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

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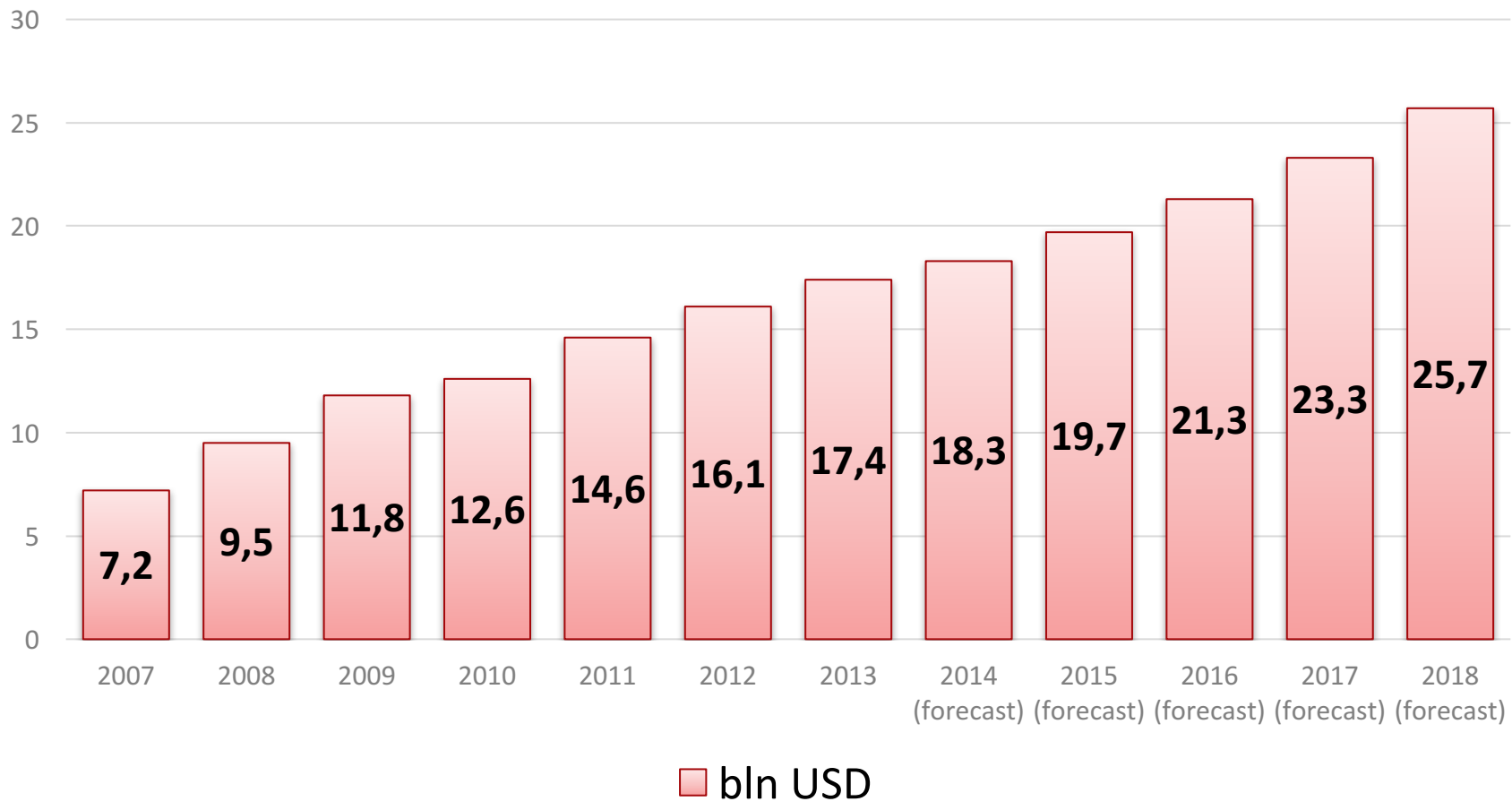
October 22-23, 2015

Frankfurt, Germany

Russian Pharmaceutical Market Turnover, Dynamics & Forecast



Source: DSM Group and IMS Health via Deloitte

Russia in the List of Countries by Pharmaceutical Market Size

	2008	2013	2017
1	USA	USA	USA
2	Japan	China	China
3	China	Japan	Japan
4	France	Germany	Brazil
5	Germany	France	Germany
6	Italy	Brazil	France
7	Canada	Italy	Italy
8	United Kingdom	United Kingdom	**Russia**
9	Spain	Canada	United Kingdom
10	Brazil	Spain	Canada
11	Mexico	**Russia**	India
12	Australia	India	Spain
13	**Russia**	Mexico	Mexico

(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

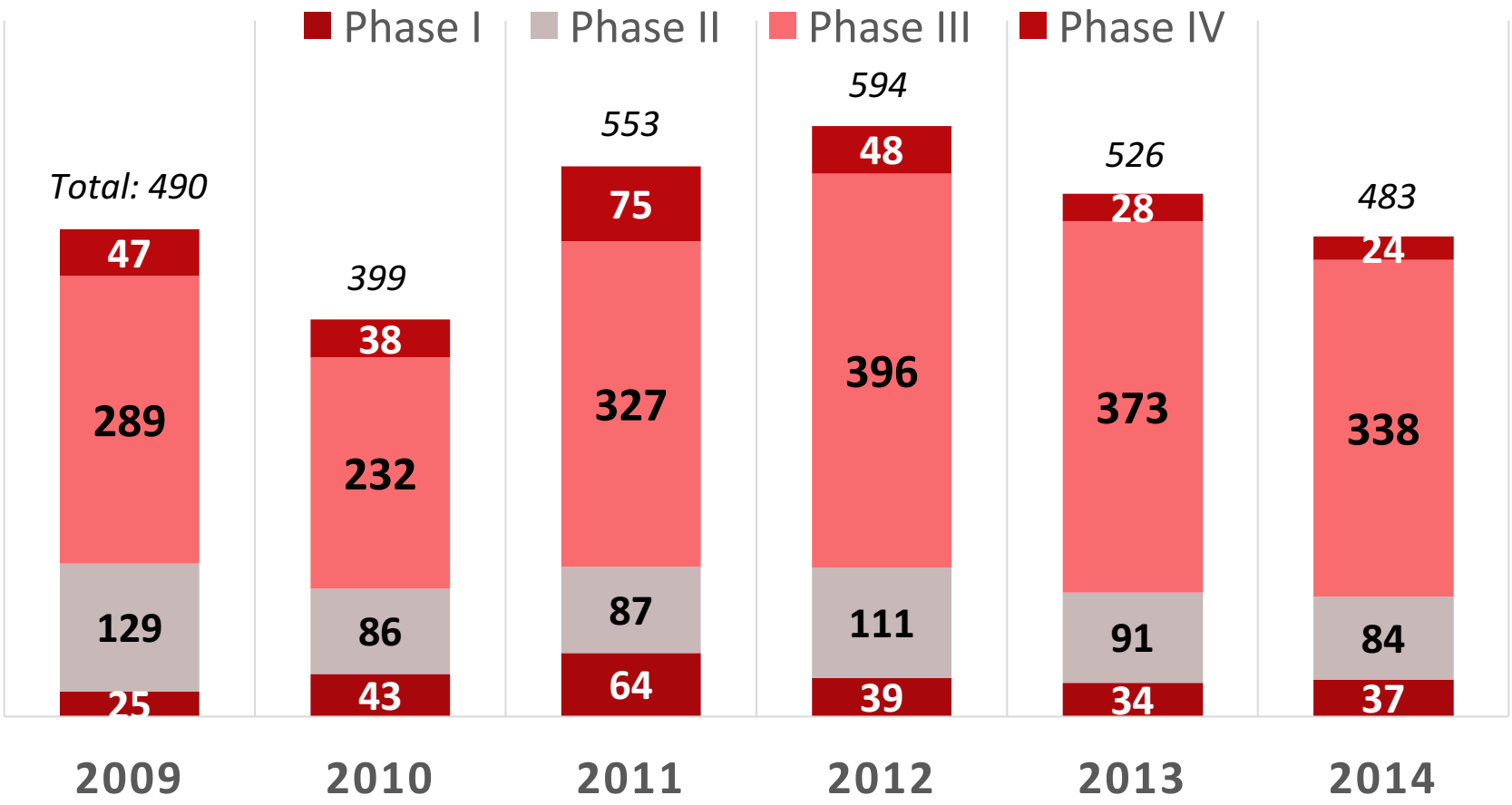
Faster recruitment

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

- Experienced and highly qualified investigators
- GCP incorporated in legislation

High quality of data

Russian Clinical Trial Market: No. of Clinical Trials by Phase



Source: Orange Paper — clinical trials in Russia by Synergy

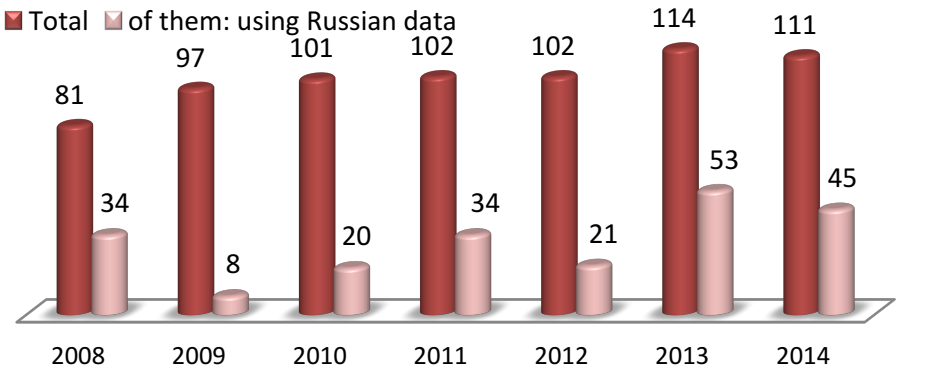
Russian Clinical Trial Market: FDA & EMEA Acknowledgement

Clinical Investigator Inspections by FDA in Russia

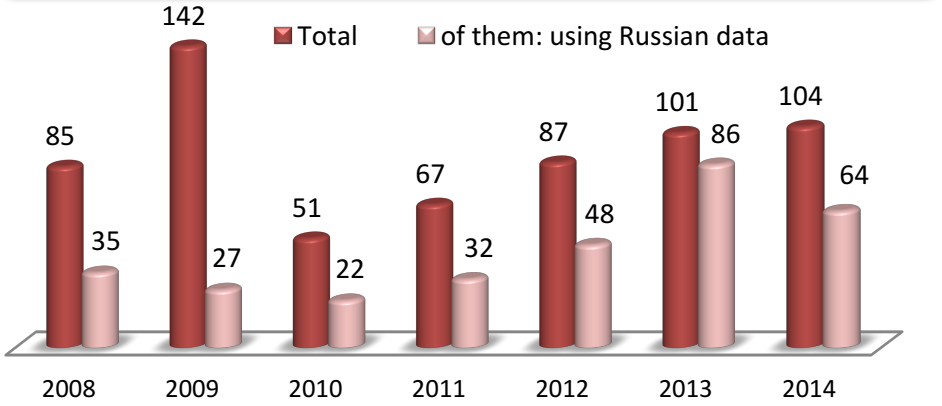
Year	FDA audits	NAI	VAI	OAI
2008	20	13	7	0
2009	15	11	4	0
2010	10	9	1	0
2011	3	2	1	0
2012	7	6	1	0
2013	4	2	2	0
Total	36	24	12	0

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

New Drugs Approved by FDA



New Drug Applications Approved by EMEA



Source: Orange Paper — clinical trials in Russia by Synergy

Regulatory Framework in Russia

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

Previously	Currently

➢ Pharmaceutical substance
  ➢ With limited definition of origin
	➢ Pharmaceutical substance
	  ➢ Any substance with pharmacological activity regardless of origin

➢ Original medicinal product	➢ Reference medicinal product
➢ Reproduced (generic) medicinal product	➢ Reproduced (generic) medicinal product ➢ Includes biological and therapeutic equivalence confirmation

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

Previously

- General MA pathway — 210 business days; clock stops for Q&A
- Expedited MA pathway — 60 business days
  - Reproduced (generic) drugs
- Confirmation of federal registration — 90 business days

Currently

- General MA pathway — 160 business days; clock stops for Q&A
- Expedited MA pathway — 80 business days
  - Orphan indications
  - First three generic drugs
  - Exclusively pediatric drugs
- Confirmation of federal registration — 60 business days (as of 01.01.17)

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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