and stakeholder expectations
  – Need to proactively manage peaks and troughs
  – Ensure easy access to plans by all concerned in multiple formats (by project, by country, by reg exec etc)

• QUALITY
  – Overall drive for the Quality value throughout function
  – Co-ordination of efforts on optimising Quality
  – Involvement in relevant audits/inspections
  – Ensure implementation and sharing of lessons learned
  – Oversees any 3rd party outsourcings to ensure seamlessness and consistency in QUALITY value
  – Ability to work inside a bigger group; capable of
Intelligence

• PEOPLE
  – Local experts globally
    – Understanding and application of official requirements
    – “How it really works....”
  – Central strategic expertise
    – Building strategies and plans across territories and programs
    – Exploiting synergies/links/bundling opportunities
    – Adjusting from experience
    – Planning for “What if....”

• SYSTEMS
  – Dedicated capture of requirements, processes, timelines
  – Ensure accurate, up-to-date Regulatory information
  – Diligent monitoring, gathering, interpreting and communicating
  – Single source knowledge base for all regulatory information
Processes

- Robust IT tracking/reporting system, able to meet all clients needs
- SOPs/WIs etc: simple, intuitive, appropriate to output, defensible
- Over time, build on intelligence/experience to offer better results in respect of time, quality, efficiencies
- Strong governance and self-auditing function
- Processes work for the function and the output, not vice-versa
Concluding Key Regulatory Success Factors

Local RA team/manager owns authority relationship and requirements

Good relationships critical
- Internal RA: central ⇔ local ⇔ external
  Supplier ⇔ Regulatory Authority
- Key functional partners: commercial, clinical, legal, BD

Regular communication
Build and store goodwill, someday you will need it (internal and external)
Business plans WILL change at short notice

Proactively add value to business
- Not “you can’t”
- “You can”

Own and solve regulatory resource issues
- Internal re-allocations
- Outsourcing/off shoring

Integrity, openness, transparency
In This presentation we covered

- Context of importance of Emerging Markets.
- Compare and contrast with ICH environment.
- Outline of major regulatory procedures, timelines and challenges; how to build and execute successful strategies.
QUESTIONS?
Acknowledgements
here if required (16pt)

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sequam es as estorum quodis con cuptate niendae.
Nam, consequid expeliciae. (14pt)

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