How Regulation can Help ... or Hinder Innovation
an industry perspective

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The contents of this presentation were discussed with colleagues in EFPIA. However, the views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the industry or EFPIA.
Content

- Regulation in EU;
- EFPIA regulatory strategy plan 4E for 2023
- A LEO Pharma Case Story
Whereas the primary purpose of any rules concerning the production and distribution of proprietary medicinal products must be to safeguard public health;

Whereas, however, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community;
EU Regulations, Directives, etc.

- REGULATION (EC) No 141/2000 (Orphan Regulation)
- DIRECTIVE 2001/83/EC (Community code relating to medicinal products for human use)
- REGULATION (EC) No 726/2004 (Community procedures for authorisation and supervision of medicinal products)
- REGULATION (EC) No 1901/2006 (Paediatric Regulation)
- DIRECTIVE 2010/84/EU (Pharmacovigilance)
- DIRECTIVE 2011/62/EU (Falsified Medicines)
- REGULATION (EU) No 536/2014 (Clinical Trials Regulation)
- REGULATION (EU) 2019/933 (SPC Manufacturing Waiver)
- Guidance documents (Notice to Applicants, EMA, WHO, ICH, OECD, etc.)
Commentaries

Orphan Medicines for Pediatric Use: A Focus on the European Union

Winona Rei Bolislis MA, Solange Corriol-Rohou MD, Claire Hill-Venning PhD, Hans Hoogland PhD, Angelika Joos MPharm, David King PhD, Victoria Kitcatt LLM, Genevieve Le Visage PharmD, Thomas C. Kühler PhD

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In view of global development ...

Regulations may not hinder innovation, as such, but lack of (global) harmonisation definitely will!

Obvious examples include:
- Different criteria for orphan designations;
- Different timing/requirements for paediatric development;
- Patient Reported Outcomes may be acceptable in one region, but not in the next;
Where is EU in the Regulatory Landscape?

New active substance (NAS) median approval time for six regulatory authorities in 2009-2018

Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.
Approval of New Active Substances

Figure 1: Number of NASs approved by six regulatory authorities by approval year 2009-2018
R&D Investments in Europe continue lagging behind US...

PHARMACEUTICAL R&D EXPENDITURE IN EUROPE, USA AND JAPAN (MILLION OF NATIONAL CURRENCY UNITS*), 1990-2016

*Note: Europe: € million; USA: $ million; Japan: ¥ million x 100
Source: EFPIA member associations, PhRMA, JPMA
A New (?) Clinical Trial Regulation …

[The old directive] … has ensured high level of patient safety, but its **divergent transposition and application** led to an unfavourable regulatory framework for clinical research, thus contributing to **a decrease of 25% of clinical trials conducted in the period between 2007 and 2011**: in 2007, more than 5000 clinical trials were applied for in the EU while by 2011 the number had dropped to 3800 (**For 2018 numbers may be similar to 2011** – HHO).

“Commission boosts clinical research in Europe by simplifying the rules for conducting clinical trials”

(EC Press Release, 17 July 2012)

“The new Regulation aims at restoring the EU’s competitiveness in clinical research and the development of new and innovative treatments and medicines by cutting red-tape and bringing patient-oriented research back to Europe”

(EC Memorandum, 2 April 2014)
In view of global development ...

EU is lagging behind other major jurisdictions!

There are good reasons to look for improvements, for example:
• Approval processes;
• Clinical Trials;
EFPIA REGULATORY STRATEGY PLAN 4E FOR 2023

VISION: to drive an agile, competitive and world-class regulatory system in Europe and beyond that embrace advances in science, technology and medicines, accelerating access to innovative healthcare solutions and optimised patient outcomes.

ENSURE
a competitive world-class regulatory system
- opportunities to keep pace with science
- Identify and prioritise options for the future

ELEVATE
multi-stakeholder engagement
- Embedded in all priority actions
- Strive for co-creation with existing partners

EVOLVE
the framework for innovation
- “Evidence REVEAL” Study (Technopolis)
- Focus on RWE/RWD and Complex Trials

EXPAND
global convergence
- Prioritise ICH topic selection consistent with evolving needs from science and technology
The EFPIA Board endorsed the Regulatory Road to Innovation Plan, which translates the “4E for 2023” regulatory strategy into a series of recommendations aiming to optimise the current regulatory framework without changes to the existing legislation in June 2019.
How Regulation can Help … or Hinder Innovation – an industry perspective

REGULATORY ROAD TO INNOVATION

Theme I: RWE / RWD
1. Develop at EU level best practices for access, use and sustainability of cross-regional data
2. Leverage pending HTA Regulation
3. International harmonisation/collaboration

Theme II: Dynamic regulatory assessment
1. Pilot project on “dynamic assessment”
2. AI supported regulatory assessments
3. Must wins (Review of variations concept, EMA pre-authorisation guidance, optimising PRIME)

Theme III: Drug-device combinations & biomarker validation
1. Improved EMA qualification process
2. Streamlined collaboration pathway of EMA and NBs in the assessment drug-device combinations, CDx and SaMD
3. Clarity in classification of software used in the medical context
4. Enabler – building up EFPIA capability and voice in MD/IVD space

Theme IV: Innovative clinical trial approaches
1. Better alignment between EU regulators in the clinical trial pathway
2. Interpretation of the clinical trial legislation to allow parallel substantial amendments
3. Awareness / education on complex clinical trial / with focus on ethic committees – from the highest level possible
4. Collaboration between global authorities

Co-creation

Co-decision legislation
Based on EFPIA Strategy and Recommendations ...

Industry, together with other stakeholders, will be working on improving the current regulatory environment:

• Ensuring a world-class competitive regulatory system;
• For the benefit of patients;
LEO Pharma: focusing on dermatology ...

• Available guidance in EU:
  - Clinical investigation of corticosteroids intended for use on the skin (1987)
  - Clinical investigation of medicinal products indicated for the treatment of psoriasis (2005)
  - Quality and equivalence of topical products (Draft, 2018)

• US Guidance for Industry:
  - Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment (May 2018)
  - Atopic Dermatitis: Timing of Pediatric Studies During Development of Systemic Drugs (October 2018)
  - Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations (June 2019)
  - Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery System for ANDAs (2018)
  - ...

LEO Pharma will be happy to reach out to CHMP’s Efficacy Working Party to discuss the need for (harmonised) additional guidance documents in the field of dermatology
LEO Pharma: focusing on dermatology ...

- **Psoriasis** is a long-lasting autoimmune disease characterized by patches of abnormal skin (typically red, dry, itchy, and scaly). The disease will affect 2–4% of the population of the western world (dependent on age, region and ethnicity).

- There is no cure. New biologics for treatment of psoriasis come with amazing efficacy, but regulatory approval of these products comes with specific challenges ...

- Psoriasis has an enormous impact on patients’ lives and is frequently associated with depression.

  And ... "it is difficult to distinguish whether improved depression is the result of the direct anti-inflammatory effect of the biologic, or the indirect effect of improved psoriasis leading to better psychological status" (Cardwell et al., 2017)
SILIQTM (brodalumab) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: SUICIDAL IDEATION AND BEHAVIOR
See full prescribing information for complete boxed warning.

- Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. (5.1, 6.1)
- Predisposing or worsening risk factors should be addressed before starting treatment.

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INDICATIONS AND USAGE

SILIQ is a human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. (1)

- Predisposing or worsening depression, anxiety, or other mood changes. (5.1)
- SILIQ is available only through a restricted program called the SILIQ REMS Program. (5.2)
Kyntheum® – Brodalumab in EU

• Indication: “Kyntheum® is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.”

• Warning under 4.4: “… If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with Kyntheum®”.

• Procedure took 613 days …

• Post-Approval Safety Study (PASS) required
Brodalumab PAS Study

• PRAC: “A large randomised clinical trial is considered the best way to properly investigate the association between brodalumab treatment and suicidal behaviour (suicide attempt or completion).”

• However: RCT is not feasible, due to large sample size and extremely long timelines (30,000 – 40,000 patients, over 10 years)

• Therefore, an innovative observational study in psoriasis patients, based on existing databases in Denmark, Norway, Sweden, Germany, the Netherlands and selected regions of Italy was proposed – and eventually accepted.

• Using case-time-control methodology (enabling comparison of time during and outside exposure in the same individual and thereby controls for confounders that are not time dependent), meaningful results can be generated as early as 2023 (first scheduled interim analysis based on 10,000 person-years).
Does Regulation Help ... or Hinder Innovation?

- Innovation can be hindered by lack of harmonisation, lack of regulation;
- Innovation can be promoted by regulation (EFPIA Regulatory Road to Innovation);
- Mostly, it will be the people working with regulations that will help, ... or hinder innovation!