Medicines Evaluation Board

Regulatory views on qualification of novel endpoints

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Disclaimer:

The views expressed in this presentation are the personal views of the presenter and may not be understood nor quoted as being made on behalf of, or reflecting the position of, CBG-MEB or EMA

Acknowledgement:

André Elferink

- Qualification procedure
- Endpoint validation
- Examples

Qualification of Novel Methodologies (QoNM)

Established as a response to the drug development bottlenecks and inefficiencies, but also to the availability of new methodologies, not yet integrated in the drug development and clinical management paradigm.

Provides a voluntary, scientific pathway to support development, evaluation and regulatory endorsement of innovative methodologies in specific contexts of use.

Promotes innovation, fosters collaboration among developers and stakeholders, and aims to integrate novel scientific approaches into medicinal product development and regulatory assessment.

A novel methodology may also be considered acceptable within a regulatory submission, e.g. Scientific advice, MAA.

Qualification of Novel Methodologies (QoNM)

Categories:

- (Bio) Marker

  AI NASH histology, Centiloid measure of Amyloid PET

- Outcome measure

  GFR slope in CKD, stride velocity 95%

- Data source

  Enroll-HD Huntington's registry, Cystic Fibrosis Society Patient Registry

- Methodologies for data analysis and decision support

  PROCOVA, recurrent event endpoint analysis

- Non-clinical methodologies

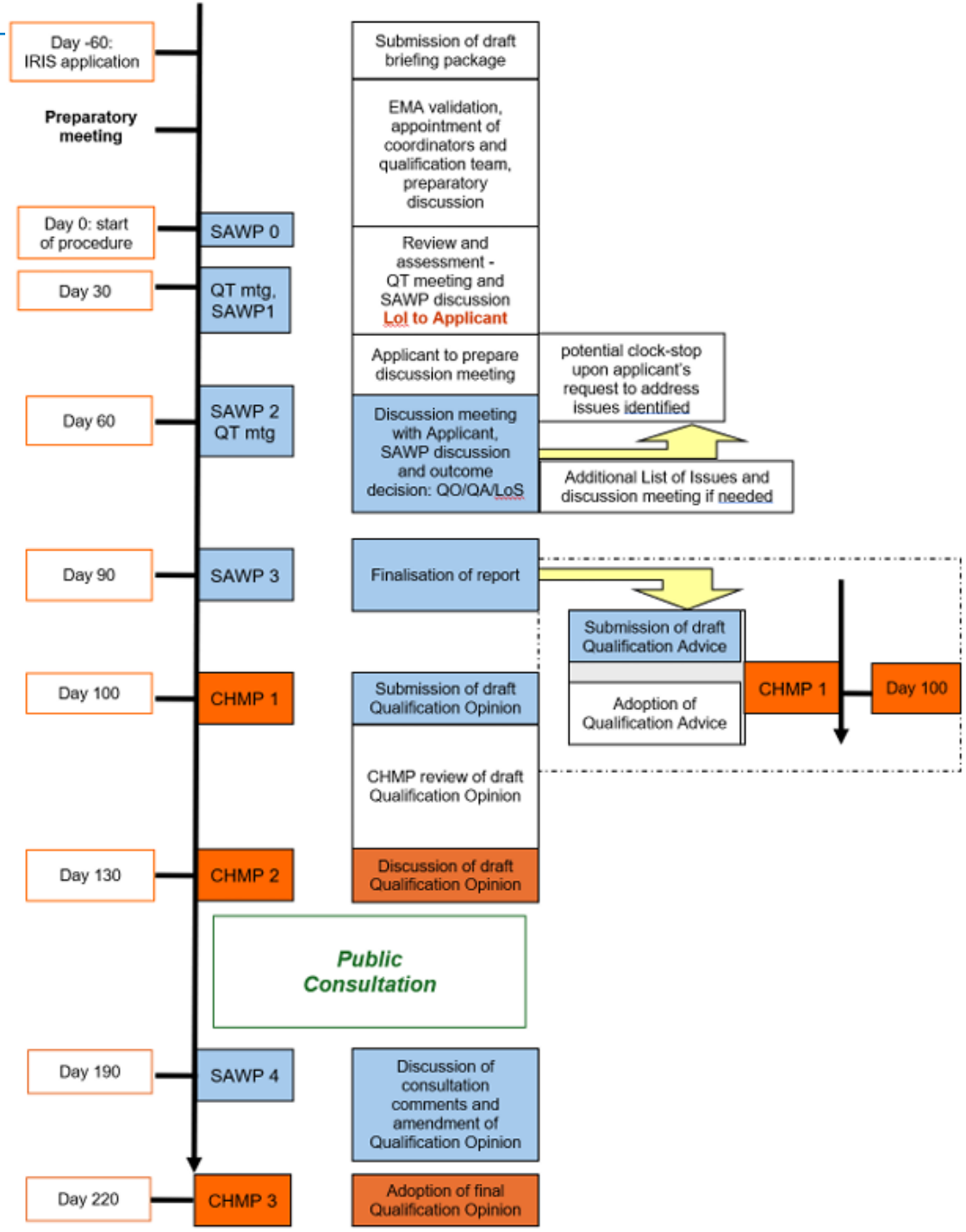
  Simcyp Simulator, hollow fiber system model of tuberculosis

Qualification procedure

Scientific Advice on innovative methods or drug development tools:

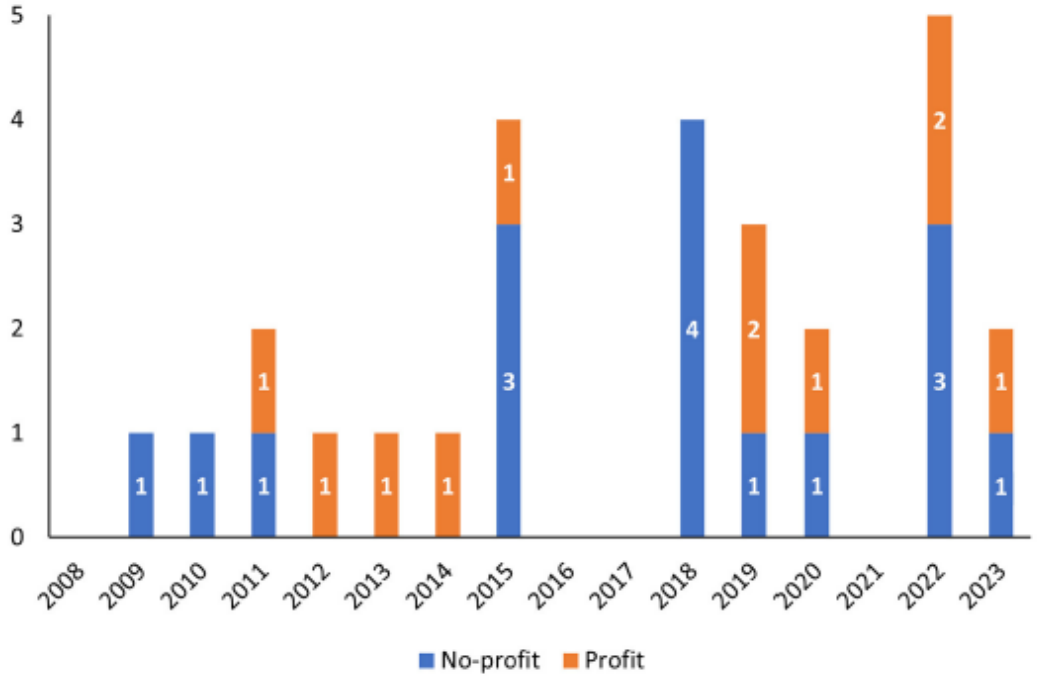
(i) CHMP Qualification Opinion - acceptability of a specific use of the proposed method

(ii) CHMP Qualification Advice - on future protocols and methods for further method development towards qualification (optional letter of support)

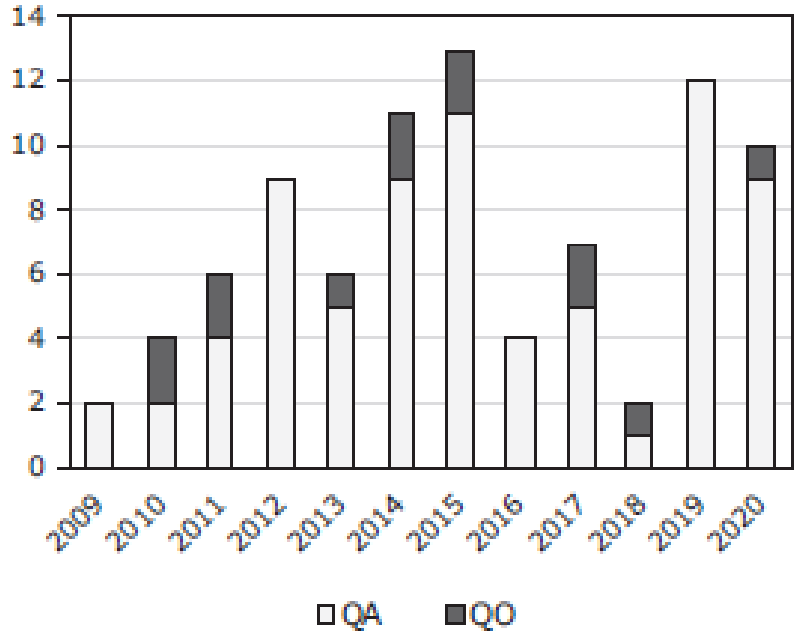


Qualification procedure

Qualification opinions per year



Biomarker qualification opinion (QO) or qualification advice (QA)



Until 2023: 208 QoNM procedures, 27 Qualification opinions and 39 Letters of support

Ref: Giannuzzi Front Med 2024, Bakker Clin Pharmacol Ther 2022

Qualification procedure

- Qualification opinions per category and per indication area

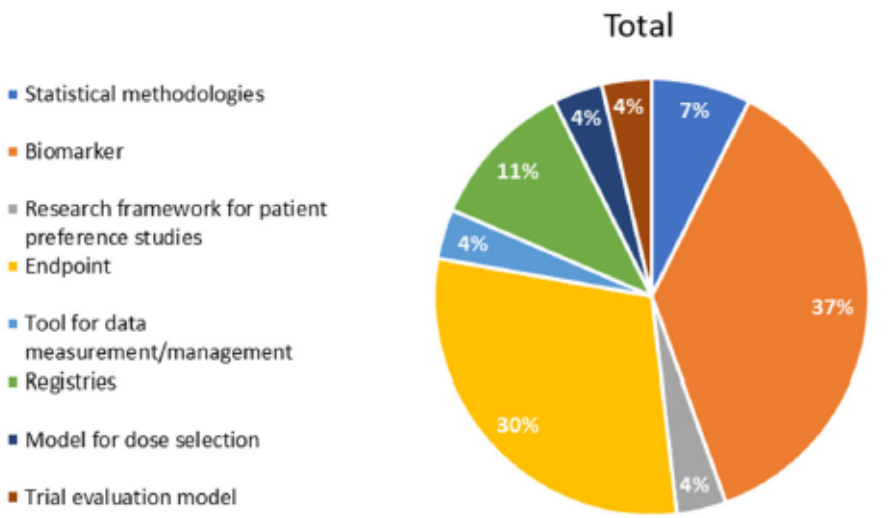
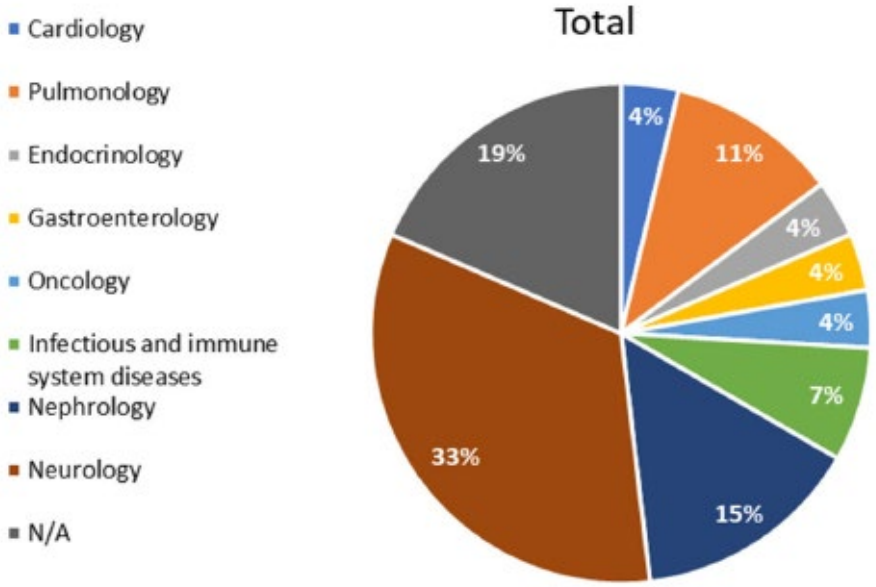


FIGURE 2
Qualification opinions grouped according to the type of methodology (total procedures and p



Ref: Giannuzzi Front Med 2024

Validation of an endpoint

- Concept/Context of use
- Face validity
- Construct validity
- Reliability
- Content validity
- Sensitivity to change
- Minimal clinically important difference
- Sensitivity to a treatment effect

All requirements addressed? Valid for use in a regulatory context

Validation of an endpoint

Cross-sectional

easier part

- Concept/Context of use ← determines degree of validation
- Face validity
- Construct validity
- Reliability
- Content validity

harder part

- Sensitivity to change
- Minimal clinically important difference
- Sensitivity to a treatment effect ← test performance in RCT, no validation without longitudinal data

longitudinal

All requirements addressed? Valid for use in a regulatory context

Example – Neurofilament light

Proposed context of use:

- Neurofilament light (NFl) protein in childhood Neurological diseases is intended as a biomarker to monitor disease activity that is related to axonal damage and to assess treatment responses in paediatric neurological diseases (<20 years old).

NfL evaluated as potential biomarker for disease activity and treatment response in various paediatric neurological diseases i.e., SMA, CLN, MS, CLN2, MLD, Mitochondrial encephalopathy

High face validity as a biomarker

Ref: Letter of Support of Neurofilament light in childhood Neurological diseases

Example – Neurofilament light

Context of use to monitor disease progression too high level, more fine-tuned expected. E.g.:

- intended as biomarker to select potential treatments in phase II;
- as endpoint in dose-finding studies;
- as tool to enrich a study population;
- as secondary endpoints in clinical efficacy studies;
- as surrogate clinical endpoint;

NfL levels do not simply correlate with disease severity within the same disorder and cannot be harmonised across disorders

EMA acknowledged the potential of NfL and is prepared to consider a future submission with a well-defined context of use

Example - Multiple sclerosis clinical outcome assessment

Most widely used endpoint in MS: Expanded Disability Status Scale (EDSS)

- focusses on motor function / ambulation

MSCOA is a battery of four performance outcome measures assessing important dimensions of MS

- walking (Timed 25-foot walk, T25FW)
- hand dexterity (9 Hole peg Test, 9HPT)
- vision (Low contrast Letter acuity, LCLA)
- mental processing speed (Symbol Digit Modalities Test, SDMT)`

Proposed context of use:

- to serve as a primary, co-primary or key secondary endpoint to assess efficacy in clinical trials at various stages, including proof of concept, dose-ranging, confirmatory and registration trials

Ref: Qualification opinion on Multiple sclerosis clinical outcome assessment (MSCOA)

Example - Multiple sclerosis clinical outcome assessment

Intended context of use was changed from a global disability score (weighted sum) into four separate measures that can be used in combination or on a single primary endpoint in support of a descriptive indication

Conclusion:

- Validation work is acknowledged: MSCOA is objective, reproducible, reliable, sensitive to change and easy to perform
- MSCOA items can neither be used as single variable or in combinations as primary endpoint
- T25FW and 9HPT can be included in a composite primary endpoint combined with EDSS
- Inclusion as secondary endpoints is accepted

Example - iAMD biomarker and novel clinical endpoint development

MACUSTAR Consortium

- goal is to develop a toolbox of clinical endpoints acceptable for clinical trials in iAMD
- functional and/or structural biomarkers as primary endpoints in exploratory and confirmatory clinical trials. PROs as secondary clinical endpoints

- MACUSTAR clinical study:
  - PROM impact of iAMD and evaluation of progression to neovascular AMD/geographic atrophy;

    assess relationship between functional and structural measures with PROM and as endpoints anchored against progression
  - Cross-sectional and longitudinal part

Ref: Letter of Support for intermediate Age-Related Macular Degeneration (AMD) biomarker and novel clinical endpoint development

Example - iAMD biomarker and novel clinical endpoint development

Three QAs:

- 1) General setup; 2) Cross-sectional results; 3) Additional baseline results and (part of) longitudinal data

Limitations

- Explorative design, confirmation needed
- Aimed at prognostic but not predictive value of biomarkers

Conclusions

- Technical evaluation of functional, structural and patient-reported candidate outcomes acceptable
- Visual function deficits, structural and functional biomarkers are potential enrichment factors but unclear whether they have prognostic value for both progression to neovascular AMD and GA
- Vision Impairment in Low Luminance (VILL) questionnaire acceptable as secondary endpoint but for full validation, data on responsiveness to an intervention is lacking

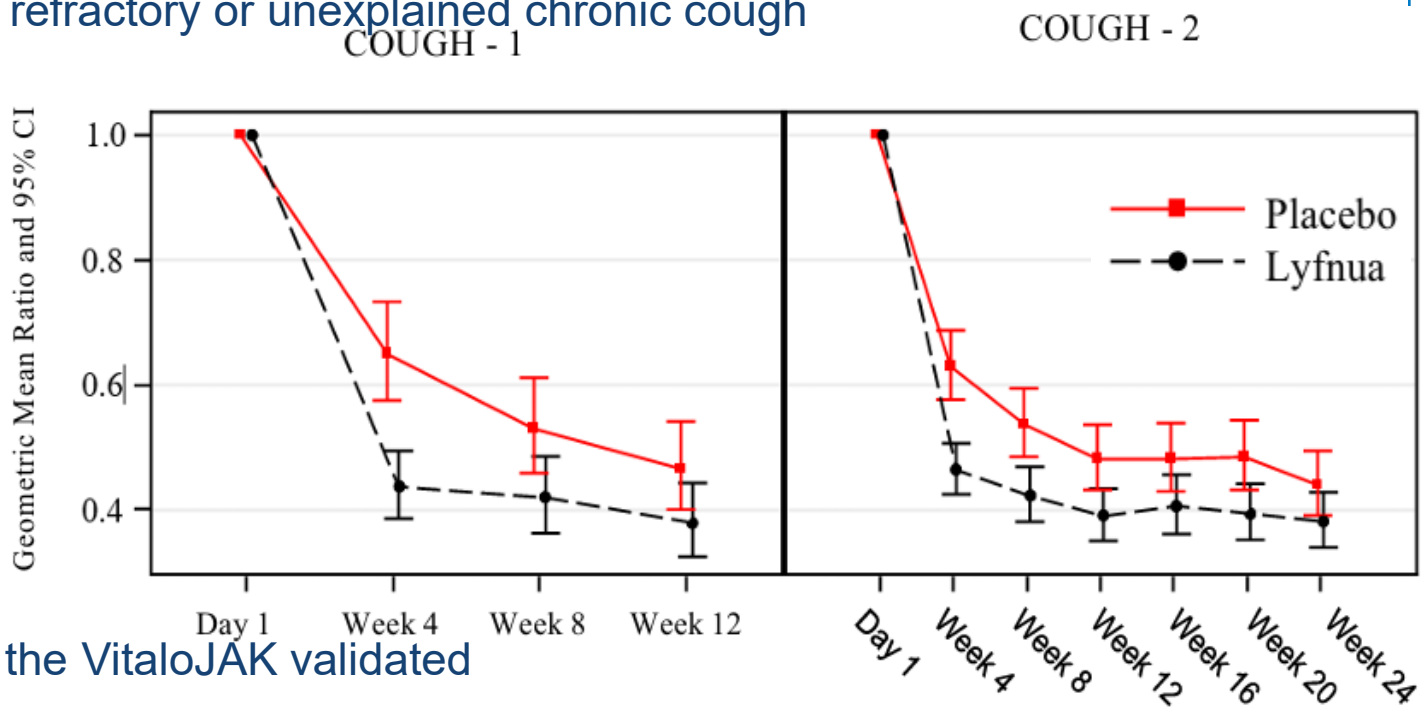
Example – Lyfnua (gefapixant) MAA

Lyfnua is indicated in adults for the treatment of refractory or unexplained chronic cough

Two pivotal studies

- Primary endpoint, coughs per hour was met
- Main AE, taste related disorders (65% vs 7%)
- Positive B/R

BUT



- 24 h manual cough count of data recorded by the VitaloJAK validated
- Recordings compressed to remove silence and non-cough sounds and cough count analyses not validated
- Validation study preformed (14 month clock stop)

  conclusion the full VitaloJAK system is valid for use in the clinical studies

Ref: Lyfnua EPAR

Summary

Qualification procedures

- Cost time and effort
- Give assurance about regulatory acceptance of novel endpoints;

  or give advice on the necessary steps to get there

- Supports developments; enhance early engagement; allows thorough discussions
- Facilitates harmonized use of endpoints across drug developers and avoids parallel developments