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MEDICINES
EVALUATION
BOARD

Regulatory approach to surrogate endpoints in cardiovascular disease – which are acceptable and why?

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BETTER

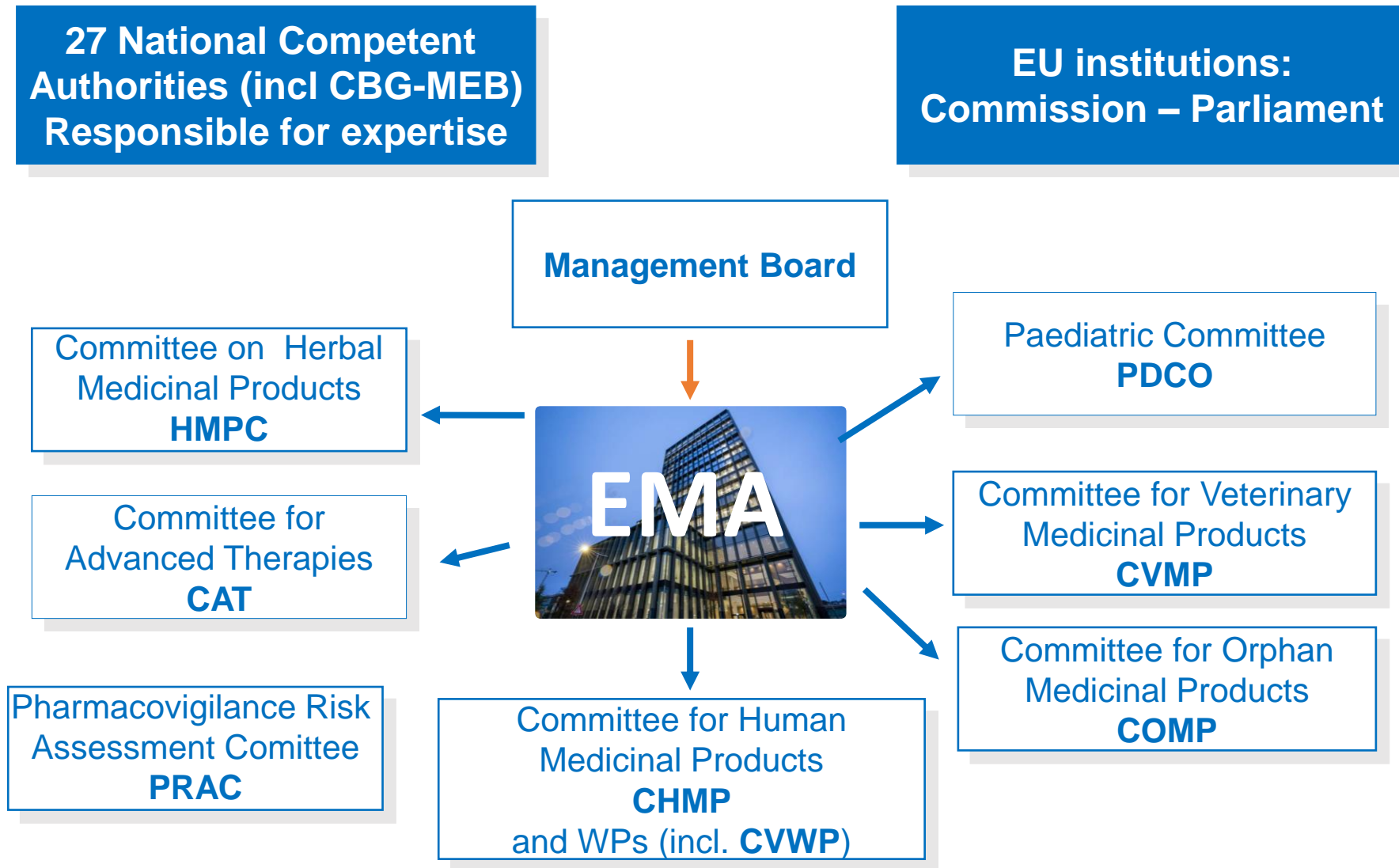
I am an employee of the Dutch Medicines Evaluation Board

Anything I will present today are my views, and cannot be understood as a formal statement or endorsement of my Agency, or the EMA

I am participating in the HORIZON PRIME-CKD, IMI-EPND and PI of the HORIZON More-EUROPA project

No other conflicts of interest to declare

European Medicines Regulatory Network (incl. EMA)



For each step in the procedure: guidelines!



The ICH logo is at the top left, with the tagline 'harmonisation for better health'. Below it is a navigation menu with 'Work Products' highlighted. The main heading is 'ICH Guidelines / Work Products / Home'. A sub-heading states: 'The ICH topics are divided into four categories and ICH topic codes are assigned according to these categories.'

Q	Quality Guidelines Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.	S	Safety Guidelines ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.
E	Efficacy Guidelines The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.	M	Multidisciplinary Guidelines Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).



Guideline purpose:
To enable adequate benefit-risk assessment

<http://www.ich.org/products/guidelines.html>

Cardiovascular surrogate biomarkers

Blood pressure

LDL-c

HbA1c

Symptomatic outcomes

- *6-MWT; e.g., PAH guideline*
- *Dyspnoea; e.g., AHF (using VAS)*
- *Treadmill test (anti-anginal)*

But not,

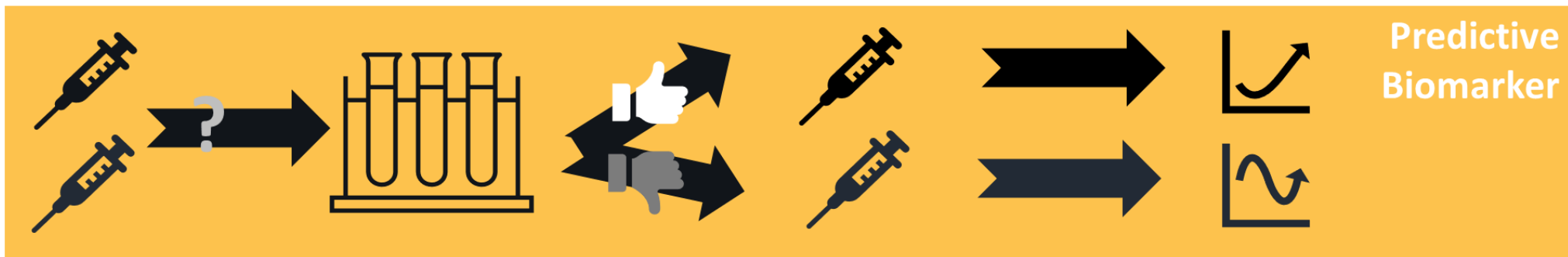
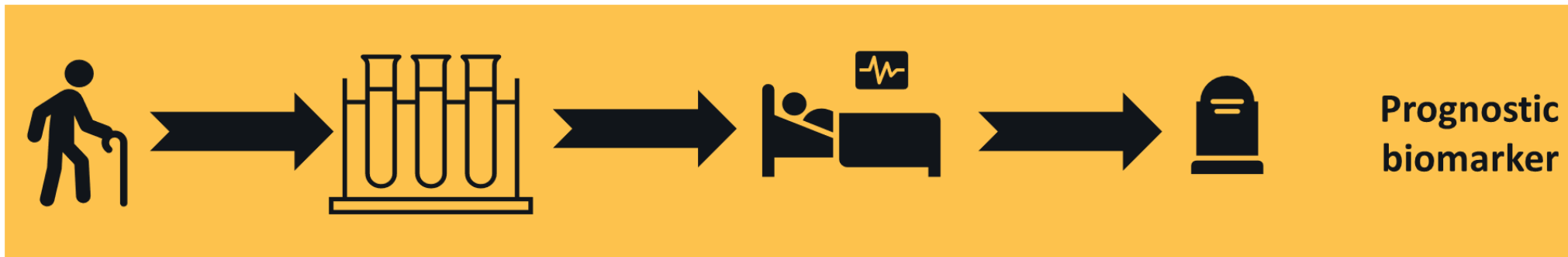
HDL-c

BNP or NT-proBNP

PVR (PAH)

The screenshot shows the European Medicines Agency (EMA) website. The main navigation bar includes 'Medicines', 'Human regulatory', 'Veterinary regulatory', 'Committees', 'News & events', 'Partners & networks', and 'About us'. The 'Human regulatory' section is active, with sub-navigation for 'Overview', 'Research and development', 'Marketing authorisation', 'Post-authorisation', and 'Herbal products'. The 'Research and development' section is selected, leading to the 'Clinical efficacy and safety: cardiovascular system' page. The page title is 'Clinical efficacy and safety: cardiovascular system' with a 'Share' button. A 'Table of contents' lists various conditions: Hypertension, Lipid disorders, Pulmonary arterial hypertension, Arrhythmias, Venous thromboembolism, Heart failure, Coronary artery disease, and Other. A key message states: 'The European Medicines Agency's scientific guidelines on the clinical evaluation of human medicines used in conditions affecting the cardiovascular system help medicine developers prepare marketing authorisation applications.' Below this, it mentions 'Public consultations' for a complete list of guidelines. A 'Hypertension' section is highlighted in blue, with a 'Guidelines' sub-section listing: 'Clinical investigation on medicinal products in the treatment of hypertension - Scientific guideline', 'ICH E12 Principles for clinical evaluation of new antihypertensive drugs - Scientific guideline', and 'Paediatric addendum to the guideline on clinical investigation on medicinal products in the treatment of hypertension - Scientific guideline'. At the bottom, there is a cookie consent banner with 'Accept all cookies' and 'Accept only essential cookies' buttons.

Biomarkers





UPPSALA
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Nov 23

Peter Mol, University Medical Center Groningen (UMCG)

*What's the **science** in regulatory science?*



Biography: Peter Mol, pharmacist and professor of drug regulatory science at the UMCG, Groningen, the Netherlands.

His research focus is on developing **new tools to support regulatory decision-making** and the exchange of knowledge between regulatory authorities, health care professionals and lay people.



Peter Mol is the Committee for Medicinal Products for Human Use (CHMP) member for the Dutch Medicines Evaluation Board, and was from 2012 to 2023 member (vice chair 2016-2022) of Scientific Advice Working Party, both at the European Medicines Agency.

Personalised Medicine & Regulatory Impact

doi:10.1002/cpt.2554

ARTICLE

Biomarker Qualification at the European Medicines Agency: A Review of Biomarker Qualification Procedures From 2008 to 2020

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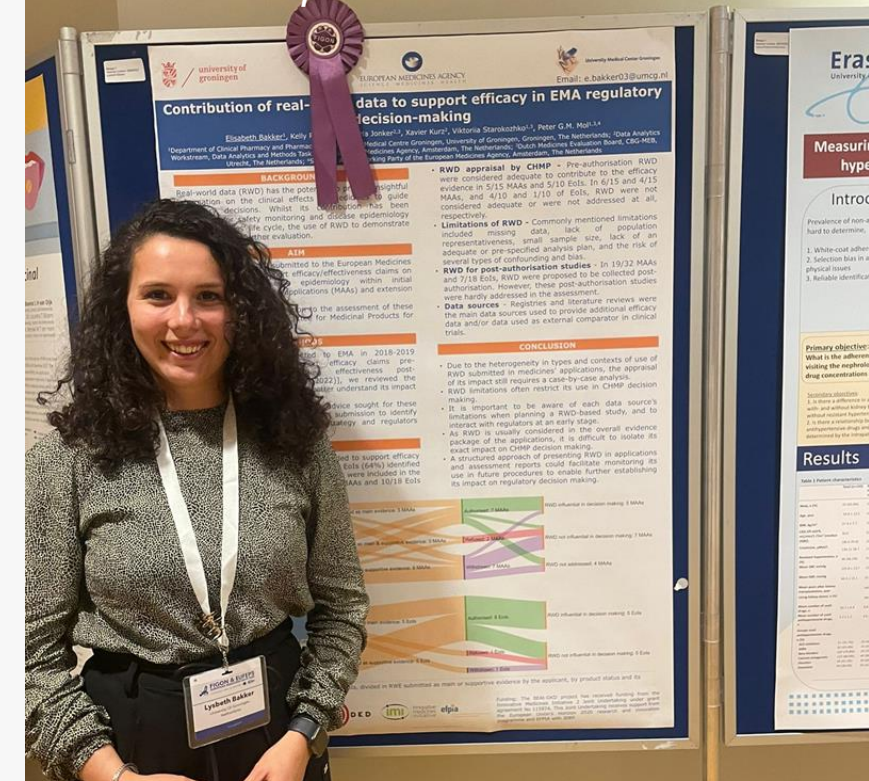
ARTICLE

Precision medicine in regulatory decision making: Biomarkers used for patient selection in European Public Assessment Reports from 2018 to 2020

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Perspectives on a Way Forward to Implementation of Precision Medicine in Patients With Diabetic Kidney Disease; Results of a Stakeholder Consensus-Building Meeting

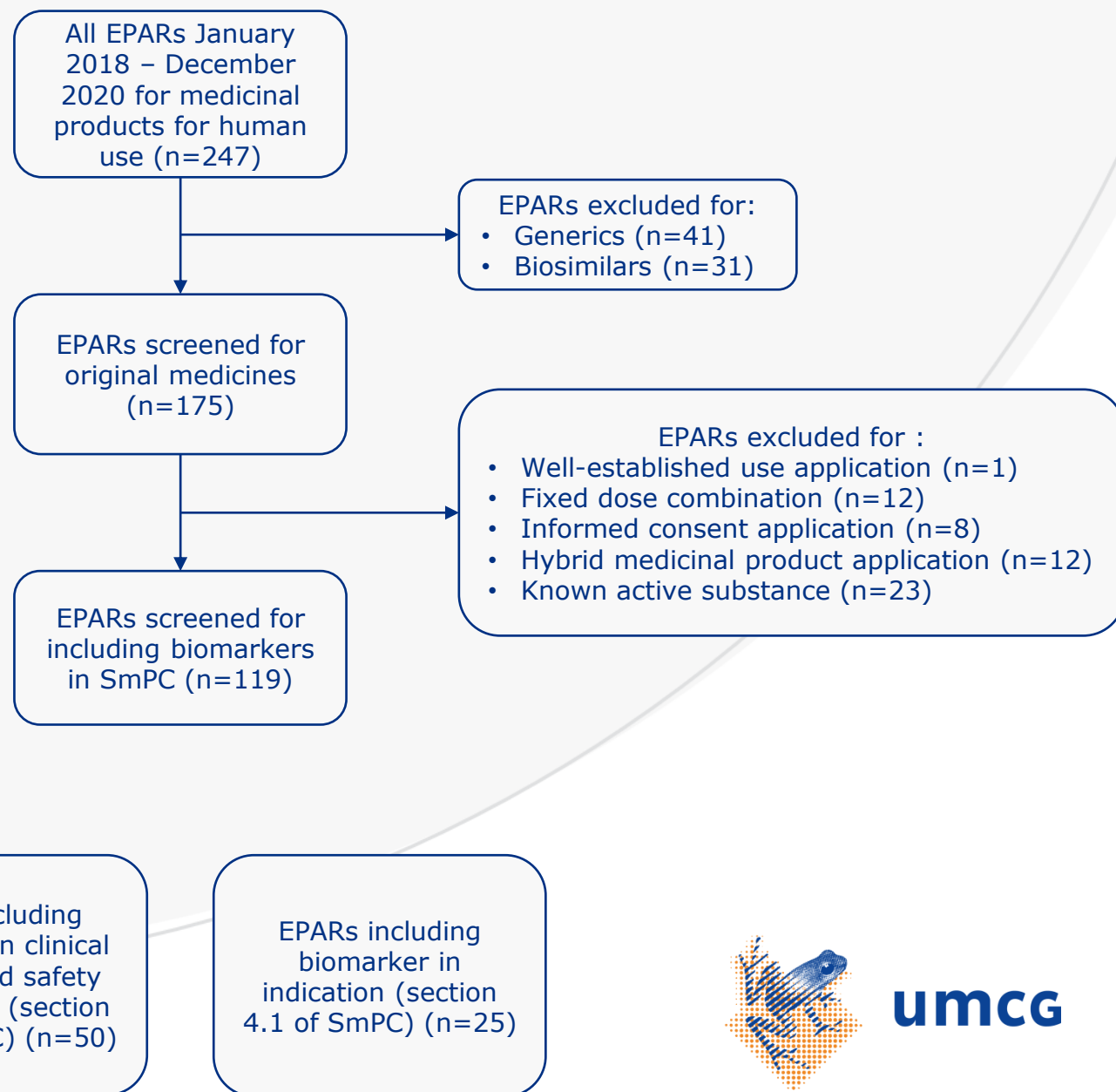
Elisabeth Bakker^{1†}, Peter G. M. Mol^{1,2,3†}, João Nabais^{4,5†}, Thorsten Vetter⁶, Matthias Kretzler^{7†}, John J. Nolan^{8†}, Gert Mayer^{9†}, Anna K. Sundgren^{10†}, Hiddo J. L. Heerspink^{1†}, Anja Schiel^{3,11}, Sieta T. de Vries^{1†}, Maria F. Gomez^{12†}, Friedrich Schulze¹³, Dick de Zeeuw^{1†} and Michelle J. Pena^{1,4†} for the BEAT-DKD Consortium

Methods

- We performed a narrative synthesis of marketing authorisation dossiers of medicinal products that were authorised from 1st of January 2018 until 31st of December 2020 that used biomarkers for patient selection

Precision medicine in regulatory decision making:
Biomarkers used for patient selection in European Public
Assessment Reports from 2018 to 2020

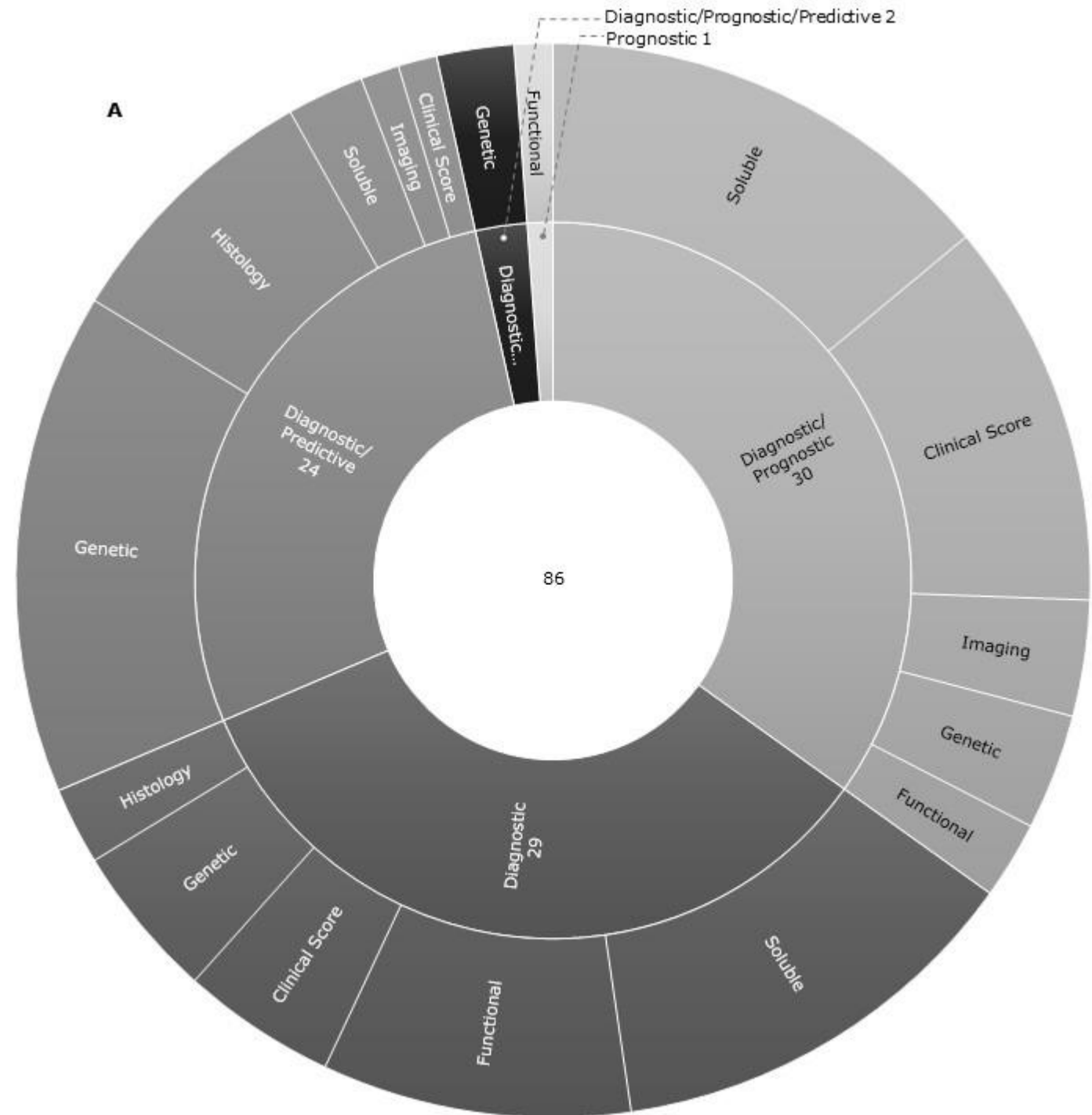
Elisabeth Bakker¹ | Viktoriia Starokozhko^{1,2} | Jet W. M. Kraaijvanger^{2,3} |
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Results: biomarkers in section 5.1

- 119 dossiers: 50 mentioned ≥ 1 biomarkers for patient selection in section 5.1
- Total of 86 biomarkers:
 - 25 soluble biomarkers (e.g., serum potassium)
 - 21 genetic biomarkers (e.g., genetic mutations)
 - 11 functional biomarkers (e.g., respiratory rate)
 - 15 clinical scores (e.g., psoriasis area and severity index (PASI))
 - 10 histology biomarkers (e.g., % superficial cells in vaginal smear)
 - 4 imaging biomarkers (e.g., multiple sclerosis lesions)
- In 25 dossiers, a biomarker was included in the medicine's therapeutic indication (section 4.1)
- Most were in the field of oncology (n=15)



Discussion/Conclusion

- Biomarkers are widely used for patient selection in recent medicines development, of which some are included in the medicines' indications:
 - For **25/119** eligible medicines approved in 2018-2020, a biomarker was included **in the indication** of the medicine
 - **50** mentioned one or more biomarkers **in the clinical efficacy and safety information** of the SmPC → **86 biomarkers in total**
- These were **often well-known biomarkers**:
 - **Very few** products were approved in this timeframe based on **new biomarkers and innovative trial designs**, leaving room for improvement regarding the approval of new precision medicines
- **Definitions** of the biomarkers were mainly **established before the clinical development**
- Discussions and adaptations requested concerning the biomarker cut-off values underline the **importance of thorough validation of these definitions** to include the right population for an optimal benefit-risk balance



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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

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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012¹
Revision 2: January 2014²
Revision 3: November 2014³
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

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

1 Qualification Opinion as agreed by CHMP

2 Based on the evidence presented in the qualification opinion request and in a discussion meeting,
3 CHMP considers that GFR slope (i.e. the mean rate of change in GFR over time) can in some trial
4 settings - if properly specified and assessed - serve as a surrogate endpoint for CKD progression in
5 clinical trials for standard marketing authorization and indication extension approvals.

6 Agreed Context of Use (CoU)

7 The proposed novel method, GFR slope, is intended to be used as a validated surrogate endpoint for
8 CKD progression in randomized controlled clinical trials for standard marketing authorization and
9 indication extension approvals.

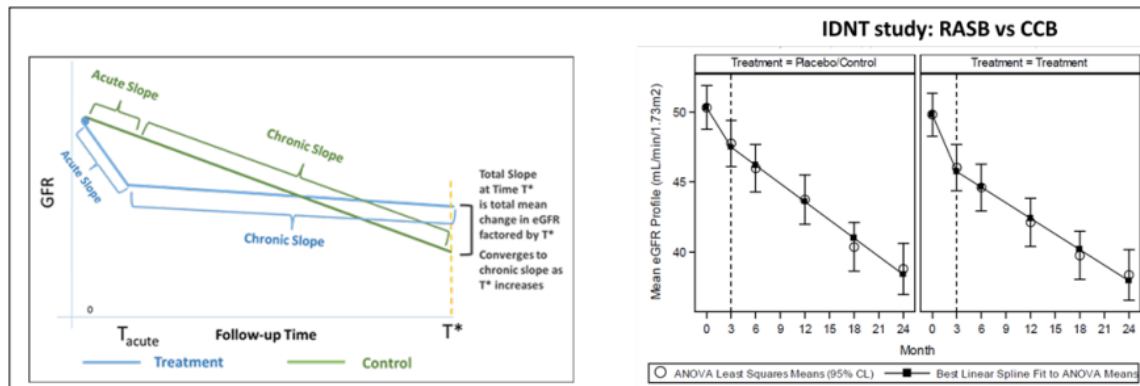


Figure R3: GFR slope by treatment arm. Left panel hypothetical example and right panel demonstration in an example study. eGFR, Estimated glomerular filtration rate; GFR, Glomerular filtration rate; RCT, Randomized controlled trial; T, Time.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

04 September 2023
Case No.: EMA/SA/00000104642
Committee for Medicinal Products for Human Use (CHMP)

DRAFT Qualification opinion for GFR slope as a Surrogate Endpoint in RCT for CKD

Draft agreed by Scientific Advice Working Party (SAWP)	11 May 2023
Adopted by CHMP for release for consultation	25 May 2023
Start of public consultation	06 September 2023
End of consultation (deadline for comments)	23 October 2023

Comments should be provided using this [template](#). The completed comments form should be sent to ScientificAdvice@ema.europa.eu

Keywords	Qualification of Novel Methodology, glomerular filtration rate (GFR) slope, surrogate endpoint, efficacy endpoint, Chronic Kidney Disease (CKD) clinical trials
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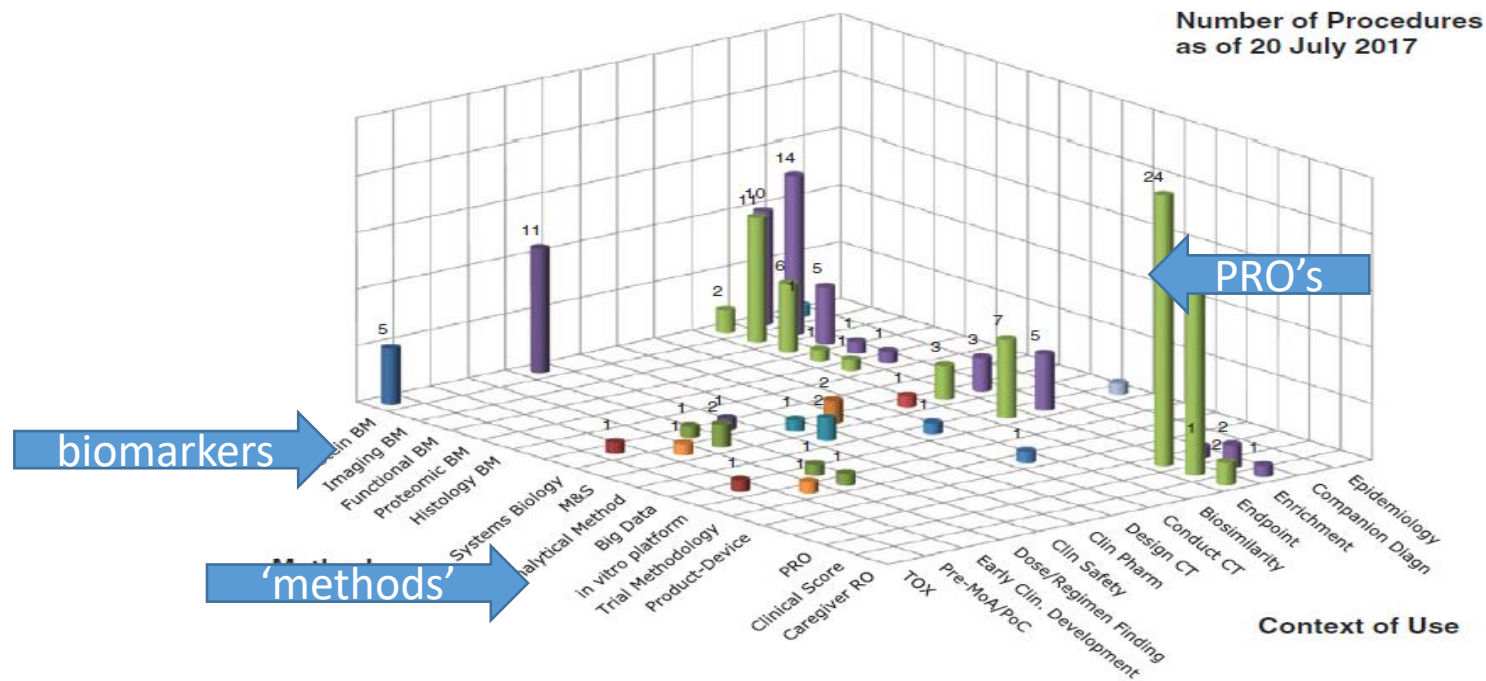


FIGURE 1 Scope of qualification of novel methodologies applications at the European medicines agency. The novel methodology (method) and their intended use (Context of Use) that were submitted to the Scientific Advice Working Party of the European Medicines Agency up to July 20, 2017 are presented in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

SmPC

4.1 Indication

“[] is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1)”

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[mavacamten](#)

Table of contents

- [Overview](#)
- [Authorisation details](#)
- [Product information](#)
- [Assessment history](#)

Overview

Camzyos is a medicine used in adults to treat obstructive hypertrophic cardiomyopathy (oHCM), a disease in which the muscle in the main pumping chamber of the heart becomes thickened or enlarged, which can block the flow of blood from the heart to the rest of the body.

It is used in adults who have symptoms of the disease (class II or class III oHCM). The 'class' reflects the seriousness of the disease: 'class II' involves slight limitation of physical activity and 'class III' involves marked limitation of physical activity.

Camzyos contains the active substance mavacamten.

[Expand section](#) [Collapse section](#)

How is Camzyos used?

5.1

“The primary outcome measure included a change at week 30 in exercise capacity measured by pVO2 and symptoms measured by NYHA functional classification, defined as an improvement of pVO2 by ≥ 1.5 mL/kg/min and an improvement in NYHA class by at least 1 OR an improvement of pVO2 by ≥ 3.0 mL/kg/min and no worsening in NYHA class.”

So why acceptable here?

*“In the EXPLORER-HCM study, **the primary endpoint (a composite of pVO2max and NYHA) is difficult to interpret and not considered appropriate** for this application. Consequently, the **individual component pVO2max**, which was the second sequentially tested secondary endpoint, is considered the most relevant efficacy endpoint.”*

Supported by:

*“The most important support for **the clinical relevance of the effect on pVO₂max** observed in the EXPLORER-HCM study **can be derived from** the ongoing VALOR-HCM study, a phase 3 randomized, double-blind, placebo-controlled study in US patients **with oHCM eligible for septal reduction therapy (SRT)** according to the ACCF/AHA 2011 guideline.”*

*“...beneficial effect on exercise capacity (pVO₂max) and **preventing patients from (progressing to) septal reduction therapy** eligibility is supported by significant improvements in **other relevant secondary/exploratory endpoints**, including post-exercise LVOT, NYHA functional class, NT-proBNP, and health status (KCCQ-23 CSS and HCMSQ SoB).”*

But, *“... **safety database remains too limited** in order to exclude a detrimental effect on cardiovascular safety.”*

- Primary endpoint – clinically meaningful
 - **Clinical benefit in terms of what patient feels and functions**
 - **PD markers rarely enough for approval**
 - Mortality and morbidity data must always be reported whatever the clinical claim
- But, while rarely excepted PD endpoints may be acceptable when
 - **Good delineation of the target population – rare disease settings (e.g., conditional approval)**
 - **Early interaction required - SAWP**
 - Scientific Advice (product related - confidential)
 - Qualification Procedure (independent – public), but a very high hurdle for qualifying a primary endpoint



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