Drug Registration in BRICS countries: Opportunities and Challenges

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“Once a drug reaches Phase I, it’s a good idea to start discussions with global regulatory authorities so that you can begin to create the worldwide development program.

The aim is to achieve a single global clinical plan that includes the major markets - the United States, Europe, Japan, and China.

This global plan will face challenges from individual market environments and regulatory requirements that can lead to having a separate development for some countries.

Once all data is available, and the regulatory dossier has been finalized, we try to submit it simultaneously globally.”

Joseph Scheeren,
PharmD
Head of Global Regulatory Affairs Pharmaceuticals and Consumer Health
Bayer

This presentation will cover the following questions

- What are emerging markets and the BRICS countries?
- Why are emerging markets of interest to pharmaceutical industry?
- How to launch a new pharmaceutical product globally?
- How to launch a new pharmaceutical product in the BRICS countries?
- What are the approval timelines in BRICS countries?
- Key RA requirements
BRICS: Brazil, Russia, India, China, South Africa

2001 - BRIC (Goldman Sachs); promising emerging markets (demographics, level of economic growth and development, influence on regional and global affairs)

2010 - BRICS, invitation of South Africa by China
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BRICS in 2015:

- ± 3.6 billion people (41% of global population)
- 26% of world’s land territory
- 22% of GDP (gross world’s product)

Brazil:
- Most regulated country in Latin America.
- 6th largest globally in terms of sales revenue

Russia:
- Ranks among top ten in the world

India:
- World’s leading IT service exporters

China:
- Second largest pharmaceutical market in the world

South Africa:
- One of the most attractive markets in Africa
Why are emerging markets of interest to the pharmaceutical industry?

Flattened growth patterns in developed markets

- Stagnation of mature markets
- Patent expirations
- Increased regulatory hurdles

Pharma market growth in emerging markets

- Huge populations
- Increasing wealth and prosperity
- Improving life expectancy
- Advantages of good healthcare

New sources of revenues in emerging markets
1. Sequential Submission
Europe/USA/Japan → CPP issuance* → emerging markets

CPP - Certificate of Pharmaceutical Product; a document generated by HA of an exporting country to establish the status of pharmaceutical product and GMP status of the applicant in this country.

2. Simultaneous Submission
Europe/USA/Japan + emerging markets, often with early inclusion into global clinical trials
Brazil
The Brazilian Sanitary Surveillance Agency (ANVISA)

- Inclusion of correspondent Brazilian Common Denomination (DCB) in the list of DCBs (60 days), if applicable
- Registration of API in Cadastro with ANVISA (no official review timelines), if applicable
- GMP Certificate issued by ANVISA or copy of inspection request plus GMP of country of manufacture
- Price information may be required by ANVISA

Local clinical trials not required!

Language of submission - Portuguese
Scientific advice not required
Stability studies for Zone IV-B

Clinical trials
Marketing approval
Submission 365 Days CPP required 734

Clinical trials
Marketing approval
RUSSIA
Federal Service on Supervision in the Sphere of Public Health Services and Social Development (Roszdravnadzor)

- Inclusion of Russia into global clinical trials
- Language of application – Russian
- Parallel submission to Ethic committee and MoH
- Import licence for the unregistered drug used in the clinical trial

Big challenge: health care system complex with constant regulatory changes: can cause delays in clinical trials of 3-4 mths
RUSSIA

- Registration dossier very similar to EU
- Scientific advice not required
- Language of submission – Russian
- CPP not required
- Stability studies for Zone I and II

- API registration in the Federal Register of Medicinal Products
- Permit for import of unregistered medicinal product for the expert assessment
- Russian GMP Certificate (since 2016)

- Russian State Pharmacopoeia only!
- Drug products need to pass laboratory control in Russian state laboratory
- Samples
INDIA
The Central Drug Standard Organization (CDSCO)

Clinical trials

Not clear if local clinical trials are required

Marketing approval

Years 1-1.5

Submission

- If inclusion of India is needed: Category A - protocol approved by regulatory agency in developed country
- Information sheet and consent form in all relevant vernacular languages
- Approval timelines: 2-4 weeks

Scientific advice not required
- Language of submission – English
- CPP not required
- Stability studies for Zone IV
CHINA
The China Food and Drug Administration (CFDA)

- **New drug**: full clinical development program in China required: Phase 1, 2 and 3 (± 5 yrs of clinical trials)
- Pre-IND meeting with CFDA within 30 days
- Language of application - Chinese

- Pre-NDA meeting with CFDA within 30 days
- Application format for drug registration different than in ICH-countries
- Language of submission - Chinese
- Stability studies for Zone II
CHINA
The China Food and Drug Administration (CFDA)

- **Imported drug**: PK and Phase 3 study in China required
- Pre-IND meeting with CFDA within 30 days
- Language of application - Chinese

- Pre-NDA meeting with CFDA within 30 days
- CTD format applicable to Chinese application for import drug
- Language of submission - Chinese

- Only one manufacturing site of imported drug product (used for the market in China) may be registered
- Samples
- Stability studies for Zone II

Months Submission 10-22 Months 10-14

Clinical trials - Marketing approval

Submission
2015: Announcement of reforms in China’s regulatory environment

Major issues in the areas of comparative quality between international standards and some local products and manufacturers

Drug lag was often > 5 years
Lack of capacity for reviewing

GOALS:
- IND/CTA timelines to be around 6 mths by end of 2018 without backlog.
- To shorten the drug lag (time period between approval outside of China vs. approval inside China)
2015: Announcement of reforms in China’s regulatory environment

- Clinical trial application changes
  - Opening of FIH Phase I trials to global development
  - Increased capacity for clinical trials: no need for credit of GCP by CFDA
  - Improvement in ethics committees review efficiency
  - Improvement of clinical trial review process:
    - Consultation with CFDA prior Phase I and Phase III trials; no comment within 60 working days then approved
  - Protection of innovator’s rights: drug-patent-link system and clinical trial data protection

- Marketing application changes
  - Additional capacity of the Center for Drug Evaluation: from 70 to 600 reviewers by end of 2016
  - Priority review (only when drug is not approved anywhere else): to encourage overseas sponsors to plan and perform clinical developments in China in parallel with USA and EU.
  - “Simplified process”: Approval process change from ’3-submission-3-approval’ to ’2-submission-2-approval’
SOUTH AFRICA
The Medicines Control Council (MCC)

- Scientific advice not required, but informal scientific advice is possible
- Communication with the MCC only through authorised pharmacist
- MAH or partner required to be locally based
- Registration dossier same format as ICH CTD
- Language of submission - English (British)
- CPP not required
- Stability studies for Zone IV

- GMP Certificate from country of manufacture (< 3 years)
- Local manufacturer not required
- Certificate of Analysis of API batch
Multi-regional clinical trial (Global)

Clinical trial application approval times:

- EU: 2 months
- USA: 1 month
- Japan: 1 month
- Brazil: No local clinical trial needed
- Russia: 1.5 - 3 months
- India: ? No local clinical trial needed?
- China: 10 - 22 months
- South Africa: No local clinical trial needed
Global marketing authorization application

Marketing authorization approval times:

- EU: 15 months
- USA: 12 months
- Japan: 12 months
- Brazil: 18 months
- Russia: 24 months
- India: 12-18 months
- China: 20 months
- South Africa: 48 months
Opportunities in BRICS countries for global sponsors

- New source of revenues and profitability
- Large costs savings on clinical trials (up to one fifth of the cost of similar trials in developed countries)
- Ease of subject recruitment, even for rare diseases / with specific admission criteria (large population)
In practice: key RA requirements

1. **Local Clinical Trials**
   - Multi-regional clinical trial: include Russia as clinical sites for Phase III studies
   - For future: Keep China in mind as well (Reform might improve CTA approval times)
   - Not clear for India if local clinical trials are needed

2. **Stability data zones**

3. **Pre-registration steps incl. GMP inspections**
   - E.g. Local GMP in Russia and Brazil

4. **Module I documents incl. CPP**
   - Brazil

5. **Local translation**

6. **Local office**
   - South Africa
In practice: key RA requirements

6. Registration samples and/or obligation to have the product marketed in the ref. country

7. What is the reference country?
   - Country of origin
   - Country of manufacturing

8. Pricing

9. Others
   - Meetings with health authority if possible
   - Health authority speed of action
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Breaking news:

South Africa may ask pharma firms for fee to clear drug review backlog

NewsPoints Desk)
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Tags: NewsPoints, Medicines Control Council, SAHPRA, Regulatory Affairs

A new proposal by the South African Health Products Regulatory Authority (SAHPRA) could require drugmakers to pay a fee to help clear the backlog of drug reviews, as reported Yahoo! Finance Monday.

"As part of this process, SAHPRA is also exploring other potential sources of revenue, including a backlog fee to speed up the registration of products in the current backlog," explained Helen Rees, chairwoman of SAHPRA’s board.

"It's the first time South Africa offers this and we would support a backlog fee, provided it is performance driven," said Stavros Nicolaou, senior executive for strategic trade at Aspen Pharmacare.
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Questions?