Qualifying Novel Tools to Monitor Drug Effects in Clinical Trials: experiences and the role of the regulator

Peter Mol

Principal clinical assessor,
CBG-MEB, Pharmacotherapy group II
Vice-chair EMA Scientific Advice Working Party
Assistant Professor, Department of Clinical Pharmacology, UMCG

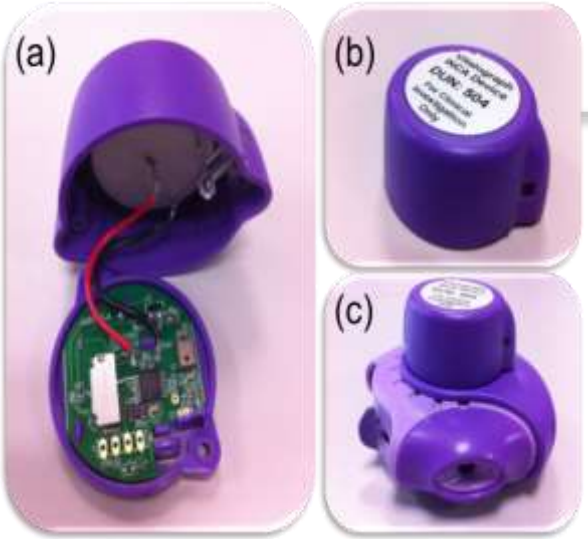
university of groningen

University Medical Center Groningen

university of groningen

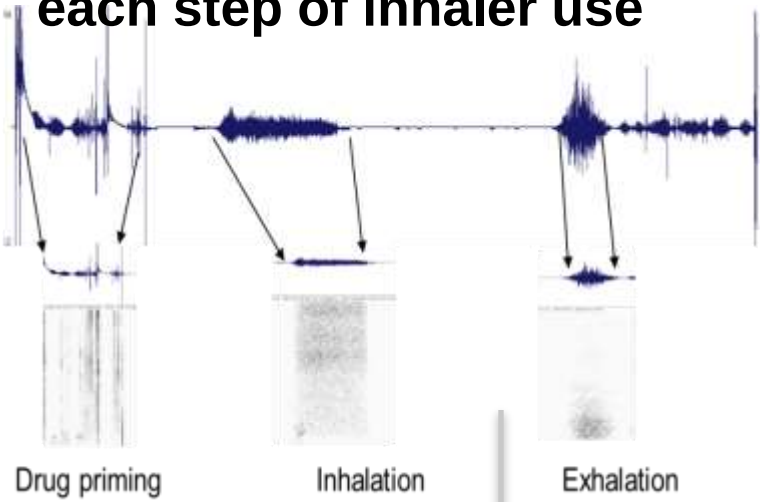
INCA Technology- Objective measurement of inhaler use

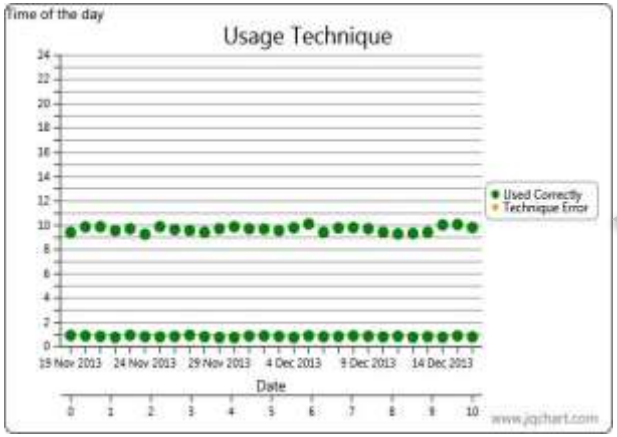
Acoustic recording device attached to inhaler



Patient "uses " inhaler

Device creates audio files of each step of inhaler use

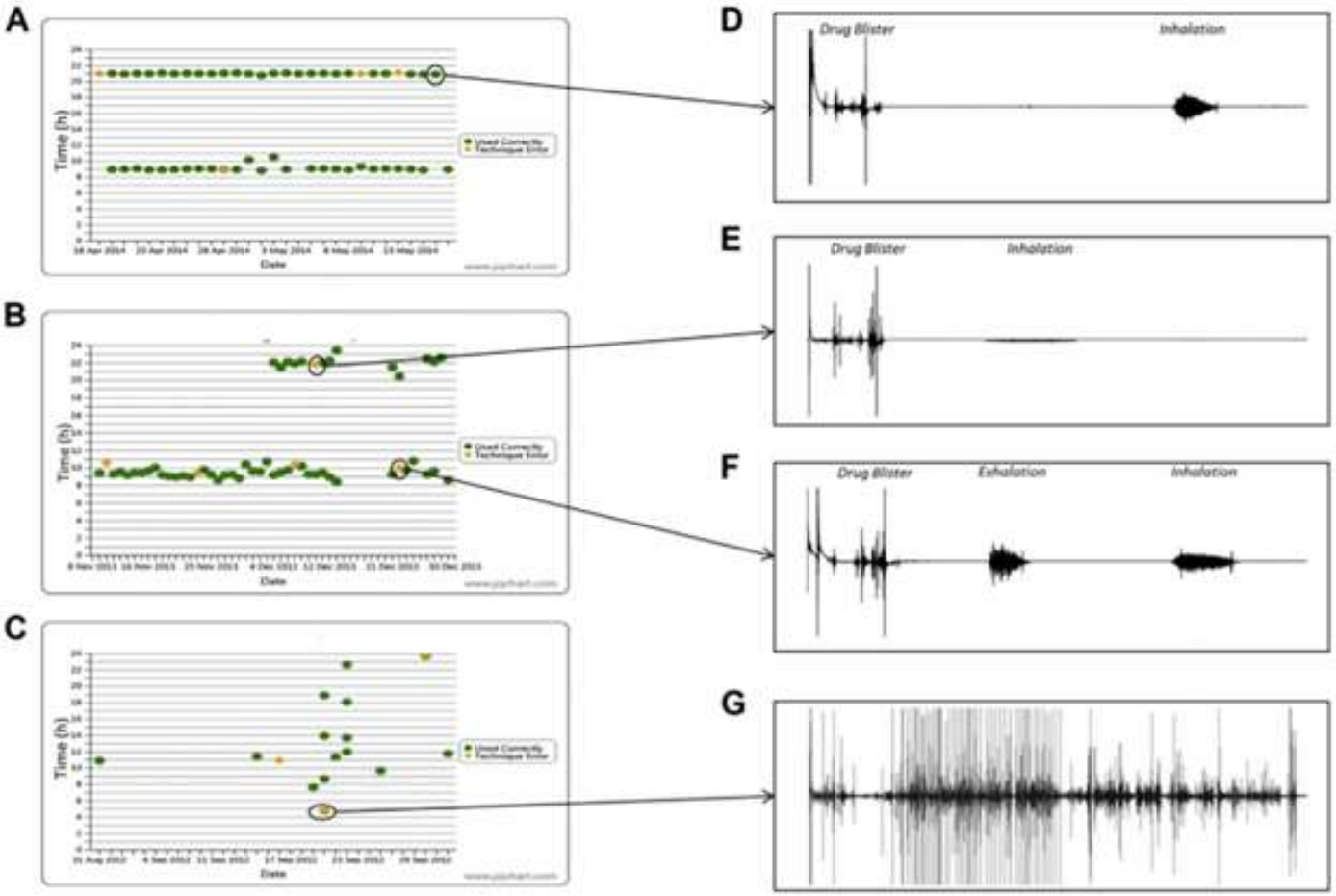




When and how well the inhaler was used

Clinician uses the information to educate the patient

D'Arcy et al. PLoS One. 2014;9(6)



Good

Poor inspiratory effort

Exhale before inhale

Drug dumping

Sulaiman. JACI in P 2016

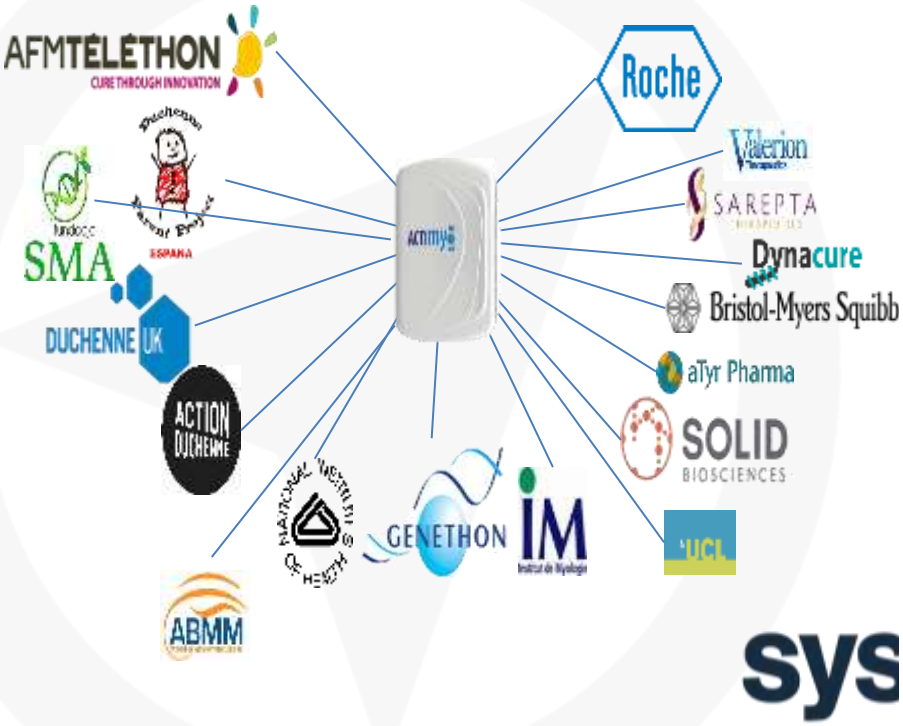
THE DMD COMMUNITY NEEDS A BETTER OUTCOME

ACTIMYO MONITORS REAL-LIFE ACTIVITY AND DECREASES VARIABILITY

- External motivations can have a significant impact on hospital-based assessments

  6MWT = strength + endurance + motivation

  Timed tests = power + physiotherapist's reflex time



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2019
EMA/CHMP/SAWP/178058/2019
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

Draft agreed by Scientific Advice Working Party	12 April 2018
Adopted by CHMP for release for consultation	26 April 2018
Start of public consultation	21 September 2018
End of consultation (deadline for comments)	30 November 2018
Adopted by CHMP	26 April 2019

Keywords	Activity monitor, Duchenne Muscular Dystrophy (DMD), Real World Data, Stride Velocity, Ambulation

Qualification Procedures: SAWP experience

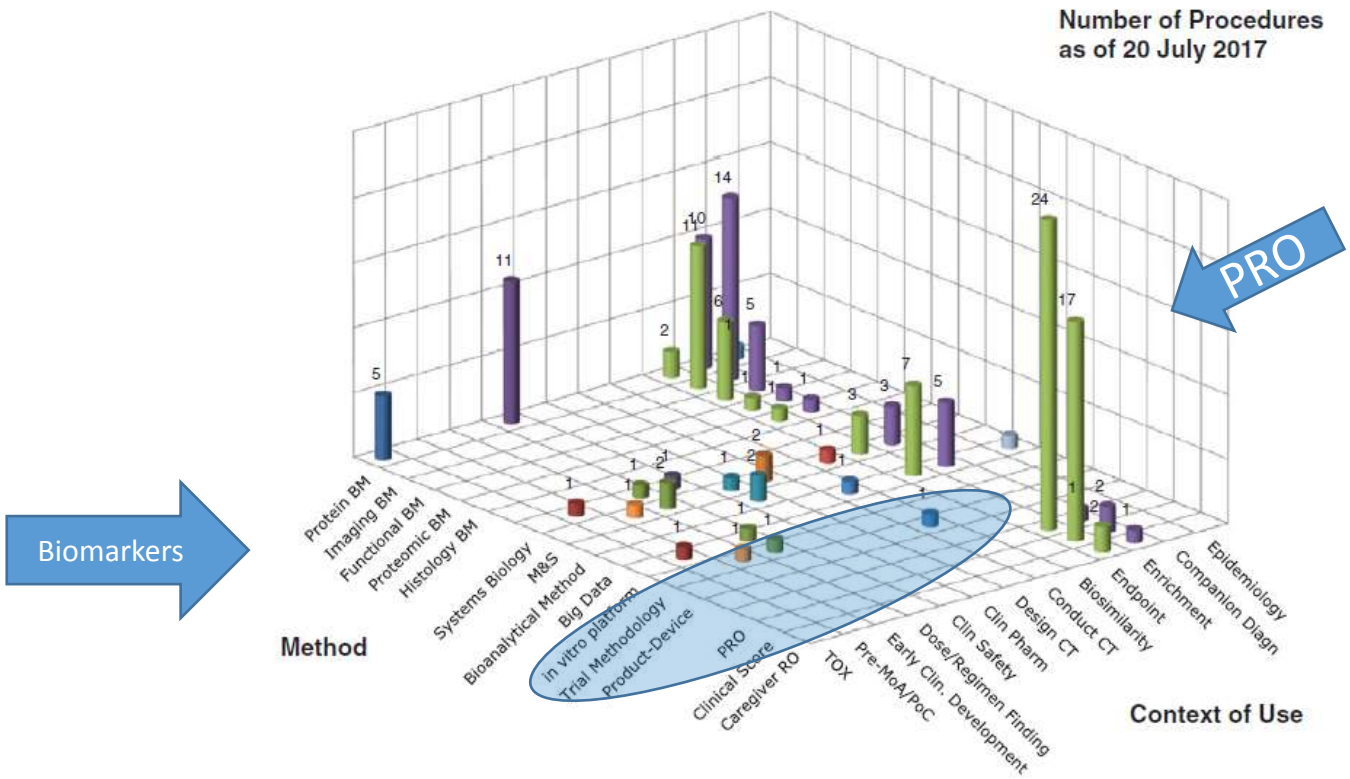


FIGURE 1 Scope of qualification of novel methodologies applications at the European medicines agency. The novel methodology (method) and their intended use (Context of Use) that were submitted to the Scientific Advice Working Party of the European Medicines Agency up to July 20, 2017 are presented in this figure. Figure courtesy of E. Manolis, EMA, London

Mol, P.G. et al. Diabetes Obes Metab. 2018

Qualification of Novel Methodologies

- …on the regulatory validity and acceptability of a specific use of a proposed method in R&D context (in non-clinical and clinical studies)
- Voluntary, scientific pathway for innovative methods or drug development tools (e.g. biomarkers) not yet integrated in the drug development and clinical management paradigm
- One procedure with two outcomes:

- Qualification Advice, OR

- Qualification Opinion


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Long-term benefits from EMA perspective: Speed-up the time to regulatory acceptance of novel approaches and time to new marketing authorisations, improve public health

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

Scientific Advice Working Party

Standing WP of the CHMP

- WP addressed in Reg. 726/2004
- Peer-review by CHMP, A*d hoc* discussions, letter signed CHMP chair
- Monthly face-to-face 4 day meetings,
- 50-70 products first reports, 20 DMs with industry sponsors

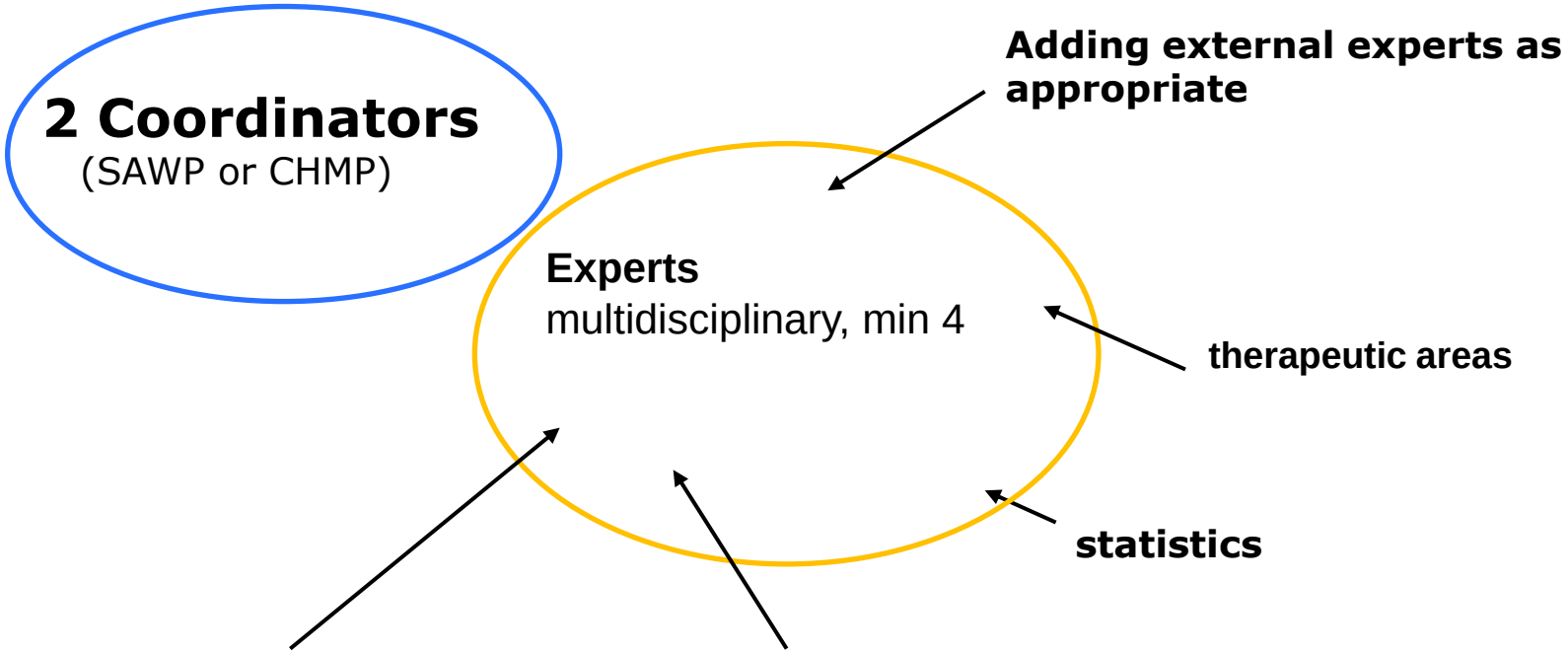
Multidisciplinary expert group

- 28 members (+alternates) selected by expertise -not EU MS-, complementary scientific competence
- 16 from NCAs, 12 from academic centers
- 3 COMP, 2 CAT, 2 PDCO, 1-2 PRAC
- 9 Scientific secretariat

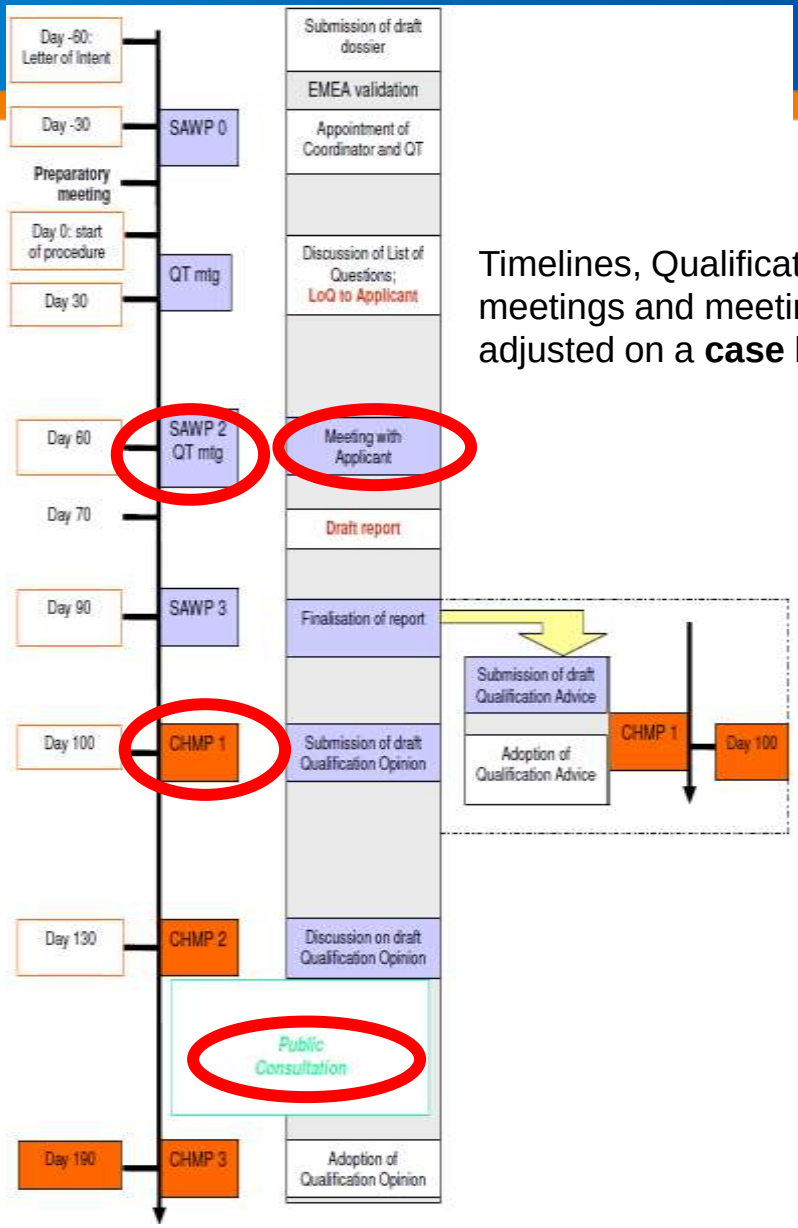
Network external experts

- NCA, academia
- Conflict of interest check
- Patient involvement (PA)

Qualification team



Process timelines



Timelines, Qualification Team (QT) meetings and meetings with applicant adjusted on a **case by case basis**

Practical Issues

- **Applicants:** Consortia, Networks, Public/Private Partnerships (e.g. IMI, Critical Path Institute), Learned societies, Academia, Pharmaceutical industry
- **Fee incentives**: Same fee reductions as in scientific advice for paediatric use, orphan conditions and SMEs (small and medium-sized enterprises)
- **Qualification Advice:** Confidential
- **Qualification Opinion:** Public consultation prior to final publication ensuring scrutiny of and alignment with scientific community and external stakeholders
- Webpage for published Qualification Opinions and Letters of Support:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0#section3

Qualification of novel methodologies

- **Qualification advice** on future protocols and methods for further development towards qualification, based on the evaluation of the ***scientific rationale and on preliminary data*** submitted, **confidential**
- **Qualification opinion** on the acceptability of a specific use of the proposed method in a R&D context, based on the assessment of data, not product-specific. Will involve all relevant scientific groups at EMA, CHMP discussion and adoption, public consultation, **publication**
- The procedural route is not fixed but will follow the assessment of the data
- **Aims:** EMA early involvement in the design of the strategy, with commitment to evaluate data from agreed studies and to provide opinion
- **Scope:** Focus on acceptability of specific use of the proposed methodology developed for a specific intended use in the context of pharmaceutical R&D **(Context of Use)**

Important considerations for Qualification strategy

- **Context of Use (CoU)** → Full, clear and concise description of the way a novel methodology is to be used and the medicine development related purpose of the use. The Context of Use is the critical reference point for the regulatory assessment of any qualification application

- **Endpoints** → Demonstration of diagnostic and prognostic performance (sensitivity and specificity), predictive value for drug response, likelihood ratios

- **Statistical Analysis plan** → Will study design and data analysis support targeted CoU?
  - Prospective/retrospective studies may be appropriate depending on CoU
  - pre-specified analysis path
  - exploratory and confirmatory datasets needed
  - If cross-validation approaches are considered (e.g. in small populations) these should be pre-specified and not considered post-hoc

Important considerations for Qualification strategy

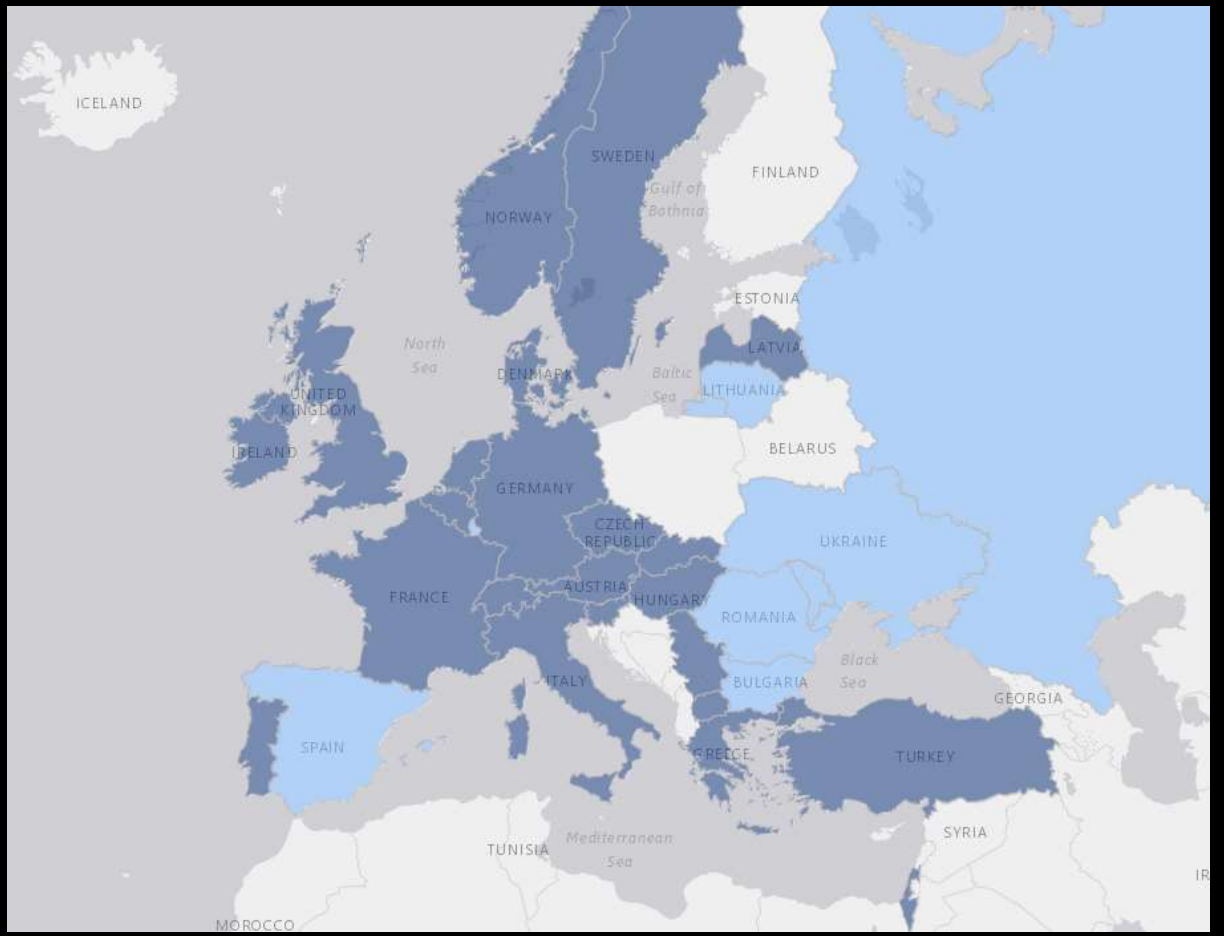
- **Demonstration of clinical utility** →Impact of methodology on **diagnostic thinking**, **patient management and clinical outcome**

- **Standard of truth/surrogate standard of truth** → Assessment of true state of a patient or true value of measurement might not exist or is invasive and/or unethical
  → Surrogate standard to be justified

- **Analytical platforms**:
  Technical/performance characteristics to be defined and justified, fit for purpose

General Queries: Coverage of ECFS Registries

- 31 Countries
- **>42,000 patients**
- 17 National Registries
  - 12 Upload
- 85 centres use ECFS Registry Software*
- GPP not currently required
- Broad coverage



* + 13 centres of the CF Registry Ireland

Presented ECFS 2017

Variables Collected by ECFSPR

Demographic	Age, Gender, Status of patient, Date and cause of death
Diagnosis	Age at diagnosis, Sweat test, Meconium Ileus, Neonatal screening, NPD
Genetics	CFTR Genotype
Growth/Lung function	FEV1 & FVC (Best annual), LCI, height and weight, FE-1
Microbiology	Pseudomonas aeruginosa, Staphylococcus aureus, B. cepacia, NTM, MRSA
Complications	Exacerbations (Days of IVs/Hospitalisations), Diabetes, Liver disease, Pancreatic status, (see next slide), more
Therapies	Antibiotics, Bronchodilators, Mucolytics, Oxygen therapy, Pancreatic enzymes, CFTR Correctors Start/Stop Dates; Dosages
Transplant	Lung/Liver transplant

Context of Use


EUROPEAN MEDICINES AGENCY

Qualification Opinion

The European Cystic Fibrosis Society Patient Registry (ECFSPR)

Draft for consultation

Drug utilisation studies

- For total recorded population and by subgroup such as CF complications, age, gender, FEV1 status, genotype, etc.

Drug efficacy/effectiveness studies

- For concurrent assessment of post authorisation efficacy/effectiveness using annual best FEV1, mortality, pulmonary exacerbations using the ECFSPR working definition or CF complications;
- As a source of historical control data ..for contextualization, e.g. for comparative purposes in the context of non-randomized clinical trials (i.e. when this would be the only reasonable option).

Drug safety evaluation

- As a tool to collect safety data with a particular focus on important identified and potential risks. *{and some fine print qualifications}*

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0#section2

Qualification exercise – experiences

- The Qualification exercise is complex and requires **collaboration** between interested parties – mostly **PPP's**. Efficient communication between Collaborators is key
- Danger to embark on overly ambitious and complex projects which may not be in line with project funding horizon
- **late initiation** of regulatory interaction to discuss the collated existing evidence, perform gap analysis, develop qualification strategy and agree on evidentiary requirements for regulatory Qualification based on a clear CoU is common challenge
- Feasibility considerations should inform (and limit) the number of targeted CoU's:
  e.g., for safety markers:
  - Time point to detect robust safety signal
  - Discrimination of the histopathologic mechanism of organ injury (e.g. necrosis, apoptosis, immune activation)
  - differentiation of likelihood of progression/regression/adaptation with ongoing exposure;

Qualification exercise – experiences

- Key: Adequate, well characterised study populations for **exploratory studies/ learning datasets**; once these analyses have identified clear candidate markers with appropriate characterisation of thresholds and time course, these will need to be **confirmed**, ideally prospectively*; alternatively a well characterised independent biobank of samples from patients who have experienced the target organ toxicity and its various clinical outcomes may be used for confirmation; SAP/methodology should be pre-specified and agreed a priori*
- Qualification will depend on **appropriate study designs** (adequate well-defined target population, **definition of a success criterion** with regard to clinical utility of the marker, rationale for sample size, methodology for internal and external validation of the statistical prediction model, adjustment for other covariates such as subject characteristics, time point of marker measurement, drug exposure) in which predictive/classification rules are established and validated in order to assess the clinical utility of the marker (panel)
- EMA Qualification Advice provides platform to agree on these considerations early

Conclusion

- Qualification is not a trivial exercise
- Limited experience with **devices**
- Regulatory requirements are case dependent and require dialogue
- Many Stakeholders:
  e.g., Regulators, Learned Societies, Patients, **Notified Bodies**
- Many Scientific Disciplines:
  e.g., Analytical Scientists, Pharmacologists, Toxicologists, Modellers, Clinicians, Statisticians
- EMA Qualification procedure is a platform for dialogue
- Identifying and agreeing evidentiary requirements to support **CoU**
- Cooperation of international regulators (FDA!) facilitates adequate study designs
- Vision: speed up/optimise drug development and utilisation,
  improve public health

umcg

CBG MEB

COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

p.mol@cbg-meb.nl

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GOEDE MEDICIJNEN GOED GEBRUIKT