



FONDAZIONE
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GIANNI BENZI
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XII Foresight Training Course

Innovative medicine and research: ethical, legal
and regulatory issues

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Health vulnerability and the European framework on access to orphan medicines

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Introduction

Definition of health vulnerability

- Usually restricted to **decisional** vulnerability
- **Individual perspective**
- **Decision-making capacity**, on the ability of the person to consent and to make rational decisions to protect his/her interests
- **Decisional vulnerability is not** the approach of this presentation

Introduction

Definition of health vulnerability

- Health vulnerability is meant as a **collective** perspective of vulnerability
- Health vulnerability will be used as a **public health concept**
- It is focused on **justice issues in health**, on
 - equity of access to health care (notably access to orphan medicines)
 - equity of access to research benefits and innovation

Introduction

Orphan diseases – Definition and facts

Conditions for orphan designation

- No satisfactory method of diagnosis, prevention or treatment of the condition
- Life-threatening, chronically or seriously debilitating condition
- Less than 5 cases in 10 000
 - (or when market is unlikely to ever be attractive enough to generate sufficient return on investment)

Rationale for European intervention

- About 7000 orphan diseases and 36 million patients in Europe
 - Scattered patients
- Scattered knowledge and expertise
 - Delays and errors of diagnostic and treatments
- Extremely high costs of research and low return on investment

Structure of the presentation

- I. The limits of the EU framework on clinical trials on orphan medicines**
- II. Regulatory challenges in light of innovative technological opportunities**

I. The limits of the EU framework on clinical trials on orphan medicines

- A. Initial framework
- B. Mitigated results
- C. Recent follow up actions

I. A. Initial framework

Incentives and tools offered by Regulation 141/2000

- Committee for Orphan Medicinal Products (COMP)
- Market exclusivity in the EU for 10 years
- Free protocol assistance from the EMA
- Fee reductions from the EMA

Funding for research and collaboration

- Growing amounts through framework programs from EC
- Expert groups within the European Commission (Rare diseases Task Force, EUCERD and since 2014 Expert Group on rare diseases)
- Funding and assistance in collaboration projects in patients' registries (Orphanet, Era Net, E-rare)

I. B. Mitigated results

Main EU reports / instruments

- 2008: EC communication and its impact assessment report
- 2009: Council of the EU recommendation
- 2017: EU resolution on improving access to medicines
- 2017: EC report “Rare diseases : a major unmet medical need”

Persistent lack of access

- Only 167 marketing authorisations (2% of the necessary treatments)
- Lack or delay in commercialisation
- Lack of reimbursement (difficulties to prove the added value)
- Instrumentalisation of the Orphan Drug designation for other purposes
- Cooperation in Europe is still poor

I. C. Recent follow up actions

Ongoing assessment of current systems

- 2017: Study on the efficacy of market incentives on actual access to orphan drugs
- 2018 Public consultations from the European Commission on several aspects of Regulation 141/2000
- Final evaluation expected by the end of 2019

Emphasis on the need for ELSI framework of collection, use and sharing of health data

- EC formulated this recommendation in its 2017 report
- February 2019: Launch of the European Platform on Rare diseases registration
 - make registries' data searchable at EU level
 - standardise data collection and data exchange

II. Regulatory challenges in light of innovative technological opportunities

A. Innovative technologies

B. European framework

C. Health vulnerability as a tool for orphan disease patient empowerment

II. A. Innovative technologies

Emerging opportunities

***In silico* trials are computer simulated trial:**

Machine learning techniques coupled with health data permit to create virtual subjects and stratify different responses to an experimental drug

Already applied especially for orphan paediatric diseases

Health data sharing:

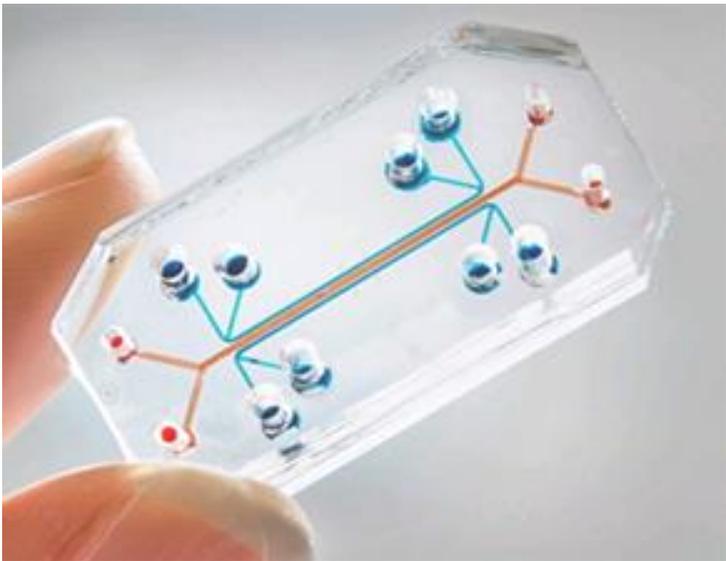
Computer simulation for **drug repurposing** in orphan diseases

High scale pharmacovigilance through online platforms assembling European or worldwide rare diseases patients' registries

II. A. Innovative technologies

How could it improve access to orphan medicines?

Scientific, economic and ethical reasons for data sharing



Source: <https://health.cxotv.news/2018/05/30/in-silico-clinical-trials-organs-on-a-chip/>

- Reduced costs
 - More research
 - Better affordability for patients
- Reduced time
 - Quicker marketing and commercialisation
- Reduced need of human participants
 - Less risky trials for patients
 - Palliate the low number of RD patients

II. A. Innovative technologies

Ethical and social challenges

Privacy risks

Pseudonymisation might be inefficient in the case of rare diseases

Social stigma on orphan disease

Discrimination in banking, insurance or work environment as orphan diseases are often chronic or life-threatening

Data management risks

Data sharing in clinical trials contradictory with patents, especially important for orphan medicines

Unreliable or biased data leads to machine learning bias

Automated decision making and profiling

II. B. European framework

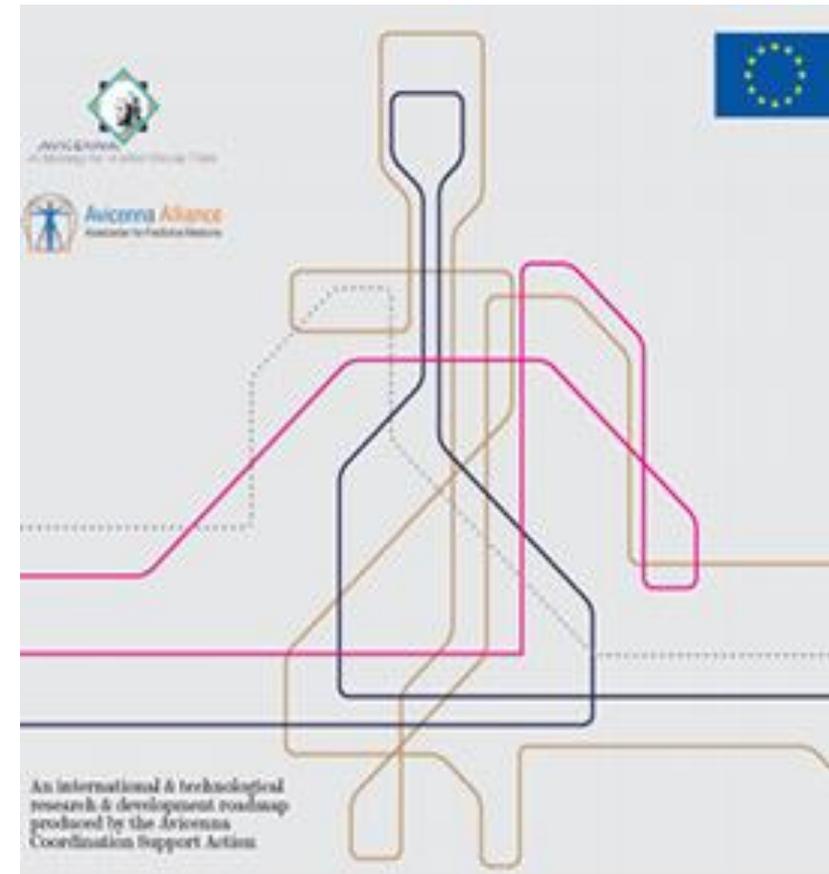
II. B. European framework on promoting innovation while protecting the privacy

Promoting innovation

- **H2020** funding of the Avicenna project on in silico trials
- European Platform on Rare diseases registration (and others like E-rare)
- **EMA Working group on modelling and simulation**
 - Enhancing competence and expertise
 - Developing standards for assessment in marketing authorisation applications for special populations
- EMA guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (into effect July 2019)



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in silico Clinical Trials:

How Computer Simulation will Transform the
Biomedical Industry

II. B. European framework on promoting innovation while protecting the privacy

Personal data protection and data sharing for health research

Council of Europe

- Convention 108+ on personal data protection
- Recommendation CM/rec(2019)2 on the protection of health related data
- European Parliament resolution of 14 March 2017 on fundamental rights implications of big data: privacy, data protection, non-discrimination, security and law-enforcement
- Recommendation on data resulting from genetic tests from 2016
- Recommendation CM/Rec(2010)13 automatic processing of personal data in the context of profiling

European Union

- 2016 General Data Protection Regulation
- A29WP guidelines
- 2019 Ethics Guidelines for trustworthy guidelines for Artificial Intelligence
- Increasingly disseminating FAIR Data principles

2016 Bottom up approach (academia, industry and funding agencies): Findable, Accessible, Interoperable, Reusable

II. C. Health vulnerability as a tool for orphan disease patient empowerment

Health vulnerability as a normative concept based on social justice

- Social justice and its extension to the health sector (health as a primary good)
- Capability theory (health as a meta-capability)
- Ethics of care (giving the means to one's own resilience)

International ethics instruments and principles

- Bioethics principles (notably beneficence and justice)
- WMA Declaration of Helsinki §§13, 19, 20 against underrepresentation in research
- 2016 CIOMS guidelines 1 and 3 against underrepresentation
- Big Health data as a common good for human kind (IBC 2017), idea of solidarity

II. C. Health vulnerability as a tool for orphan disease patient empowerment

A human rights approach to a public health concept

- Oviedo Convention, article 3: equitable access to health care of appropriate quality
 - Notably as its growing importance has been emphasized in the 20th anniversary conference of the Oviedo Convention
 - Additional Protocol on genetic testing, article 5
- EU: Growing importance of equality and non-discrimination with the Charter of Fundamental Rights
- Universal Declaration on Human Rights, article 27: right “to share in scientific advancement and its benefits
 - Declaration on the human genome and human rights, article 12

II. C. Health vulnerability as a tool for orphan disease patient empowerment

A prospective interpretation of the ECHR Case law

- Towards a legal claim for **states to actively promote a reliable and equitable knowledge production system** in the context of pharmaceutical product development
- Based on a broad interpretation of
 - The right to life
 - the right to information
 - the right private and family life
 - the right to health protection
- Growing importance of vulnerability in the ECHR case law

Conclusion

Vulnerability as a guiding value

For access to orphan medicinal product

For access to innovation

- Consensual
- Protection of individual rights and freedoms
 - Collective sense of solidarity and equity
 - Sense of priority
 - Triggers innovation

**Thank you
for your attention!**

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