Workshop ALTEMS
Università Cattolica del Sacro Cuore

La sfida dell'innovazione terapeutica centrata sui bisogni della persona: aspetti regolatori e accesso alle terapie

In collaborazione con Farmindustria
Ore 10.00-13.00
Sala Capranichetta - Hotel Nazionale
Piazza di Montecitorio 131

Roma, 15 Marzo 2022

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EFFICIENCY IN CLINICAL RESEARCH

Innovazione farmaceutica e analisi del valore: il panorama europeo post- pandemia Covid-19

Lettura introduttiva – Prof. Guido Rasi

La governance regolatoria durante la pandemia COVID-19

- Measures to reduce the spread of COVID-19 (ECDC – National Health Authorities)
- EMA COVID-19 **Steering Group**
- **Business continuity plan** for the European medicines regulatory network
- Working with EU and international partners
- COVID-19 EMA pandemic **Task Force - Rolling Review**

EMA's governance during COVID-19 pandemic webpage: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/emas-governance-during-covid-19-pandemic Access 8 March 2022

Aspects that seem likely to emerge as most affected in the post-COVID-19 era

- Shifting Greater Patient Numbers To Remote Care
- Improved Emphasis on Surveillance Systems and Data Analysis
- Development of Legislative, Political, and Healthcare Management Systems
- Development of Communication Technology-Based Approaches
- Development of Financial Models to Support Scientific Research, Cooperation, and Crisis Preparedness

Emerging learnings from the ongoing pandemic

1	Provide rapid and coordinated feedback to medicines' developers during a crisis.
2	Establish a mechanism and resources to ensure sustainability of the ETF for future crisis preparedness
3	Establish a mechanism to enable rapid advice and approval of large, well designed trials, to avoid fragmentation in clinical research.
4	Establish pan-European research investigator networks with effective infrastructural support, to enable large trials by public research bodies or industry
5	Improve collection, coordination and analysis of health data across the EU.
6	Enhance data analytics to support public confidence in the regulatory supervision of vaccines and therapeutics.
7	Invest in RWE to complement evidence from clinical trials (e.g. research contracts on vaccine effectiveness and safety).
8	Support research to define optimal tools for risk communication and data visualization.
9	Strengthen collaboration and communication with ECDC, national public health authorities and NITAGs.
10	Strengthen international collaboration and explore ways to increase harmonization and speed of data sharing.
11	Coordinate and support MSs' activities in preventing and mitigating supply disruptions of critical medicines during crisis.
12	Support EU-level coordination and scientific, technical and clinical evaluation of certain medical devices and in vitro diagnostics during emerging health threats.

Shaping EU medicines regulation in the post COVID-19 era, Marco Cavaleri et al. The Lancet Regional Health - Europe, Volume 9, 2021, 100192, ISSN 2666-7762, https://doi.org/10.1016/j.lanepe.2021.100192.

Un cambio di paradigma

Dalla tassonomia anatomo-funzionale a quella molecolare (e oltre?)

Dalla terapia alla cura

Dalla prescrizione del farmaco alla procedura terapeutica

Dalla cura alla prevenzione

Dai RCT alla RWE (e oltre)

Dalla farmacovigilanza passiva al monitoraggio attivo (lifetime?)

Dal beneficio/rischio alla misurazione del valore clinico aggiunto

Dall'approvazione del farmaco all'accesso alla cura.

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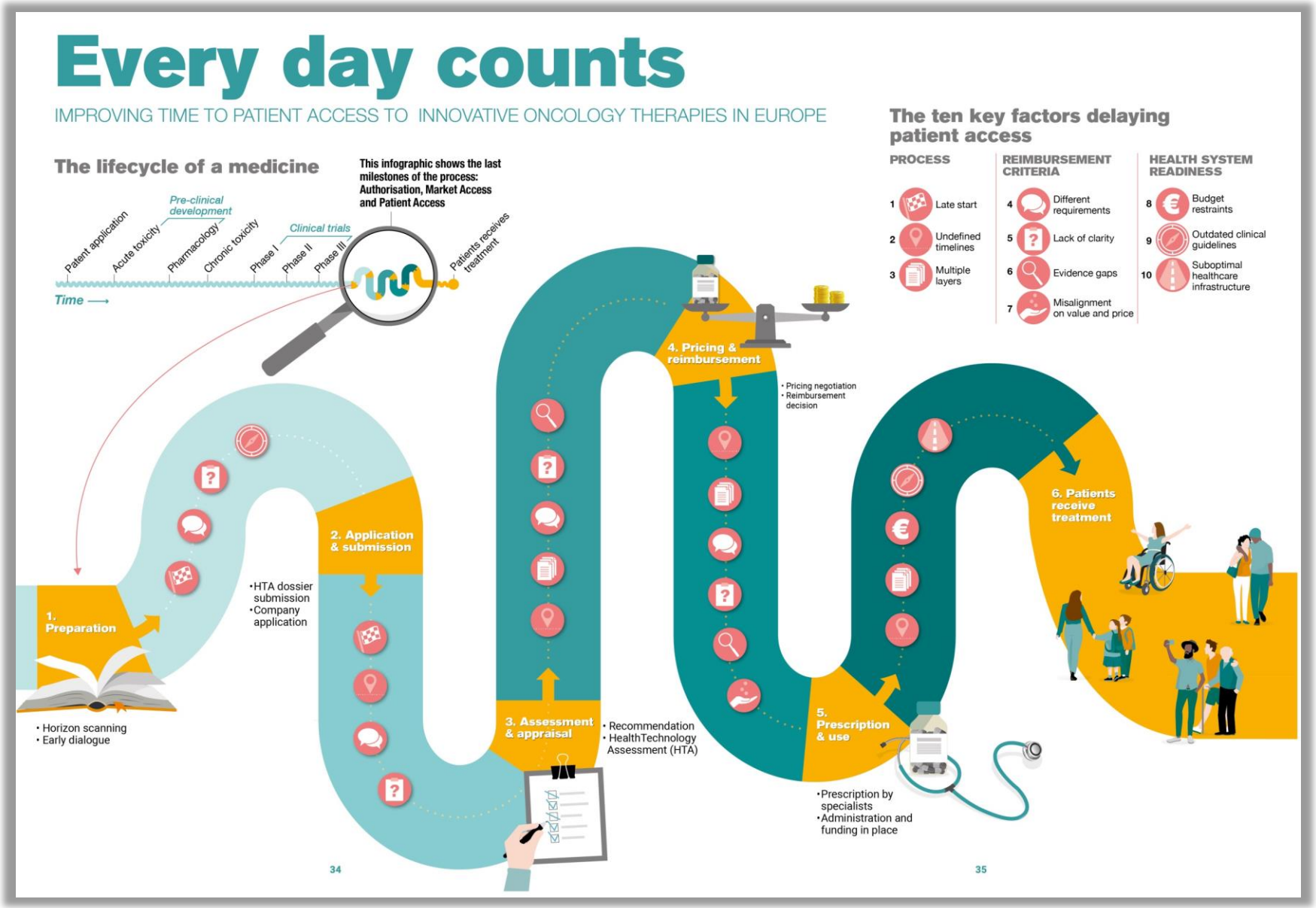

IMPROVING TIME TO PATIENT ACCESS TO INNOVATIVE ONCOLOGY THERAPIES IN EUROPE EVERY DAY COUNTS July 2020 Authored by Vintura: Christel Jansen Bas Amesz In collaboration with: ASC Academics Hague Corporate Affairs

Tensions in the medicines' ecosystem: not new but rising

Early access for patients	⟷	Maturity of evidence
Sustainability of pharma R&D	⟷	Expectations of rising evidence standards
Personalised medicine	⟷	«broad, representative» clinical trials
Fair incentives for growing number of orphanised drugs	⟷	Sustainable health care budgets
Single pathway to EU market, equity of access	⟷	Health care decision making on national level

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Different evidentiary standards

- Different evidentiary standards between regulators and payers may lead to divergent appraisals of benefit-risk versus cost-effectiveness;
- This calls for good understanding and interaction between the two communities, possibly in the format of iterative discussions and agreement during drug development.

Eichler, H. G. et al. (2015). From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients. Clin Pharmacol Ther, 97(3), 234-246. doi: 10.1002/cpt.59

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The NEW ENGLAND JOURNAL of MEDICINE

Drug Regulation and Pricing — Can Regulators Influence Affordability?

H.-G. Eichler, H. Hurts, K. Broich, and G. Rasi | N Engl J Med 2016;374:1807-1809

Free Full Text

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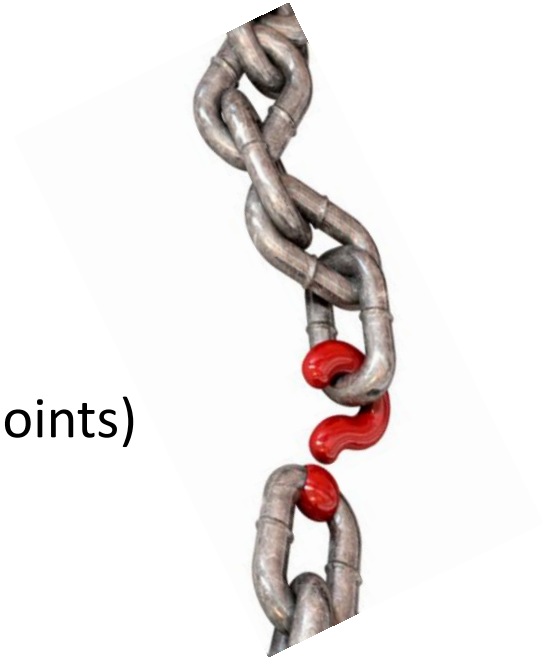
“Evidence by design” – facilitating patient access through data that serves the entire decision-making chain

- **Starting point:** decision makers (regulators, HTAs and payers):
  - Answer different questions
  - Have different requirements in term of evidence
- **Aim:** alignment of the design of the evidence generation plan:
  - Planned studies (populations/comparators/trial design/endpoints)
  - Requirements for post-licensing evidence generation



Expectation: Optimised evidence generation plan ➔ Improve access for patients

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Review > Clin Pharmacol Ther. 2021 May;109(5):1212-1218. doi: 10.1002/cpt.2083. Epub 2020 Nov 12.

Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth

Hans-Georg Eichler [1 2], Francesco Pignatti [1], Brigitte Schwarzer-Daum [2 3], Ana Hidalgo-Simon [1], Irmgard Eichler [1], Peter Arlett [1 4], Anthony Humphreys [1], Spiros Vamvakas [1], Nikolai Brun [5], Guido Rasi [1 6]

Affiliations + expand

PMID: 33063841 PMCID: PMC8246742 DOI: 10.1002/cpt.2083

Free PMC article

Abstract

Compared with drugs from the blockbuster era, recently authorized drugs and those expected in the future present a heterogenous mix of chemicals, biologicals, and cell and gene therapies, a sizable fraction being for rare diseases, and even individualized treatments or individualized combinations. The shift in the nature of products entails secular trends for the definitions of "drugs" and "target population" and for clinical use and evidence generation. We discuss that the lessons learned from evidence generation for 20th century medicines may have limited relevance for 21st century medicines. We explain why the future is not about randomized controlled trials (RCTs) vs. real-world evidence (RWE) but RCTs and RWE-not just for the assessment of safety but also of effectiveness. Finally, we highlight that, in the era of precision medicine, we may not be able to reliably describe some small treatment effects-either by way of RCTs or RWE.

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Clin Pharmacol Ther. 2019 Apr;105(4):912-922. doi: 10.1002/cpt.1226. Epub 2018 Oct 14.

Data Rich, Information Poor: Can We Use Electronic Health Records to Create a Learning Healthcare System for Pharmaceuticals?

Hans-Georg Eichler [1], Brigitte Bloechl-Daum [2], Karl Broich [3], Paul Alexander Kyrle [2], Jillian Oderkirk [4], Guido Rasi [1], Rui Santos Ivo [5], Ad Schuurman [6], Thomas Senderovitz [7], Luke Slawomirski [4], Martin Wenzl [4], Valerie Paris [4]

Affiliations + expand

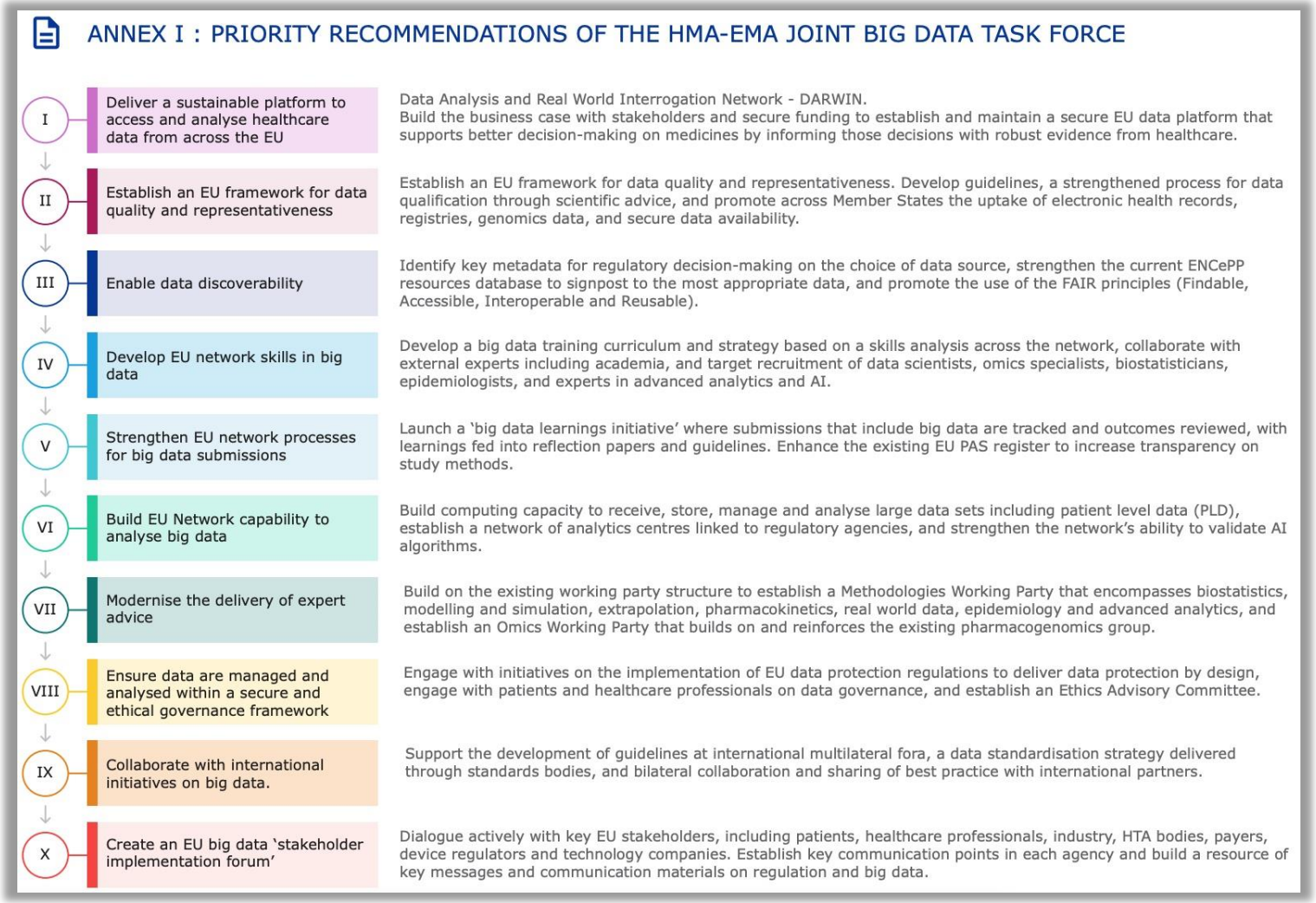
PMID: 30178490 PMCID: PMC6587701 DOI: 10.1002/cpt.1226

Free PMC article

Abstract

Judicious use of real-world data (RWD) is expected to make all steps in the development and use of pharmaceuticals more effective and efficient, including research and development, regulatory decision making, health technology assessment, pricing, and reimbursement decisions and treatment. A "learning healthcare system" based on electronic health records and other routinely collected data will be required to harness the full potential of RWD to complement evidence based on randomized controlled trials. We describe and illustrate with examples the growing demand for a learning healthcare system; we contrast the exigencies of an efficient pharmaceutical ecosystem in the future with current deficiencies highlighted in recently published Organisation for Economic Co-operation and Development (OECD) reports; and we reflect on the steps necessary to enable the transition from healthcare data to actionable information. A coordinated effort from all stakeholders and international cooperation will be required to increase the speed of implementation of the learning healthcare system, to everybody's benefit.

Data analytics, digital tools & digital transformation

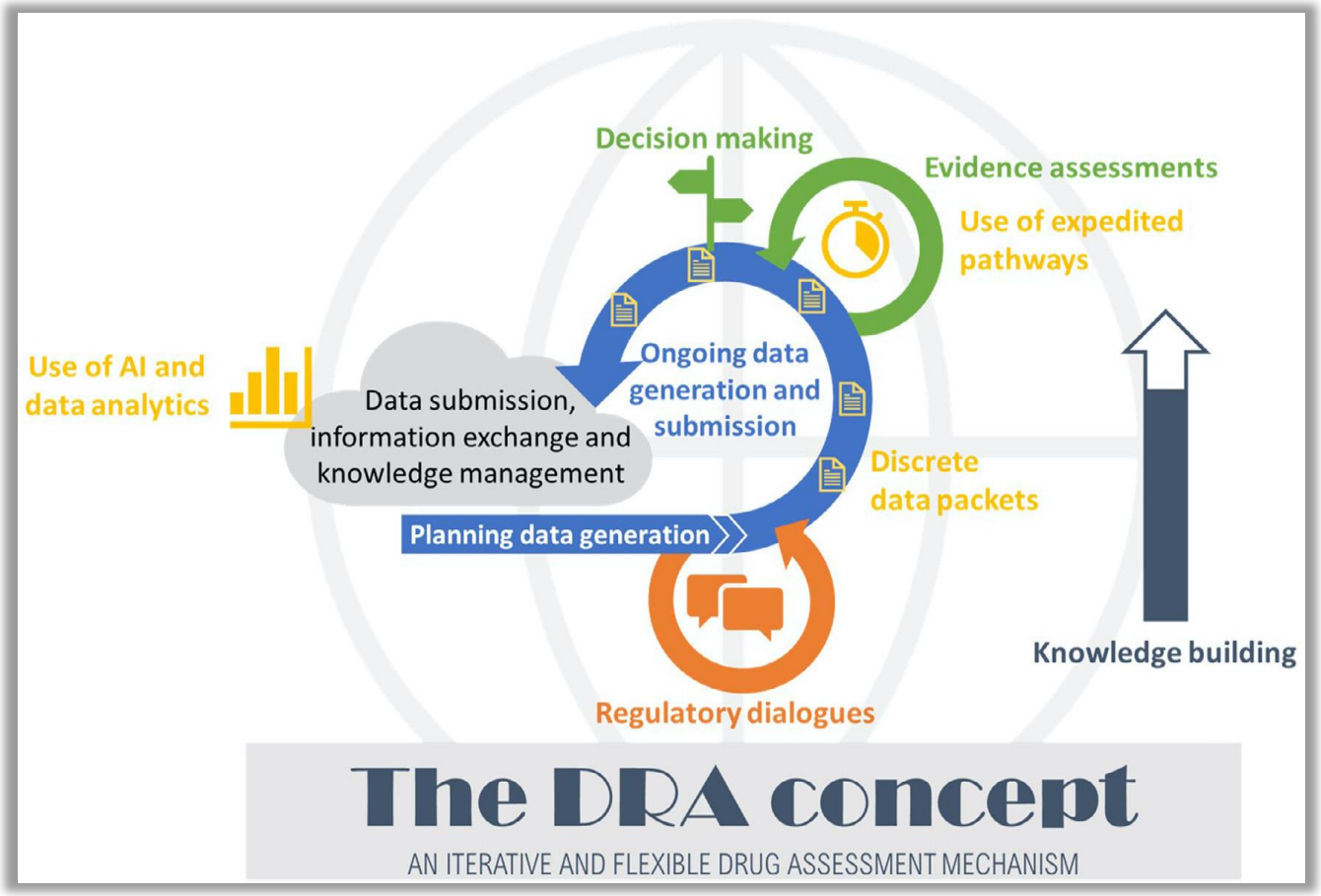


ANNEX I : PRIORITY RECOMMENDATIONS OF THE HMA-EMA JOINT BIG DATA TASK FORCE

I	Deliver a sustainable platform to access and analyse healthcare data from across the EU	Data Analysis and Real World Interrogation Network - DARWIN. Build the business case with stakeholders and secure funding to establish and maintain a secure EU data platform that supports better decision-making on medicines by informing those decisions with robust evidence from healthcare.
II	Establish an EU framework for data quality and representativeness	Establish an EU framework for data quality and representativeness. Develop guidelines, a strengthened process for data qualification through scientific advice, and promote across Member States the uptake of electronic health records, registries, genomics data, and secure data availability.
III	Enable data discoverability	Identify key metadata for regulatory decision-making on the choice of data source, strengthen the current ENCePP resources database to signpost to the most appropriate data, and promote the use of the FAIR principles (Findable, Accessible, Interoperable and Reusable).
IV	Develop EU network skills in big data	Develop a big data training curriculum and strategy based on a skills analysis across the network, collaborate with external experts including academia, and target recruitment of data scientists, omics specialists, biostatisticians, epidemiologists, and experts in advanced analytics and AI.
V	Strengthen EU network processes for big data submissions	Launch a 'big data learnings initiative' where submissions that include big data are tracked and outcomes reviewed, with learnings fed into reflection papers and guidelines. Enhance the existing EU PAS register to increase transparency on study methods.
VI	Build EU Network capability to analyse big data	Build computing capacity to receive, store, manage and analyse large data sets including patient level data (PLD), establish a network of analytics centres linked to regulatory agencies, and strengthen the network's ability to validate AI algorithms.
VII	Modernise the delivery of expert advice	Build on the existing working party structure to establish a Methodologies Working Party that encompasses biostatistics, modelling and simulation, extrapolation, pharmacokinetics, real world data, epidemiology and advanced analytics, and establish an Omics Working Party that builds on and reinforces the existing pharmacogenomics group.
VIII	Ensure data are managed and analysed within a secure and ethical governance framework	Engage with initiatives on the implementation of EU data protection regulations to deliver data protection by design, engage with patients and healthcare professionals on data governance, and establish an Ethics Advisory Committee.
IX	Collaborate with international initiatives on big data.	Support the development of guidelines at international multilateral fora, a data standardisation strategy delivered through standards bodies, and bilateral collaboration and sharing of best practice with international partners.
X	Create an EU big data 'stakeholder implementation forum'	Dialogue actively with key EU stakeholders, including patients, healthcare professionals, industry, HTA bodies, payers, device regulators and technology companies. Establish key communication points in each agency and build a resource of key messages and communication materials on regulation and big data.

Fonte: https://www.ema.europa.eu/en/about-us/how-we-work/big-data:

Dynamic regulatory assessment (DRA)



- Starting counter-clockwise from the bottom left (6 o'clock), early, iterative multi-stakeholder discussions will facilitate generation of discrete data packets (documents or data, 3 o'clock) for regulatory assessment (1 o'clock) supporting regulatory decision-making (12 o'clock).
- Advanced analytics (9 o'clock) could be applied to augment or even automate human postmarketing surveillance efforts.
- Over time, regulatory assessment(s) (perhaps expedited) will be performed as dynamic regulatory assessment (DRA) continues through the product's life cycle.
- Information technology facilitates information sharing and assessment, analysis (from multiple data sources), and institutional memory of regulatory actions (greyish cloud at 9 o'clock).
- The system will be cyber secured to protect patient and company confidential information.

AI = artificial intelligence

Herrero-Martinez E, Hussain N, Roux NL, MacDonald J, Mayer M, Palacios R, Kühler TC. Dynamic Regulatory Assessment: evolving the European Regulatory Framework for the Benefit of Patients and Public Health-an EFPIA View. Clin Ther. 2021 Nov 27:S0149-2918(21)00456-2. doi: 10.1016/j.clinthera.2021.11.001. Epub ahead of print. PMID: 34848082.

Looking to the future: How would regulation look like in 2030?

What will remain the same:

- Clinical trials remain the bedrock of clinical evidence generation
- Authorisation of medicines based on quality, safety and efficacy and positive benefit risk
- Decision-ready evidence relies on quality data and robust study methods

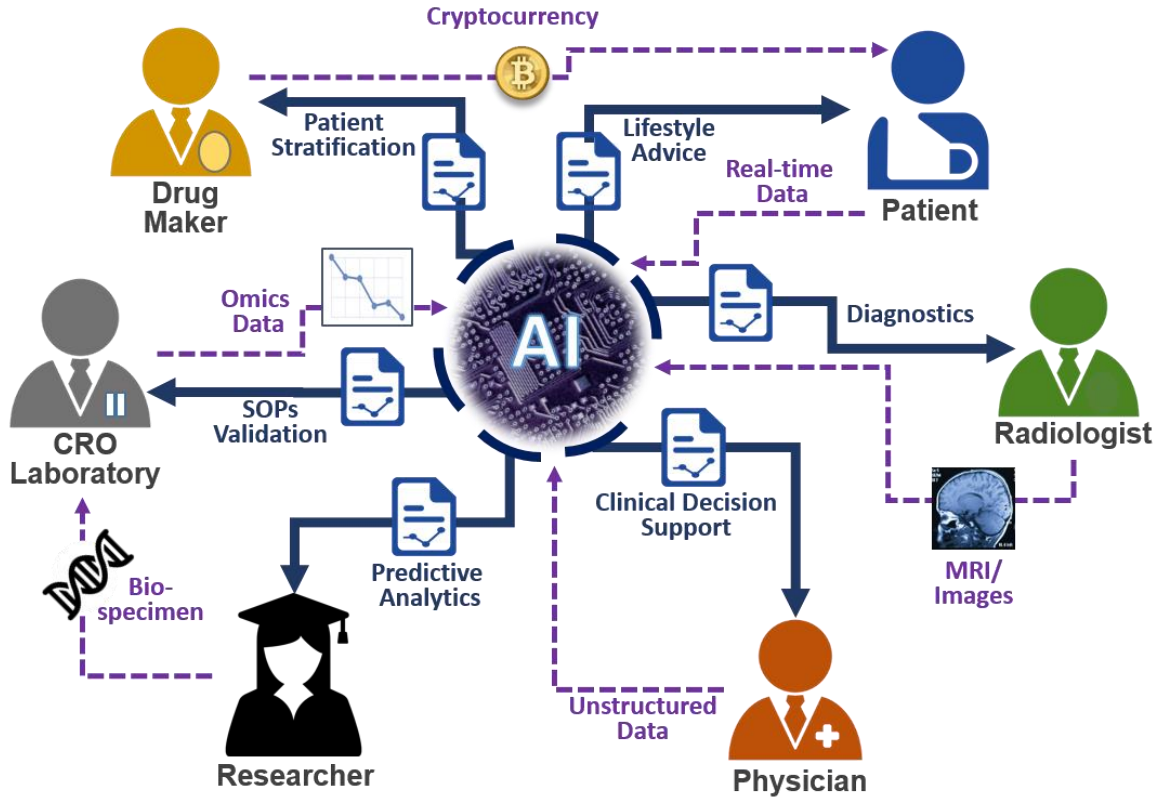
What will change:

- Role of real-world evidence established across spectrum of regulatory use cases
- Regulation more data driven: includes analysis of raw data from industry and RWD independent of industry
- Better evidence supports better decisions on medicines for patients

Fonte: Peter Arlett (EMA) Introductory session: What is on European regulator's mind? Where are we with the workplan 2021? What guidelines are planned to be updated? What is industry constantly missing in submissions? Session on Decentralized trials: What is the impact on evidence generation? 6th EFSPI Regulatory Statistics Workshop 13 September 2021

Profound transformation of the healthcare landscape

- Biotechnology and genomics are integrated with digitalisation, novel data generation, electronic health records;
- Validated models for analysis of large and unstructured data sets will become the norm, driven by AI or cognitive computing.



1. Artificial intelligence

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2. Blockchain

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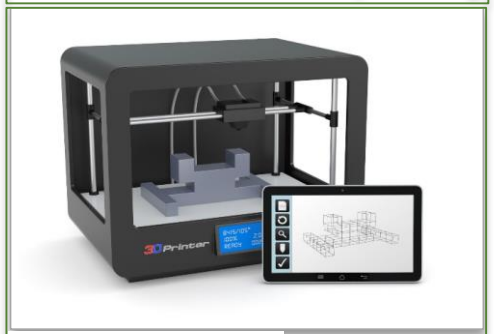
3. Open-source technologies

© Enzozo / Shutterstock.com

4. Telehealth technologies

© AndreySuslov/ Shutterstock.com

5. Three-dimensional printing



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European Parliament

Ten technologies to fight coronavirus

6. Gene-editing technologies

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7. Nanotechnology

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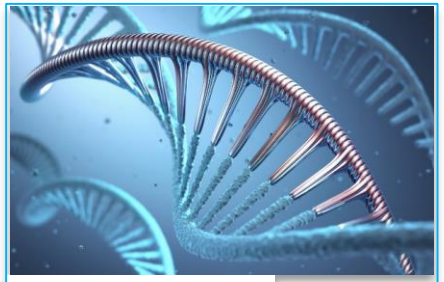
8. Synthetic biology



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9. Drones

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10. Robots

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CONCLUSIONI

- Ridefinire le regole pubblico privato per promuovere l'innovazione
- Definire l'innovazione
- Costruire nell'immediato sull'esperienza EMA per COVID
- Pianificare la generazione dell'evidenza pre-e post approvazione (RCT/RWE)
- Definire il valore terapeutico in maniera ciclica
- Integrare le regolamentazioni (de-frazionamento)
- Contestualizzare l'intervento terapeutico nella gestione della patologia

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“A series of reasonable decisions does not necessarily lead to a reasonable outcome”