Medicines regulation beyond product licensing

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Regulatory systems

- Patient safety
- Public health
- Innovation

In addition, regulatory science should evaluate and study regulatory systems in terms of their ability to ensure patient safety, enhance public health, and stimulate innovation (*1*–*3*). During the past decades, the introduction of new innovative drugs has dropped, despite impressive investments and progress in biomedical research and development. Although the reasons for this innovation deficit are not fully understood, many observers see the increasing demands of the regulatory systems as one of the main drivers.

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Science 2011 Apr 8; 332(6026): 174-5.

EU legislation

https://ec.europa.eu/health/human-use/legal-framework_en

The requirements and procedures for marketing authorisation, as well as the rules for monitoring authorised products, are primarily laid down in Directive 2001/83/EC and in Regulation (EC) No 726/2004. They also include harmonised provisions for the manufacture, wholesale or advertising of medicinal products for human use.

Additionally, EU legislation provides for common rules for the conduct of clinical trials (to test the safety and efficacy of medicines under controlled conditions) in the EU. Various rules have also been adopted to address the particularities of certain types of medicinal products and promote research in specific areas:

- Medicinal products for rare diseases ('Orphan medicines') Regulation (EC) No 141/2000
- Medicinal products for children Regulation (EC) No 1901/2006
- Advanced therapy medicinal products Regulation (EC) No 1394/2007

The authorisation of medicines builds on three key criteria, namely quality, safety and efficacy, to ensure that products administered to patients are of suitable quality and provide a positive benefit-risk.

A river as metaphor for drug development and use:

Upstream, e.g. basic science, discovery, R&D, clinical development, manufacturing

Downstream, e.g. drug use, clinical guidelines, HTA/reim-bursement, pharmacovigilance

Transition between up- and downstream is marked by a marketing authorisation.

Azusa River, Kamikochi National Park, Japan, May 2018

Drug development and use over time, a mixture of upstream and downstream regulatory interventions

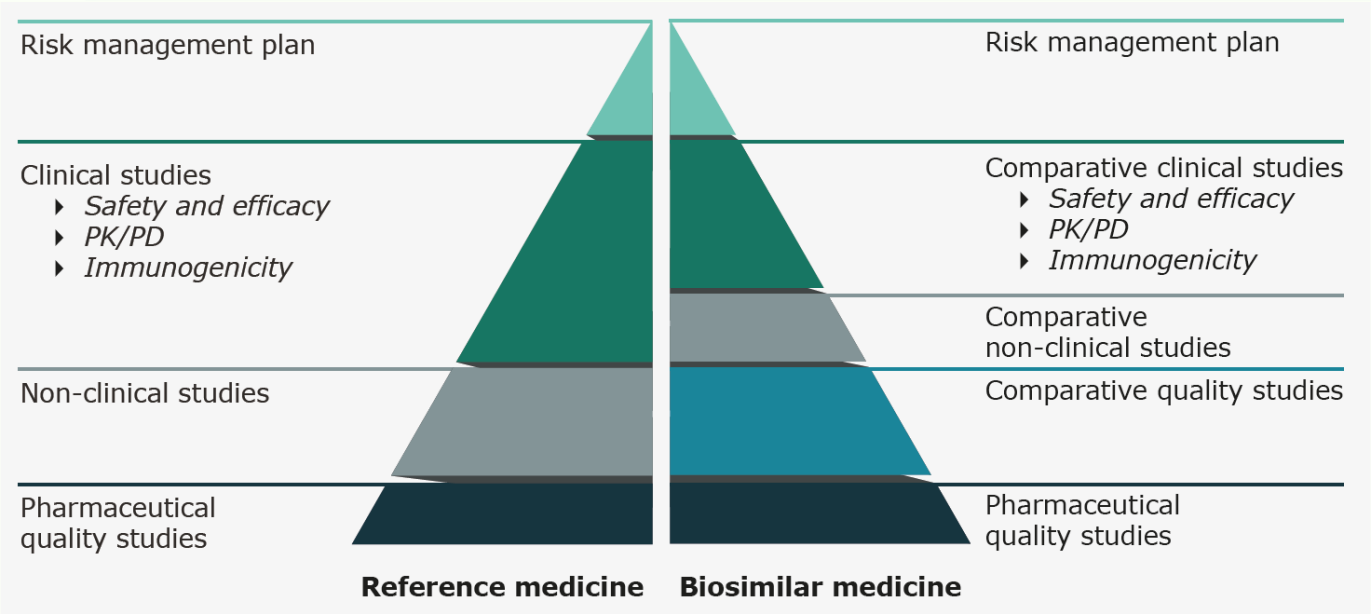
Upstream		Downstream
High level of convergence		Low level of convergence
Scientific advice, protocol assistance		Appropriate use/ clinical guidelines
Scientific guidelines, public consultation		HTA/payer interactions
GCP oversight of registration trials	Magic moment of marketing authorisation (license)	Input for vaccine strategy
Conditional approval, expedited schemes		Management of drug shortages
Etc., etc., ……		Etc., etc., ….

Observation 1:

We see more upstream regulatory interventions with downstream impact:

- regulation of biosimilars > mixed acceptance by prescribers and patients.
- conditional approval > uneasiness at HTAs and payers.

Regulation of biosimilars: biosimilarity assessment of quality parameters, how to align with the prescriber?



EMA, 2017

Ebbers HC, Pieters T, Leufkens HG, Schellekens H. Effective pharmaceutical regulation needs alignment with doctors. Drug Discov Today. 2012 Feb; 17(3-4): 100-3.

Alsamil AM, Giezen TJ, Egberts TC, Leufkens HG, Gardarsdottir H. Comparison of consistency and complementarity of reporting biosimilar quality attributes between regulatory and scientific communities: An adalimumab case study. Biologicals. 2021 Jan; 69: 30-37.

Ten years (2006-2016) of conditional marketing authorization procedures in the EU

Comparison of assessment procedure by CHMP for medicines granted standard or conditional MA.

	Standard (n = 265)	Conditional (n = 29)
Median [IQR] length of CHMP assessment procedure (in days)	337 [281–400]	421 [329–491]
Authorised with CHMP consensus*	231 (90%)	18 (64%)
Authorised based on first CHMP opinion	263 (99%)	24 (83%)
	Standard (n = 265)	Conditional (n = 29)
Request for standard MA	263 (99%)	16 (55%)
Request for conditional MA	2 (1%)	13 (45%)

Hoekman J, Boon, W. Soc Sci Med 2019; 222: 76-83.

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Observation 2:

There is increasing convergence/reliance in upstream regulatory policies:

- Standard setting and worksharing regulatory review by European network (EMA+NCAs).
- International collaboration (ICH, WHO, ICDRA, ICMRA).

Key questions when regulating a medicine

Question	Today's challenges
Robust definition and diagnosis of disease?	Stratification of cancers, agnostic indications
Clinically relevant endpoints to evaluate drug effects?	PFS/OS/RR in cancer, 6-MWT in PAH, HbA1C in diabetes
Identifiable target population (indication) that may benefit?	Biomarkers to identify responders and non-responders
What kind of comparison is useful, needed and feasible?	Placebo, active controls and natural course of disease

Observation 3:

There is increasing lack of convergence in downstream policies and decision making:

- Differences in HTA and payer decisions across Europe.
- Clinical guidelines do not always follow the SmPC.
- Management of safety issues national vs Europe (e.g. gadolinium, valproate, cyproteron/EE, nitrosamines).
- Management of drug shortages.
- National Covid-19 vaccine strategies differ between countries and with EMA positions.

Weighing of evidence by HTA bodies for conditionally approved drugs in EU (9/27 controlled, until June 2016)

1999-2014 approvals without controlled data

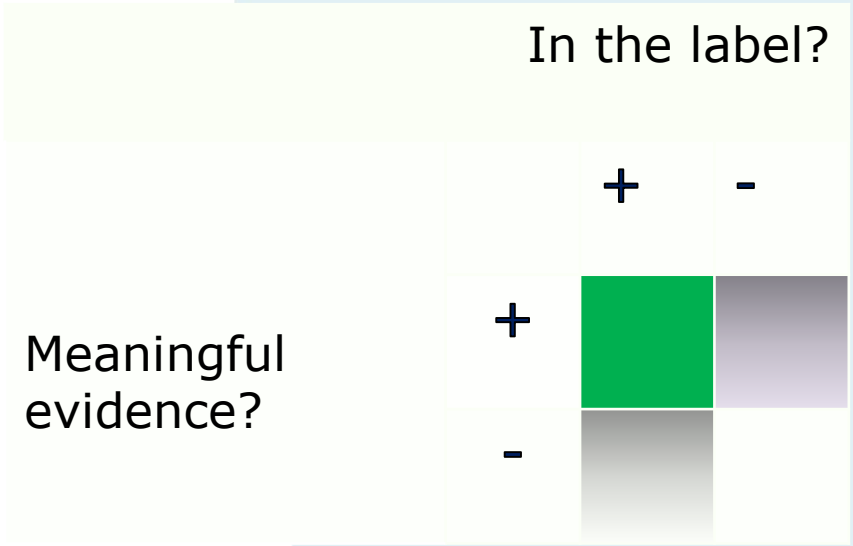
EMA 35/415
FDA 54/403

Hatswell AJ et al. BMJ Open 2016; 6:e011666.

Vreman RA et al. Clin Pharmacol Ther 2019 Mar; 105(3): 684-691.

Who owns the label?

What's in the label is a mixture of evidence building, industry initiative and regulation …..



Not everything relevant for the prescriber or the patient is in the label.

RESEARCH

Enabling appropriate use of antibiotics: review of European Union procedures of harmonising product information, 2007 to 2020

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- 15 antibiotics with a referral procedure (2007-2020)
- 12 were Article 30 Directive 2001/83/EC, Article 31 of Directive 2001/83/EC.
- 4 were triggered by a MS, others (11) by the EC.
- In 13 referrals deletion of indication main regulatory action.
- In all 15 referrals harmonization and updating of warnings and posology.

Euro Surveill 2020 Nov; 25(45): 2000035.

EDITORIAL

Regulatory science: Regulation is too important to leave it to the regulators

Leufkens HG. Br J Clin Pharmacol. 2019 Apr 10. doi: 10.1111/bcp.13917.

On 19 December 2018, the European Medicines Agency (EMA) published its draft "Regulatory Science to 2025" strategy for a 6-month public consultation. In this EMA publication, regulatory science has been defined as "the range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine …." Earlier in 2011, the US Food and Drug Administration of being too risk averse in the interest of giving patients access to new promising therapeutic options.[3]

Reality of regulatory decision making shows that this is not always a straightforward yes or no. Scanning the EMA website for European public assessment reports (EPARs) makes this very visible in situations where products are approved on the basis of majority votes and not on consensus view. Obviously, individual members of the CHMP come

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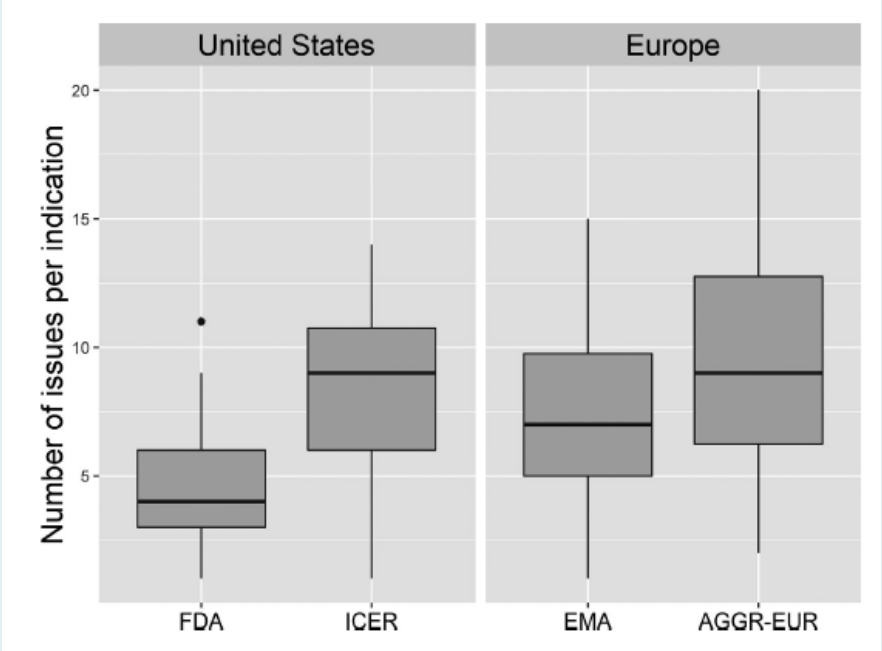
There are no regulatory/HTA dossiers without clinical uncertainties

Category name	Examples of the types of uncertainties
Safety issues	Safety sample size too small
	Causality of adverse events uninterpretable
	Long-term safety unclear
Trial validity	Selection bias
	Performance bias
	Detection bias
	Attrition bias
	Reporting bias
Population	Population does not match practice
	Relevant subgroups not adequately studied or reported
Intervention	Unreliable or missing information on interactions with other medication
	Unreliable or missing information on monotherapy or combination regimens
	Unreliable or missing information on appropriate treatment duration
Comparators	Unreliable or missing information on effects against relevant comparators
	Unreliable indirect comparisons
	Unreliable or missing information on appropriate treatment line

33 pairs of medicines (US/Europe) were evaluated; uncertainty: explicitly or implicitly reported as an unresolved shortcoming, question, or issue.



Vreman R et al. Clin Pharmacol Ther 2020; 108: 350-357.

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Benefit-Risk of regulatory policies and systems

EU regulatory innovation	Positive	On the flip side …..
Orphan medicinal products (2000)	Huge surge of approvals OMPs for unmet needs	At the borders, 'perverse' pricing, monopolies
Biosimilars (2006)	Impressive knowledge gain biologicals	At huge costs, sustainable business model?
Conditional marketing approval (2006)	More and timely approvals	Uneasiness due to limited data for HTAs and payers
ATMPs (2007)	In Europe harmonized regulatory approach	Not in ROW, not on a national level (GMO, GMP)
Pharmacovigilance (2012)	Timely risk management, innovation in RWD	At significant costs, increased bureaucracy

European Commission

A European Health Union:
A Pharmaceutical Strategy for Europe

Affordable, accessible and safe medicines for all: the Commission presents a Pharmaceutical Strategy for Europe

Brussels, 25 November 2020

The Commission has today adopted a Pharmaceutical Strategy for Europe to ensure patients have access to innovative and affordable medicines and to support the competitiveness, innovative capacity and sustainability of the EU's pharmaceutical industry. The Strategy will allow Europe to cover its pharmaceutical needs, including in times of crisis, through robust supply chains. A key component of building a stronger European Health Union, as called for by President **von der Leyen** in her State of the Union Speech, the Strategy will help to establish a future-proof and crisis-resilient EU pharmaceutical system.

Europe's Pharmaceutical Strategy has four main objectives:

- Ensuring **access to affordable medicines** for patients, and addressing unmet medical needs (e.g. in the areas of antimicrobial resistance, cancer, rare diseases);
- Supporting **competitiveness, innovation and sustainability** of the EU's pharmaceutical industry and the development of high quality, safe, effective and greener medicines
- Enhancing **crisis preparedness and response** mechanisms, and addressing security of supply;
- Ensuring a **strong EU voice in the world**, by promoting a high level of quality, efficacy and safety standards.

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Regulatory learning: missed opportunity

Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity?

Hans-Georg Eichler[1,2,*], Marco Cavaleri[1], Harald Enzmann[3,4], Francesca Scotti[1], Bruno Sepodes[4,5], Fergus Sweeney[1], Spiros Vamvakas[1] and Guido Rasi[1,6]

The scientific community has risen to the coronavirus disease 2019 (COVID-19) challenge, coming up with an impressive list of candidate drugs and vaccines targeting an array of pharmacological and immunological mechanisms. Yet, generating clinical evidence of efficacy and safety of these candidate treatments may be frustrated by the absence of comprehensive trial coordination mechanisms. Many small stand-alone trials and observational studies of single-agent interventions are currently running or in planning; many of these will likely not deliver robust results that could support regulatory and patient-level treatment decisions. In this paper, we discuss actions that all stakeholders in the clinical trial ecosystem need to take to ensure that the window of opportunity during this pandemic will not shut, both for patients in need of treatment and for researchers to conduct decision-relevant clinical trials.

Clin Pharmacol Ther 2020; 108: 73-33.

Regulatory innovation: opportunities for informed impact, particularly post-covid ……

- For sure, there are lessons to be learned on rolling review, crisis management, efficiency gains, etc.
- Regulation beyond product licensing, many opportunities, but also huge challenges.
- Upstream involvement will bring many advantages, be careful about regulatory capture.
- More downstream involvement puts the European system at risk, national interests may prevail.
- Investments in regulatory science are needed to bridge and to cement ……