



Medicines & Healthcare products
Regulatory Agency

Rare diseases and orphan drugs: A Regulator's (clinical) Perspectives

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Disclaimer: These views are my own and should not be considered to be the views of the MHRA and or EMA

EU regulatory framework

- Member States (MS) have one or more medicines Competent Authorities
- For example, the MHRA is UK medicines authority based in London
- The European Medicines Agency (EMA) is an agency of the EU
- The EMA coordinates, through its scientific committees, the evaluation of new medicines under the centralised procedure scope:
 - CHMP, COMP, PRAC, CAT & PDCO
- MS and the EMA work together in a regulatory network, shaped by Regulations and Directives and guidelines
- Opportunities for scientific advice nationally & EMA Scientific Advice Working Party
- Extensive collection of EU scientific & regulatory guidance documents

What is a small population group?

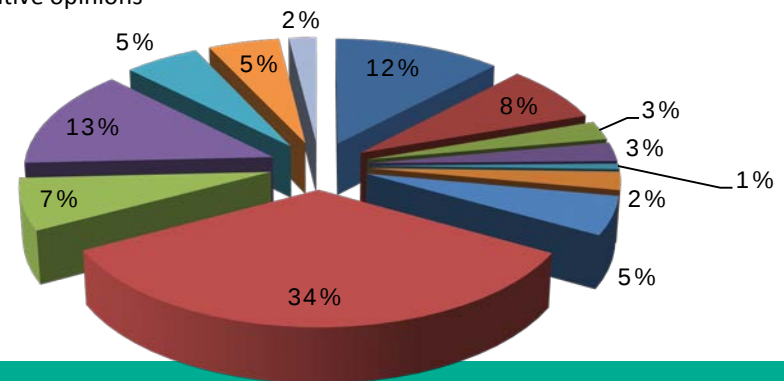
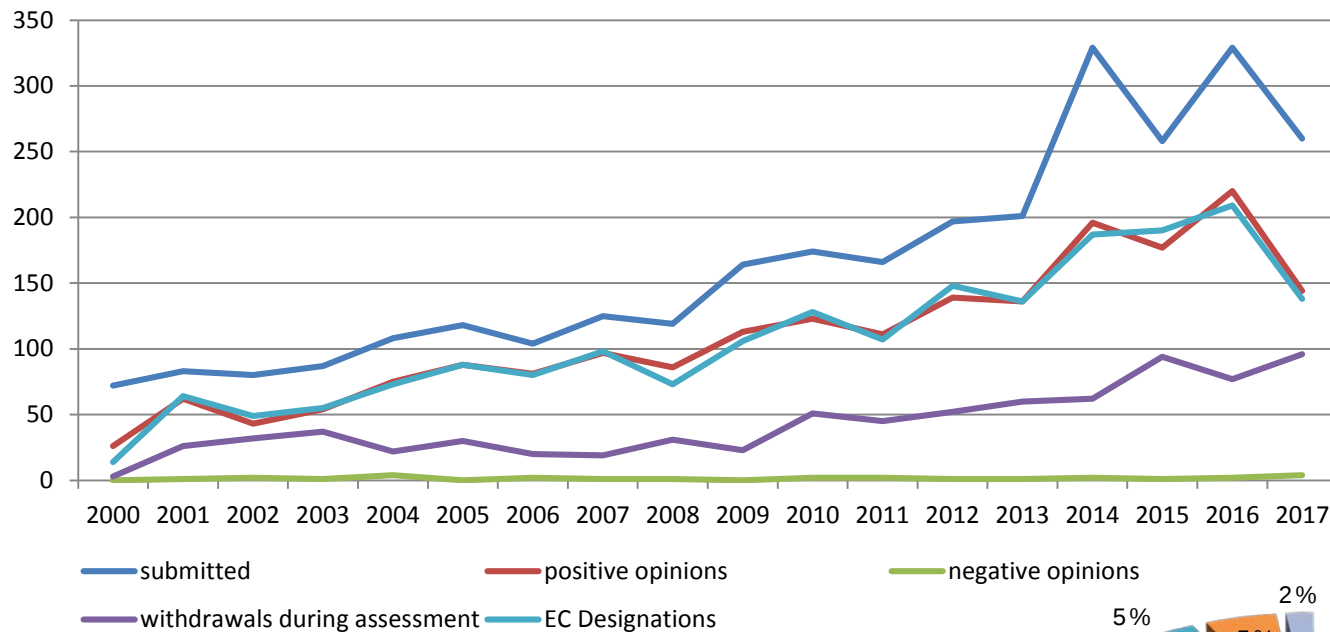
- How small is small? What is small?
- At COMP (EMA orphan committee) we work with 'defined' rare conditions, where research by definition involves small numbers of patients
- The main regulatory definition of small is found in the orphan drugs regulation
 - Prevalence of the condition in the EU must not be more than 5 in 10,000
 - Regulatory impact with orphan incentives (fees, protocol assistance, market exclusivity), eligibility criteria for conditional marketing etc.
- There is also a new description of an ultra rare condition in the Clinical Trial Regulation defined as fewer than 1 in 50,000
 - Ultra rare CTs should be fostered, rapid assessment is of particular importance for ultra rare and rare

Orphan drug regulation – why?

- Stimulate the development and marketing of drugs for rare diseases
- Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients
- The pharmaceutical industry unwilling to develop these medicinal products under normal market conditions
- Some conditions occur so infrequently that the cost of developing and bringing a drug to the market would not be recovered by the expected sales
- An orphan drug is one that has been developed to treat one of these rare conditions
- Free to apply – specific grants attached to orphan designated products (H2020)

Orphan conditions

- Estimated 5000–8000 rare diseases affecting around 350 million people
~1800 designations spread over 450 separate conditions (oncology products represents 34%)



The rise of the small population - cancer

- Clinical application of biomarkers has resulted in identification of many 'rare' cancers within common cancer types
- Shift from histological classification to molecular classifications
- A common theme in small population research is that there are usually insufficient numbers of patients to carryout a 'standard' clinical development programme - phase I, II & III (confirmatory) trials
- Data to support regulatory decision making may rely on extrapolation of the data between different tumour types e.g. basket studies



Subsetting in common diseases

- Subset of a common condition (prevalence > 5 in 10, 000)
 - 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
- A subset of a disease could be considered a valid condition if patients in that subset present with distinct and unique characteristics that are essential for the medicinal product to carry out its action
- Challenging to define as an orphan condition per se – a rare event!



Flexibility in the FDA approach to orphan drug development

Nina L. Hunter, Gayatri R. Rao and Rachel E. Sherman

Scientific advances, in combination with government incentives and commercial opportunity, have fuelled strong investment in orphan drugs, resulting in many innovative therapies.

- ‘FDA will need to take advances in genomics and precision medicine into account as it considers what constitutes an orphan disease or condition’
 - Whether a disease should be defined in a tissue agnostic manner
 - May support the designation and approval of certain drugs across multiple rare tumour types
 - As more targeted therapies are developed, more drugs may qualify for orphan designation based on orphan subsets

Small populations - what are the challenges?

- Clinical development programmes which involve large numbers of patients are not be feasible
- The total number of eligible subjects may be very limited, which impacts the choice of study design and the statistical methodology
- There can be challenges in recruiting the necessary number of study subjects, where investigators may 'compete' for the same patient in crowded areas;
 - Screen many more patients to find eligible recruits
 - Coordination of numerous clinical study sites throughout the world
- Smaller studies are also more susceptible to the effects of variability, and missing data is more likely to have a greater impact on the study conclusions

What are the challenges?

- Scarcity of expertise in some disease settings may impact the ability to conduct the study in all geographical areas
- Lack of knowledge on the natural history of the disease may impact the selection of the most appropriate endpoints
- Disproportionate number of rare diseases affect children, adding to the complexity of trial designs
- Policy makers, including medicines regulators and medicines payers, have to make decisions on less data, which can imply decisions made with a greater degree of uncertainty
- Smaller pre-market exposure equates with increased importance of and emphasis on post-market monitoring and data collection
 - What is the role of real world evidence?

Impact of 'small' on drug development?

- For new products entering phase III trials, less subjects are studied in rare diseases:
 - Median of 538 patients enrolled in orphan drug trials before phase III
 - 1,558 in non-orphan drug trials
- Less subjects are included across the clinical trial development
 - Rare disease trials enrolled a median of 29 patients per trial
 - 62 patients for non-rare disease trials
- Rare disease trials are more likely to be of single arm design
 - 63.0% vs. 29.6% for non-rare disease trials
- Source: International Rare Diseases Research Consortium report (July 2016):
 - Methodologies for Clinical Trials: Small Population Clinical Trials: Challenges in the Field of Rare Diseases
 - Workshop to identify points of agreement between the different stakeholders regarding non-classical designs
 - http://www.irdirc.org/wp-content/uploads/2016/11/SPCT_Report.pdf

Small disease research – trial design

- Randomised controlled trials may be difficult to design and conduct for small populations
 - What can be done and what are the alternatives?
- There is no magic bullet for coping with small populations of patients in clinical trials
- Regulatory guidance is available – general and disease specific
- Drug developers have the possibility to seek scientific advice from regulatory authorities
 - Increasing interest in joint advice with HTA



Small disease research – alternative trial designs

- 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)

**INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM**

**Small Population Clinical Trials Task Force
Workshop Report and Recommendations**

July 2016

Small disease research – regulatory views

- The need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results; the latter being the most important
- There are no special methods for designing, conducting or analysing clinical trials but there are approaches to increase the efficiency of clinical trials
- Most regulatory guidelines, including those on clinical trial methodology, are also applicable to rare diseases
- Controlled evidence on efficacy and safety of a new treatment may not be possible in all circumstances but
 - Controls and comparator groups remain very important and are expected to be utilised where ethical and feasible

Small disease research – regulatory views

- Detailed knowledge of the epidemiology and pharmacology of the medicine may help when designing studies, helping to identify sources of heterogeneity
- Scientifically justified surrogate endpoints may be acceptable but their relationship to clinical efficacy must be clear
- Patient registries may supply important information on the natural course of the disease, helping in the assessment of efficacy and safety, and as a source for historical controls
- It is strongly recommended that scientific advice/protocol assistance be sought

- Guidelines provide a basis for how MS/EMA interpret & apply the requirements for demonstration of quality, safety & efficacy for drug approval



London, 27 July 2006
Doc. Ref. CHMP/EWP/83561/2005

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

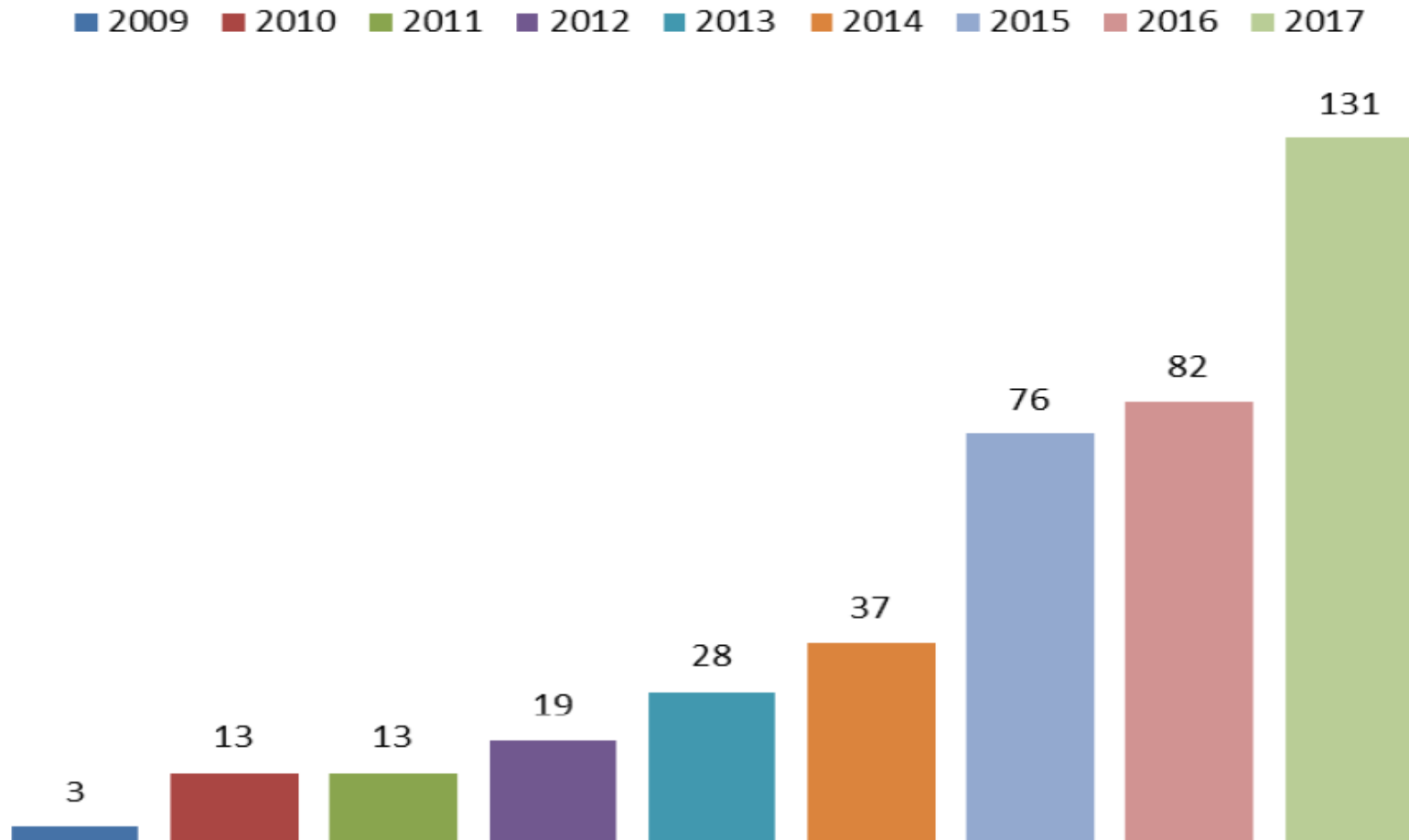
DRAFT AGREED BY EFFICACY WORKING PARTY / AD HOC GROUP ON CLINICAL TRIALS IN SMALL POPULATIONS	May 2002 – January 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	March 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	September 2005
AGREED BY EFFICACY WORKING PARTY	July 2006
ADOPTION BY CHMP	27 July 2006
DATE FOR COMING INTO EFFECT	1 February 2007

Small disease research – involving the patient

- Maximising the participation of eligible subjects is key and this can be achieved through international and multicentre collaboration, and active engagement with patient advocacy groups
- Adequate patient education by research staff can also help ensure that the dropout rates and loss to follow up are minimised
- For severe rare diseases, travel to research centres may be impossible
 - Solutions may include monitoring patients remotely, setting up community centres to include patients in trials
- Patient experiences and input can add a valuable dimension to scientific advice requests and regulatory decision making, including endpoint selection

EMA patient regulatory activities

- Patient involvement in regulatory activities e.g. protocol assistance and scientific advice, is growing and diversifying year on year:



Small disease research – safety data

- Safety is an essential component of the benefit-risk assessment
 - Often a scientific advice question - is my safety database of sufficient size?
 - What would constitute an adequate safety data? Challenging to define
 - Clinical trial data alone may be very limited with regards to safety profile
- For a complete picture, all relevant data sources should be considered:
 - Registry data, electronic health records, signals from non-clinical data, extrapolation, compassionate use setting
- Risk management plan & post-marketing/ post-approval safety data become key to the regulatory approval

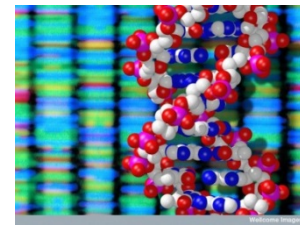
Small disease research – regulatory flexibilities

- The challenges of coping with small populations of patients in clinical trials are recognised through flexibilities in the regulatory framework
- In order to meet unmet medical needs of patients and in the interest of public health:
 - Approval under exceptional circumstances: feasible to grant marketing authorisations on the basis of less complete data than is normally required
 - Conditional marketing authorisation: Benefit of immediate availability outweighs the risk of less comprehensive data than normally required
 - 10 year report July 2006 – June 2016
 - 30 CMAs including 24 targeting debilitating/ life-threatening conditions & 14 orphan medicines
 - 17 oncology therapeutic area
 - CMA converted to a standard MA within an average of 4 years

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
 - It encompasses basic and applied medicinal science and social sciences, and contributes to the development of regulatory standards and tools
- Single arm trials:
 - EMA & ESMO, workshop on single-arm trials including the strengths and weaknesses of different approaches
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/05/event_detail_001285.jsp&mid=WC0b01ac058004d5c3
- Small population clinical trials task force workshop:
 - EMA & the International Rare Disease Research Consortium (IRDiRC) workshop to identify points of agreement between the different stakeholders regarding non-classical designs
<http://www.irdirc.org/recommendations-for-the-design-of-small-population-clinical-trials/>

Evolving regulation science



- Challenges for the approval of anti-cancer immunotherapeutic drugs:
 - EMA-CDDF joint meeting, challenges on how to bring these agents through regulatory approval and into clinical practice.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2015/12/event_detail_001244.jsp&mid=WC0b01ac058004d5c3

- Addressing challenges of innovative cancer immunotherapy medicines workshop:
 - Workshop discussing the scientific and regulatory challenges of immunotherapy medicines based on genetically modified T-cells

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/08/news_detail_002591.jsp&mid=WC0b01ac058004d5c1

- Workshop on site and histology – Independent indications in oncology :
 - Workshop discussing when a viable option and the associated challenges in terms of drug development

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/11/event_detail_001550.jsp&mid=WC0b01ac058004d5c3

7th Framework initiatives

- European Union has funded three projects to explore new approaches for clinical studies in small populations within the Seventh Framework Programme: IDEAL, InSPiRe & ASTERIX
- EMA workshop in March 2017 discussed progress
- Feed into regulatory system?

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/02/event_detail_001393.jsp&mid=WC0b01ac058004d5c3

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FP7

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Research and Innovation funding 2014-2020

FP7 was the European Union's Research and Innovation funding programme for 2007-2013. The current programme is Horizon 2020 but there are many projects funded under FP7 which are still running.

19 January 2016 – the Commission adopts ex-post evaluation of FP7

The Commission adopted today a package on the ex-post evaluation of the 7th Framework Programme. This consists of a Communication responding to the recommendations of an external High Level Expert Group and a Staff Working Document in which the Commission services have evaluated FP7 on the basis of the five evaluation criteria of the Better Regulation package (efficiency, effectiveness, coherence, relevance and EU added value).

EU RESEARCH FUNDING 2007-2013
7TH FRAMEWORK PROGRAMME
EVALUATION SNAPSHOT

- Press Release: EU research funding boosts scientific excellence and competitiveness, report finds
- Commission presents its evaluation of the 7th Framework Programme for Research
- Q&A on the Evaluation of the 7th Framework Programme for Research 225 KB
- Communication on the Ex-Post Evaluation of FP7 255 KB
- Annex to the Communication 250 KB
- Staff Working Document accompanying the Communication 3.0 MB
- Executive Summary of the Staff Working Document 120 KB

Related sites

- Innovation Union
- European Research Council
- Joint Technology Initiatives (JTIs)
- Article 185 Initiatives
- Technology Platforms
- Regional aspects of FP7
- EBA
- ERAWATCH
- Practical Guide to EU Funding
- Participant portal
- FAQs about FP7
- The CORDIS guide to FP7 (mainly for participants)

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Real world data complementing CTs

- Patient registries are organised systems that use observational methods to collect uniform data over time
- An EMA cross-committee task force on registries is conducting an initiative to 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 and if it meets regulators' and other stakeholders' data and information requirements
- The main objective is to facilitate the use of patient registries, in order to collect and analyse high quality data that can inform regulatory decisions
- Role of the European Reference Networks to collect real world data?
- Recent EMA meeting to discuss how ERN's can add value to clinical research

Repurposing medicines

- Drug repurposing is the process of identifying a new use for an existing drug in an indication outside the scope of the original indication
 - Could lead to faster development times, reduced costs
- In the broadest view, repurposing might include:
 - ❖ New therapeutic uses for already known drugs
 - ❖ Developing different formulations for the same drug
 - ❖ Creating new combinations of drugs previously used as separate products
 - ❖ Creating new combinations of drugs with medical devices
- Identifying repurposing opportunities comes from a variety of processes including knowledge mining of existing scientific databases, in silico approaches, in vitro and in vivo experiments, clinical observations, epidemiology and post-hoc analysis
 - Drug repurposing constitutes a dynamic field of drug development that can offer real benefits to patients

Repurposing medicines

- There are regulatory incentives to support repurposing, and ongoing regulatory initiatives at an EU and UK level looking closely at drug repurposing issues
- The STAMP has identified a number of barriers and potential solutions from case studies including:
 - Perceived lack of interest from & difficulties in engaging with the pharmaceutical industry
 - Consideration of the need for specific incentives to support the uptake of new indications and how to identify an ‘interested’ manufacturer
- Next steps include proposals from industry regarding a repurposing framework
- What might the data requirements be?

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?

Earlier access to medicines

- 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
 - With greater medical needs, it is acceptable to make decisions based on a greater degree of uncertainty in the data
- In 2014, two regulatory initiatives were launched to try and address some of the pressing patient access issues:
 - A European initiative, adaptive (licensing) pathways, an emerging concept of *‘staggered marketing authorisation approval’*, using existing regulatory tools
 - A UK initiative, **E**arly **A**ccess to **M**edicines **S**cheme (EAMS), which aims to give access to unlicensed medicines

Earlier patient access: adaptive pathways

- EMA ran a pilot project between March 2014 - August 2016 to explore the practical implications of an adaptive pathways concept
 - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp
- Adaptive pathways can be defined as a prospectively planned, iterative approach to bringing medicines to market, initially targeting the development in a well-defined group of patients that is likely to benefit most from the treatment:
 - Using the existing regulatory framework for medicines
 - Multistakeholder input and dialogue into development pathways
 - Real-world data can complement the evidence collected from clinical trials
 - A final pilot report was published in August 2016

Earlier patient access: PRIME: priority medicines

- PRIME is an EMA scheme aimed at enhancing the support for the development of medicines that target an unmet medical need, launched in March 2016
- The scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so medicines can reach patients earlier
- PRIME builds on the existing regulatory framework:
 - Proof of concept phase: availability of preliminary clinical evidence to demonstrate the promising activity of the medicinal product
 - Proof of principle phase: In exceptional cases, applicants from the academic and SME sectors only may submit an eligibility request at an earlier stage of development with compelling nonclinical data and first in man studies

Summary and perspectives

- Regulatory requirements evolve as regulators gain experience and react to changing science, and public health needs
- Generating the best evidence base as possible can be achieved through rigorous planning and early engagement with the regulatory authorities
 - Acceptability of novel and innovative methodology should be prospectively agreed
 - Early consideration of regulatory tools such as adaptive pathways, PRIME, conditional marketing approval
 - Patient involvement in the overall development programme is increasing
- For approvals based on smaller pre-registration data, post-approval risk management becomes more important, as does the collection of robust post-marketing data to fill in missing information
- Ultimately, there are challenges and compromises to be made in terms of the scientific evidence base for decision making of a variety of stakeholders

Thank You

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