New Russian Drug Law: Changes Concerning Clinical Studies and Marketing Authorization and Their Implications

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Russian Pharmaceutical Market Turnover, Dynamics & Forecast

Source: DSM Group and IMS Health via Deloitte
## Russia in the List of Countries by Pharmaceutical Market Size

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2013</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>USA</td>
<td>USA</td>
<td>USA</td>
</tr>
<tr>
<td>2</td>
<td>Japan</td>
<td>China</td>
<td>China</td>
</tr>
<tr>
<td>3</td>
<td>China</td>
<td>Japan</td>
<td>Japan</td>
</tr>
<tr>
<td>4</td>
<td>France</td>
<td>Germany</td>
<td>Brazil</td>
</tr>
<tr>
<td>5</td>
<td>Germany</td>
<td>France</td>
<td>Germany</td>
</tr>
<tr>
<td>6</td>
<td>Italy</td>
<td>Brazil</td>
<td>France</td>
</tr>
<tr>
<td>7</td>
<td>Canada</td>
<td>Italy</td>
<td>Italy</td>
</tr>
<tr>
<td>8</td>
<td>United Kingdom</td>
<td>United Kingdom</td>
<td>Russia</td>
</tr>
<tr>
<td>9</td>
<td>Spain</td>
<td>Canada</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>10</td>
<td>Brazil</td>
<td>Spain</td>
<td>Canada</td>
</tr>
<tr>
<td>11</td>
<td>Mexico</td>
<td><strong>Russia</strong></td>
<td>India</td>
</tr>
<tr>
<td>12</td>
<td>Australia</td>
<td>India</td>
<td>Spain</td>
</tr>
<tr>
<td>13</td>
<td><strong>Russia</strong></td>
<td>Mexico</td>
<td>Mexico</td>
</tr>
</tbody>
</table>

(Source: IMS Health via Deloitte)
Russian Clinical Trial Market: Facts and Figures

Clinical trials approved in 3 months
Centralized healthcare, specialized hospitals
Low migration rates, thus high retention
Lower access to state-of-the-art treatment protocols
Treatment-naïve patients in many indications
Experienced and highly qualified investigators
GCP incorporated in legislation

Faster recruitment

In our recent 7 clinical studies, enrollment rates at Accell’s sites were 1.4 to 7 times higher than in the rest of the world

High quality of data
Russian Clinical Trial Market: No. of Clinical Trials by Phase

<table>
<thead>
<tr>
<th>Year</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>129</td>
<td>86</td>
<td>25</td>
<td>47</td>
</tr>
<tr>
<td>2010</td>
<td>38</td>
<td>64</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>2011</td>
<td>327</td>
<td>111</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td>2012</td>
<td>396</td>
<td>91</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>2013</td>
<td>526</td>
<td>84</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>2014</td>
<td>483</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total: 490

Source: Orange Paper — clinical trials in Russia by Synergy
Russian Clinical Trial Market: FDA & EMEA Acknowledgement

**Clinical Investigator Inspections by FDA in Russia**

<table>
<thead>
<tr>
<th>Year</th>
<th>FDA audits</th>
<th>NAI</th>
<th>VAI</th>
<th>OAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>20</td>
<td>13</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>15</td>
<td>11</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2012</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>24</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

* NAI = no action indicated
VAI = voluntary action indicated
OAI = official action indicated
Source: FDA

**New Drugs Approved by FDA**

- **2008:**
  - Total: 81
  - Using Russian data: 34

- **2009:**
  - Total: 101
  - Using Russian data: 20

- **2010:**
  - Total: 114
  - Using Russian data: 34

- **2011:**
  - Total: 102
  - Using Russian data: 21

- **2012:**
  - Total: 111
  - Using Russian data: 53

- **2013:**
  - Total: 114
  - Using Russian data: 45

- **2014:**
  - Total: 104
  - Using Russian data: 64

**New Drug Applications Approved by EMEA**

- **2008:**
  - Total: 85
  - Using Russian data: 35

- **2009:**
  - Total: 142
  - Using Russian data: 27

- **2010:**
  - Total: 51
  - Using Russian data: 22

- **2011:**
  - Total: 67
  - Using Russian data: 32

- **2012:**
  - Total: 87
  - Using Russian data: 48

- **2013:**
  - Total: 101
  - Using Russian data: 86

- **2014:**
  - Total: 104
  - Using Russian data: 64

Source: Orange Paper — clinical trials in Russia by Synergy

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Regulatory Framework in Russia

- **Ministry of Health and Central Ethics Committee**
  - Parallel submissions
  - 40 work days (2 months)

- **Local Ethics Committee**
  - Present at most sites
  - LEC approval required when present
  - **2-4 weeks**

- **Import/export license**
  - Required for any IMP, materials originating from outside Russia
  - Required for export of all materials, samples outside Russia
  - **5 work days**

- **IMP import**
- **Site initiation**
- **First patient in**

- **Feasibility and dossier preparation**
- **1 month**

- **Site initiation**
- **3 months**

- **IMP import**
- **1 month**

- **5 months total**
Legislative Framework for Medicinal Products in Russia

- Federal Law # 61-FZ dated April 12, 2010 “On circulation of medicinal products”
  - Federal Law #429-FZ amends Law #61-FZ
  - Majority of changes to #61-FZ law took effect on July 1, 2015; certain provisions will take effect January 1, 2017
- National Standard of Russian Federation «Good Clinical Practice» GOST-R 52379-200 (effective September 27, 2005)
- December 23, 2014 — an Agreement on Common Principles and Rules of Drug Circulation in the Eurasian Economic Union was signed, and will be in effect following ratification by all parties but no earlier than January 1, 2016
General Regulatory Approach to Changes to 61-FZ Drug Law

- “Old Law” had some inherent flaws in the areas of:
  - Definitions
  - Correlation with global best practices
  - Legal framework for generic drugs
  - Inconsistency with the current state of the pharmaceutical market and its development

- “New Law” approved after consultations and review by the industry and aims to optimize the quality of regulatory processes and enhance the experience of companies applying for Marketing Authorization in Russia
## Improvements to Existing Definitions

<table>
<thead>
<tr>
<th>Previously</th>
<th>Currently</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical substance</td>
<td>Pharmaceutical substance</td>
</tr>
<tr>
<td>With limited definition of origin</td>
<td>Any substance with pharmacological activity</td>
</tr>
<tr>
<td></td>
<td>regardless of origin</td>
</tr>
<tr>
<td>Original medicinal product</td>
<td>Reference medicinal product</td>
</tr>
<tr>
<td>Reproduced (generic) medicinal product</td>
<td>Reproduced (generic) medicinal product</td>
</tr>
<tr>
<td></td>
<td>Includes biological and therapeutic equivalence</td>
</tr>
<tr>
<td></td>
<td>confirmation</td>
</tr>
</tbody>
</table>
New Definitions in 2015 Law

- New Law adds definitions for:
  - Orphan medicinal product
  - Biological medicinal product
  - Biotechnology-based medicinal product
  - Immunobiological drugs
  - Gene therapy medicinal product
  - Homeopathic drugs
  - Biosimilar drugs
  - Therapeutic equivalency

- Addition of new definitions creates new regulatory pathways for certain categories of drugs
- Former law did not define these categories of drug separately
Biosimilars VS. Generic

- New law for the first time introduces the difference between “generic” and “biosimilar” medicinal products
- Difference in handling marketing authorization by the regulator
Interchangeable Medicinal Products

- Definition initiated by Federal Antimonopoly Service (FAS) to improve competition for federal procurement of drugs
- Starting January 1, 2018 information about interchangeability of drugs is subject to inclusion to the Federal Drug Registry
- Interchangeability is determined by the panel of experts during the marketing authorization dossier review
- For drugs registered prior December 22, 2014 interchangeability must be defined by December 31, 2017
GxP

Ministry of Health now responsible for approval and implementation of

- GLP
- GCP
- GMP
- Good Storage and Transport Practice
- Good Distribution Practice
- Good Pharmacy Practice
- Good Pharmacovigilance Practice
Clinical Trials for Medicinal Products

- Previously, clinical trials were subject to review in the framework of the Marketing Authorization submission.
- Key change: clinical trial application review process (EC and MOH) is excluded from the marketing authorization process.
- Standalone approach to clinical trial dossier review simplifies and streamlines the application and review process.
- Clinical trials conducted in part or in whole in Russia are still a requirement for Marketing Authorization approval.
Scientific Advice: New Opportunity

Previously
- No mechanism for scientific advice was present; no feedback from Ministry of Health

Currently
- Scientific advice option is available under the new law for
  - Preclinical studies
  - Clinical trials
  - Marketing authorization
  - Quality, efficacy, safety review
- For fee service of Ministry of Health
- Written response to inquiries for scientific advice
Marketing Authorization Dossier Composition Changes

- Definition for MA Holder is added to the Law (previously absent)
- Effective 01.01.2016; Format: Standard Technical Document
  - Administrative section
  - Chemical, pharmaceutical, biological section
  - Pharmacology and toxicology section
  - Clinical section
- Format should be established by the Ministry of Health
- Law stipulates a detailed list of required documents generally as well as allowed exceptions
## Marketing Authorization Timelines

<table>
<thead>
<tr>
<th>Previously</th>
<th>Currently</th>
</tr>
</thead>
<tbody>
<tr>
<td>General MA pathway — 210 business days; clock stops for Q&amp;A</td>
<td>General MA pathway — 160 business days; clock stops for Q&amp;A</td>
</tr>
<tr>
<td>Expedited MA pathway — 60 business days</td>
<td>Expedited MA pathway — 80 business days</td>
</tr>
<tr>
<td>Reproduced (generic) drugs</td>
<td>Orphan indications</td>
</tr>
<tr>
<td>Confirmation of federal registration — 90 business days</td>
<td>First three generic drugs</td>
</tr>
<tr>
<td></td>
<td>Exclusively pediatric drugs</td>
</tr>
<tr>
<td></td>
<td>Confirmation of federal registration — 60 business days (as of 01.01.17)</td>
</tr>
</tbody>
</table>
Marketing Authorization: New Exception Examples, Generics

Generic drugs:

- Allows to provide scientific literature review of preclinical studies of the reference drug IN LIEU of the Sponsor’s own preclinical studies of the generic drug.
- Clinical Study Report for Bioequivalency studies only in lieu of the full clinical trial program (previously full program of clinical studies was required).
- Effective 01.01.2016: drug makers can apply for generic marketing authorization in
  - 4 years from reference product registration — for biosimilar drugs
  - 6 years from reference product registration for generic drugs
Marketing Authorization: New Exception Examples, Orphan Drugs

Orphan drugs:
- New MA application pathway for orphan drugs
- Allows the Sponsor to provide reports of preclinical and clinical studies performed outside of Russian Federation in accordance with GCP and GLP

Orphan and biotechnology-based drugs:
- MA holders are now required to provide for a fee their reference product for the purpose of clinical trials, at cost not in excess of registered price in the country (effective 01.01.2016)
New Additional Provisions for MA Cancellation

- Lack of registered drug on the market for over 3 years from registration date
- Lack of PV reporting
- Refusal of MA holder to amend MA with newly discovered information on risks outweighing the benefits
- Voluntary MA cancellation by the MA holder
Pharmacovigilance

- Definitions added to the new Law for
  - Pharmacovigilance
  - Risk Management Plan
- Regulator will analyze all monitored information (safety, efficacy, risks) not only in Russia but globally
- MA holders are required to:
  - Collect, analyze, retain and report to the Regulatory Authorities information on side effects, SAE, SUSAR, drug-drug interaction, tolerability and other factors posing potential health threats
- Effective 01.01.16 frequency of PVG reporting changes to:
  - Once every 6 months for the first two years post-registration
  - Annually for the subsequent three years
  - Once every 5 years thereafter
Implications of Changes to Drug Law for Foreign Sponsors

- Drug law correlates with latest international standards
  - Transparency
  - Robust definitions
  - Ministry of Health Scientific Advisory option.
- Expanded definitions of biological, biosimilar, immunobiological, and other drugs created new regulatory pathways.
- Reduction of overall time to market for the drugs.
- Streamlined clinical trial application process.
- Competitive landscape for participation in the federal procurement process for drug makers.
- Opens up the Russian market for easier access for pharmaceutical companies specialized in generic, orphan and pediatric drug development.
Thank you for attention!

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