Medicines & Healthcare products Regulatory Agency

# European regulatory approaches to drugs for rare diseases

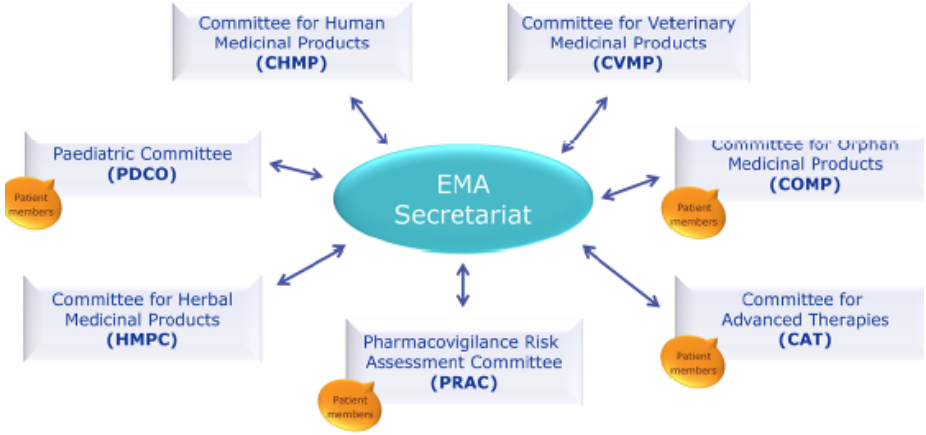
Rare International Dialogue Conference, Toronto, Canada

**Dr Daniel O'Connor – Medical Assessor - May 2019**

CPRD NIBSC MHRA

# EU regulatory framework

- Member States (MS) have one or more medicines Competent Authorities
- MHRA is UK medicines authority based in London – Canary Wharf
- European Medicines Agency (EMA) is agency of the EU based in The Netherlands
- EMA coordinates, through scientific committees, the evaluation of rare disease medicines




- MS work together in a network, shaped by Regulations, Directives & guidelines
- Extensive collection of EU scientific & regulatory guidance documents

# Guidelines and workshops

- Guidelines: basis for practical harmonisation of how MS/EMA interpret / apply the requirements for drug licensing

- Workshops tackle challenging areas of drug development

# Access to regulatory expertise

- MHRA offers:
  - Scientific advice service that can be requested at any stage of the development of a medicinal product, in face to face meetings
  - A broader scope meeting is also available - general approaches
  - Joint meetings with NICE (HTA body)
  - PIM designation meeting for Early Access to Medicines Scheme (EAMS)

- MHRA's Innovation Office provides a (free) single point of contact, to help companies / academics navigate regulatory processes and promote early dialogue
  - One stop shop service of access to the four regulators in the field of regenerative medicine and consolidated joined up advice (HRA, HFEA, HTA)

- EMA scientific advice and protocol assistance are given by the SAWP:
  - Protocol assistance for orphan drugs, parallel advice with the FDA/ HTA
  - Qualification of novel methodologies for medicine development

- EMA's Innovation Task Force (ITF)

# Committee for Orphan Medicinal Products

- The COMP is responsible for reviewing applications from sponsors seeking orphan medicinal product designation – monthly meetings (except August)

  - One member nominated by each Member State
  - Three members nominated by the European Commission including 2 patients' organisations
  - One member nominated by Iceland and Norway
  - Medicines for human use, not medical devices
  - No fee is charged for the procedure
  - Sponsors can be a company or an individual
  - Apply any stage in the development before the application for marketing authorisation is made

# Formal designation criteria (Regulation 141/2000)

A medicinal product shall be designated orphan medicinal product if the sponsor can establish:

(a) That it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating **condition** affecting no more than 5 in 10 000 persons in the Community when the application is made (so-called **prevalence** criterion), Or

if without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary **investment,** and

(b) That there exists **no satisfactory method** of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such a method exists, that medicinal product will be of **significant benefit** to those affected by the condition

# The condition

COMMENT

- Recognised distinct medical entities are generally considered valid conditions

- Defined in terms of their specific characteristics, e.g. pathophysiological, histopathological, clinical characteristics

## Defining orphan conditions in the context of the European orphan regulation: challenges and evolution

*Daniel J. O'Connor[1,12*], Maria E. Sheean[2,3,12], Matthias P. Hofer[2,12], Stelios Tsigkos[2], Segundo Mariz[2], Laura Fregonese[2], Kristina Larsson[2], Virginie Hivert[4], Kerstin Westermark[5], Frauke Naumann-Winter[6], Violeta Stoyanova-Beninska[7], Ingeborg Barišić[8], Giuseppe Capovilla[9], Armando Magrelli[10] and Bruno Sepodes[11]*

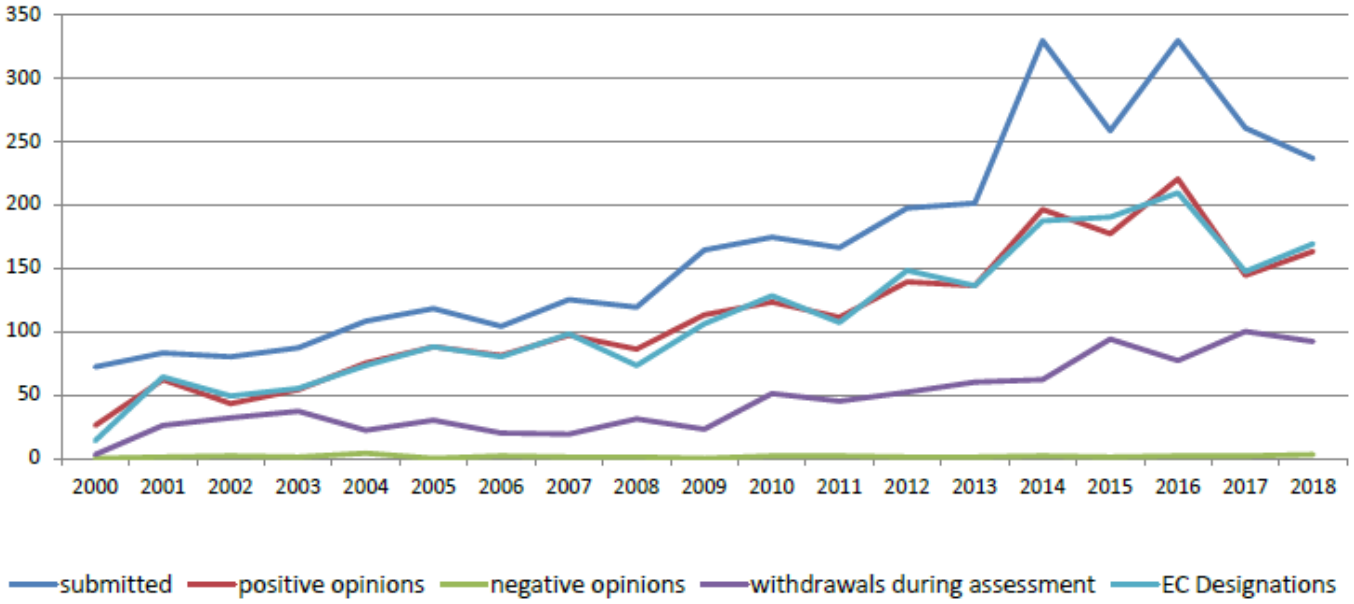
The definition and acceptability of an orphan condition is pivotal for the assessment of European orphan medicinal product designation applications, and consequently the eligibility for incentives. Here, based on the experiences of the Committee for Orphan Medicinal Products, we discuss how to define orphan conditions in the context of the European regulatory framework.

- Different degrees of severity or stages of a disease are generally not considered as distinct conditions

- Subset of a common condition: the fact that a subset of patients exists in whom the medicinal product is expected to show a favourable benefit/risk would generally not be sufficient to define a distinct condition

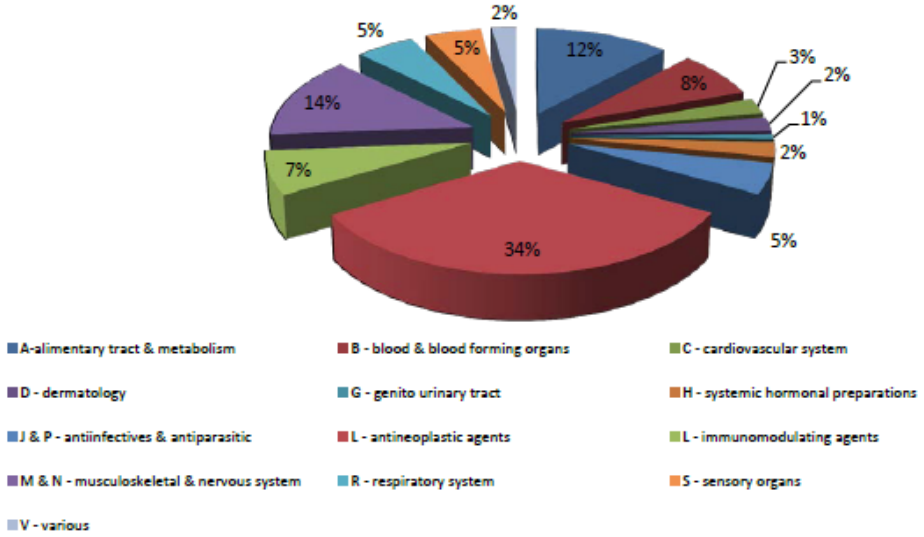
  - ➢ Unless patients in that subset present with distinct and unique characteristics that are essential for the medicinal product to carry out its action

# Orphan designations in numbers




- Estimated 5000–8000 rare diseases ~ 350 million people

- 2134 designations spread over 524 conditions (oncology products represents 34%)




**Source: EMA, 2018**

# Incentives

- **Fee reductions** - A special fund from the European Commission, agreed annually by the European Parliament, is used by the EMA for a variety of fee reductions

- **Protocol assistance** - EMA can provide scientific advice to optimise development and guidance on preparing a marketing authorisation dossier
  - Maximise the chances of the marketing authorisation being successful
  - Importance of requesting and adhering to scientific advice cannot be understated

- **Market exclusivity** - Member States shall not, for a period of 10 years, accept another application for the same therapeutic indication, in respect of a similar medicinal product

- **Regulatory flexibilities** - approval under exceptional circumstances, conditional marketing authorisation and expeditated approvals

  - More common for rare diseases

# Expeditated approvals

- A key challenge confronting regulators and other stakeholders is earlier patient access to innovative medicines, particularly in areas of unmet medical need
- Fine balance between ‘denying’ patients potentially useful drugs and approving products for which the drug development is considered as immature
- UK Early Access to Medicines Scheme (EAMS) aims to give access to unlicensed medicines and address some of the pressing patient access issues
- EMA’s Adaptive pathways, a scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine
- EMA’s PRIME is a scheme aimed at enhancing the support for the development of medicines that target an unmet medical need
  - Enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation

# Evolving regulation science

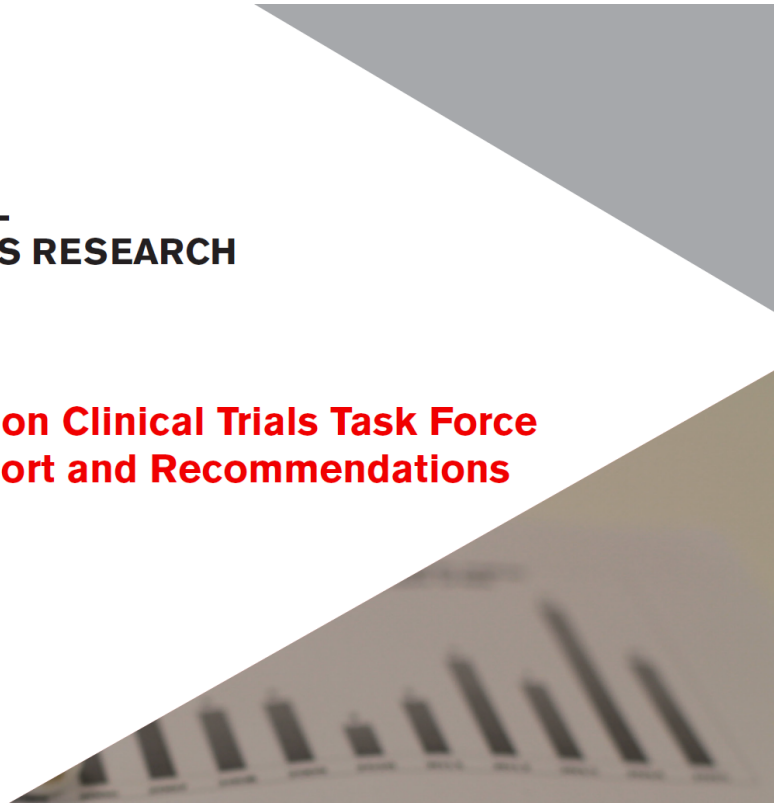
- Regulatory Science is a range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine

- Encompasses basic and applied medicinal science and social sciences, and contributes to the development of regulatory standards and tools

  - Small population clinical trials methodology
  - Small disease research – involving the patient more in regulatory decisions
  - Increasing regulatory agency collaboration
  - Orphan Drug Development Guidebook Task Force
  - Real world data complementing clinical trials
  - Drug repurposing

# Small population clinical trials methodology

- Adaptive randomisation design
- Bayesian design
- Crossover design
- Enhanced trial design
- Factorial design
- Group sequential design
- High-risk allocation design
- Platform design
- N-of-1 or single-subject design
- Parallel group design
- Patient preference trial
- Prospective inception cohorts
- Randomised controlled trials
- Randomised withdrawal, and early escape designs
- Sample size re-estimation
- Sequential Multiple Assessment Randomised Trial (SMART) design
- Small n Sequential Multiple Assignment Randomised Trial (snSMART)



# 7th Framework initiatives - small-population research methods

- 3 EU projects to explore new approaches for clinical studies in small populations within the 7th Framework Programme: IDEAL, InSPiRe & ASTERIX

- Aim to translate and promote results and novel methodologies into tangible recommendations to advance the clinical research and development of medicines and new treatments for patients with rare diseases / personalised medicines

- EMA workshop in March 2017 discussed progress
  - ➢ Feed into regulatory system?

# Small disease research – involving the patient

- The patient is a key partner in drug development, enhancing the understanding of the disease and treatment impact, helping to select what is important and most relevant to measure

- Increasing involvement of the patient in EMA scientific advice meetings

## Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada

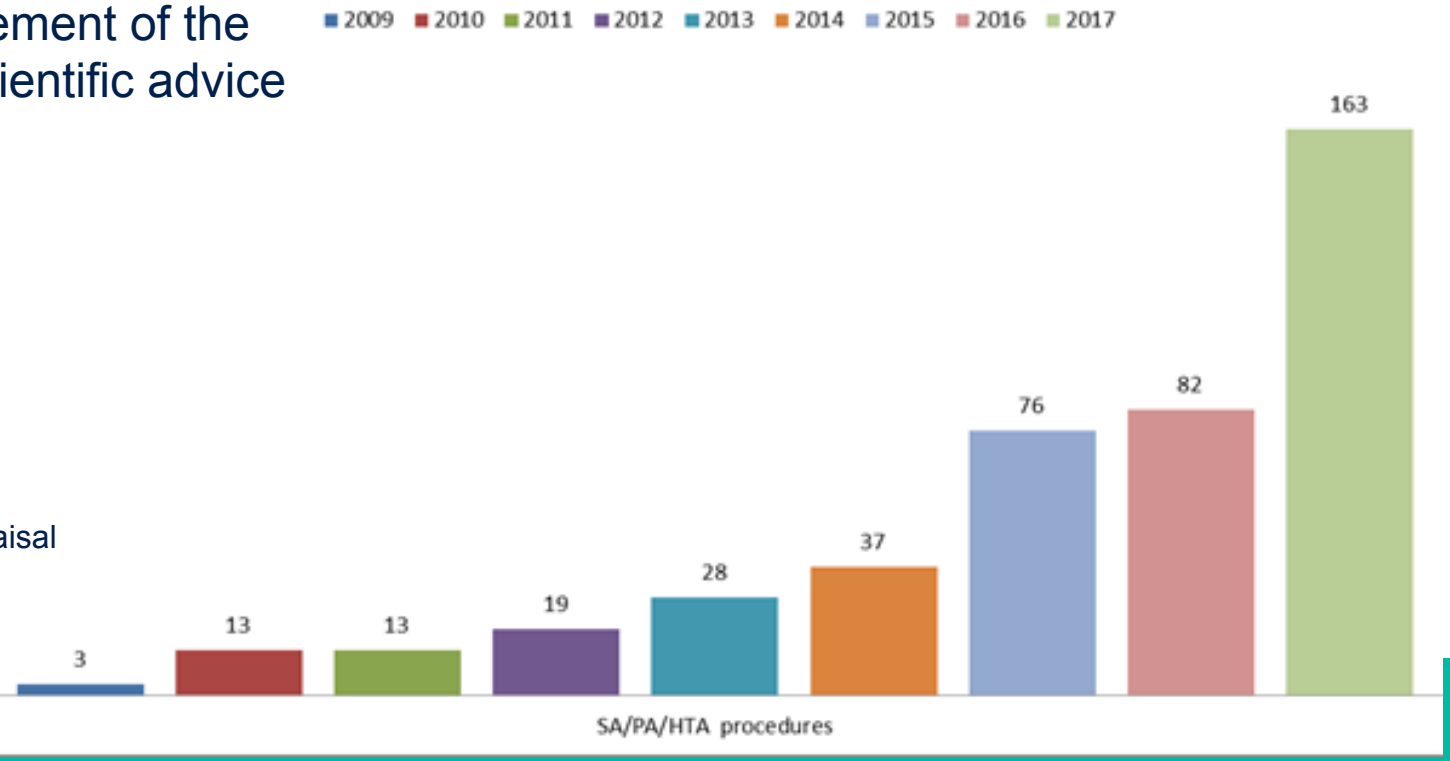
*Paul G Kluetz, Daniel J O'Connor, Katherine Soltys*

The clinical development of cancer therapeutics is a global undertaking, and incorporation of the patient experience into the clinical decision-making process is of increasing interest to the international regulatory and health policy community. Disease and treatment-related symptoms and their effect on patient function and health-related quality of life are important outcomes to consider. The identification of methods to scientifically assess, analyse, interpret, and present these clinical outcomes requires sustained international collaboration by multiple stakeholders including patients, clinicians, scientists, and policy makers. Several data sources can be considered to capture the patient experience, including patient-reported outcome (PRO) measures, performance measures, wearable devices, and biosensors, as well as the careful collection and analysis of clinical events and supportive care medications. In this Policy Review, we focus on PRO measures and present the perspectives of three international regulatory scientists to identify areas of common ground regarding opportunities to incorporate rigorous PRO data into the regulatory decision-making process.

*Lancet Oncol* 2018; 19: e267-74

See Comment page 595

Oncology Center of Excellence, US Food and Drug Administration, Silver Spring, MD, USA (P G Kluetz MD); Medicines and Healthcare Products Regulatory Agency, London, UK (D J O'Connor PhD); and Therapeutic Products Directorate, Health Products and Food Branch, Health Canada, Ottawa, ON, Canada




**Source EMA, 2017**

SA: scientific advice

PA: Protocol assistance

HTA: Health Technology Appraisal

# Innovative Medicines Initiative project – Paradigm

- **P**atients **A**ctive in **R**esearch and **D**ialogues for an **I**mproved **G**eneration of **M**edicines – Paradigm - is a public-private partnership, co-led by the European Patients' Forum and EFPIA

- Provide a unique framework that enables structured, effective, meaningful, ethical, innovative and sustainable patient engagement and demonstrates the 'return on the engagement' for all players

- Develop processes and tools for three key decision-making points:
  - Research priority setting
  - Design of clinical trials
  - Early dialogue

- Ensure maximum synergies with other initiatives focusing on the patient's voice in the life cycle of medicines

# Increasing regulatory agency collaboration

- The EMA, FDA, HealthCanada, TGA, Swissmedic… hold regular meetings by phone or videoconference in so-called ‘clusters’

  - Objectives include sharing review information of marketing authorisation applications

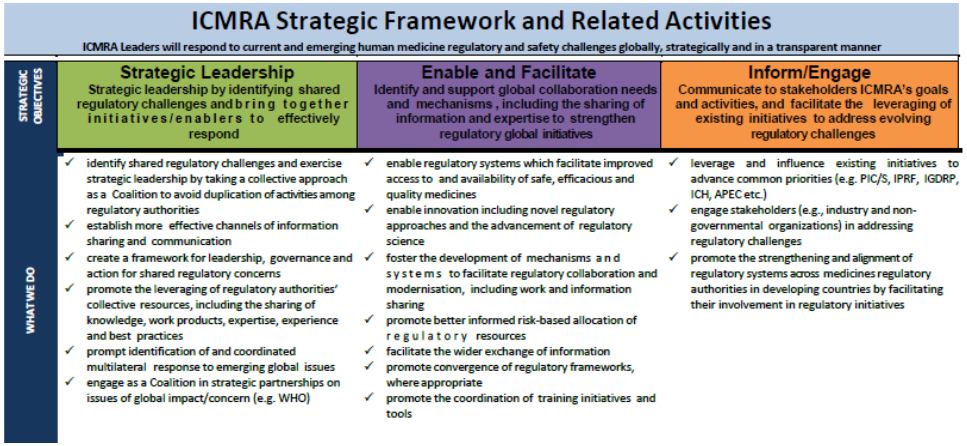
- In June 2016, the EMA and FDA set up a new cluster on patient engagement, in order to reinforce collaboration on patient engagement

- Other collaborative activities include parallel scientific advice and qualification procedures of Clinical Outcome Assessments (COAs) with FDA

- FDA and EMA share information on orphan medicines under their confidentiality arrangement, have regular teleconferences and the two authorities have also developed common procedures for applying for orphan designation, collaborate on workshops

# International Coalition of Medicines Regulatory Authorities (ICMRA)

- ICMRA is a voluntary, strategic coordinating and leadership entity of regulatory authorities that work together to address current and emerging human medicine regulatory and safety challenges – over 30 organisations
- Provide direction for areas and activities common to many regulatory authorities' missions
- Identify areas for potential synergies
- Leverage existing initiatives/enablers and resources

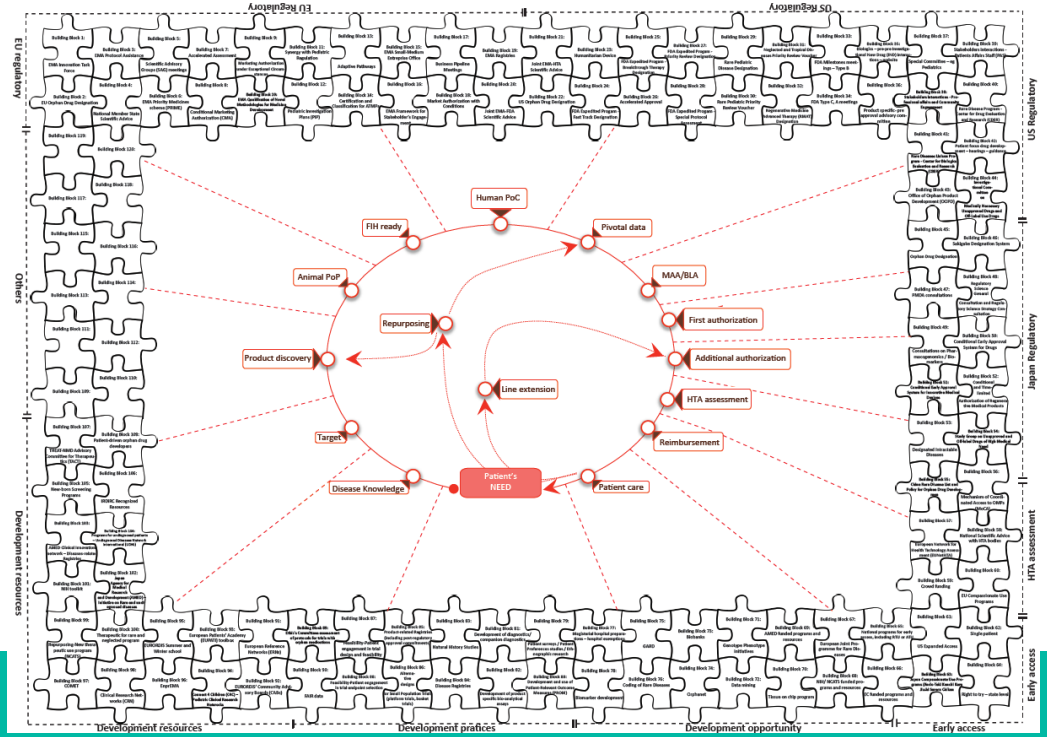



- Provide a global architecture to support enhanced communication, information sharing, crisis response and address regulatory science issues

# Orphan Drug Development Guidebook Task Force - IRDIRC

- Project aims at creating a simple guidebook for academic and industrial drug developers describing the available tools and initiatives specific for rare disease development and how best use them

- Task Force members from Europe, US, Japan and China
  - Series of interlinking ‘Building Blocks’

# Real world data complementing clinical trials

- Patient registries are organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time

- An EMA cross-committee task force is conducting an initiative:
  - Identify and evaluate existing data sources
  - Develop a methodological toolkit for establishing new registries if needed

- The initiative started with a pilot phase to test different components of the patient registry strategy

- Main objective is to facilitate the use of patient registries, to collect and analyse high quality data that may inform regulatory decisions

# Real world data complementing clinical trials

- Based on the pilot phase and several specific disease–related workshops, the cross-committee task force published a paper:
  - Use of patient disease registries for regulatory purposes – methodological and operational considerations (Nov 2018)
  - Out for public consultation until the end of June 2019
  - https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries
- Focuses on important principles from a regulatory perspective and makes proposals on what might be considered good registry practice to support collection of high quality registry data
- EMA is willing to support interactions and provide tools to facilitate recognition of disease registries as data sources to conduct studies for regulatory purposes
  - Natural history, evidence of efficacy, validation of endpoints, contextulise single arm efficacy?

# European Reference Networks (ERN)

- European Reference Networks (ERNs) are virtual networks involving healthcare providers across Europe

- Aim to tackle complex or rare diseases and conditions that require highly specialised treatment and a concentration of knowledge and resources
  - Pooling knowledge, expertise, registries, data and funding
  - Maximising synergies between Member States

- Following a call for proposals in July 2016, the first ERNs were approved in December 2016 and launched in March 2017

- Over 900 healthcare units from nearly all EU Member States will work together in 24 thematic networks

- By cooperating and exchanging life-saving knowledge, patients across the EU will have access to the best expertise available

- https://ec.europa.eu/health/sites/health/files/ern/docs/2017_brochure_en.pdf

# Drug repurposing

- Dynamic and innovative field of drug development
- MHRA pilot: propranolol for angiosarcoma
- Engagement with the regulators is standard practice for pharmaceutical companies, but not for the academic and not-for-profit sector
- '*For those of us who had not previously participated in a scientific advice meeting, the experience proved to be extremely useful*'

COMMENT

## Scientific advice — is drug repurposing missing a trick?

*Pan Pantziarka*[1,2]

Scientific Advice meetings are a mechanism to improve communications between drug developers and regulators during the drug-development process. While standard practice for industry, the benefits provided by these meetings are under-utilised by academia. In the context of drug repurposing, can scientific advice, as part of a proposed new R&D tax credits scheme, help to unblock some of the obstacles in the way to clinical adoption?

- EC Expert Group on Safe and Timely Access to Medicines for Patients
- Working group has developed elements of a repurposing pathway including the role of a Champion

# UK Strategy for Rare Diseases

- 2013: Publication of the UK strategy for rare diseases

- 2018: Rare diseases implementation plan for England
  - Seen as a landmark for patients
  - Creation of opportunities for patient engagement through the Rare Disease Policy Forum
  - Improve the ‘diagnostic odyssey’ of rare diseases patients
  - Continue progress of the 100,000 Genomes Project
  - Increase research activities through the National Institute for Health Research

- 2019: update to the Implementation Plan for England
  - Theme 1: Empowering Those Affected by Rare Diseases
  - Theme 2: Identifying and Preventing Rare Diseases
  - Theme 3: Diagnosis and Early Intervention
  - Theme 4: Coordination of Care
  - Theme 5: The Role of Research in Rare Diseases
  - Actions to implement the 51 commitments (2019/20)

Department of Health & Social Care

# Summary and perspectives

- Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients with more common diseases
- The EU orphan drug Regulation offers important incentives for the development and marketing of medicinal products for rare diseases
- Interest in developing drugs for rare diseases has increased substantially, reflected in the numbers of orphan designation applications
- Generating the best evidence base as possible can be achieved through rigorous planning and early engagement with the regulatory authorities
- Regulatory science changes and is responsive to changing science and public health needs; interest in earlier approvals, novel clinical trial designs, real world data et al
- Personalised medicine is challenging the traditional definition of a ‘condition’

Thank You

daniel.oconnor@mhra.gov.uk

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