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CBG MEB
MEDICINES EVALUATION BOARD

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

GOOD MEDICINES USED BETTER

# Presenter Disclosure

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)

**27 National Competent Authorities (incl CBG-MEB) Responsible for expertise**

**EU institutions: Commission – Parliament**

**Management Board**


Committee on Herbal Medicinal Products **HMPC**

Committee for Advanced Therapies **CAT**

Pharmacovigilance Risk Assessment Comittee **PRAC**

Committee for Human Medicinal Products **CHMP** and WPs (incl. **CVWP**)

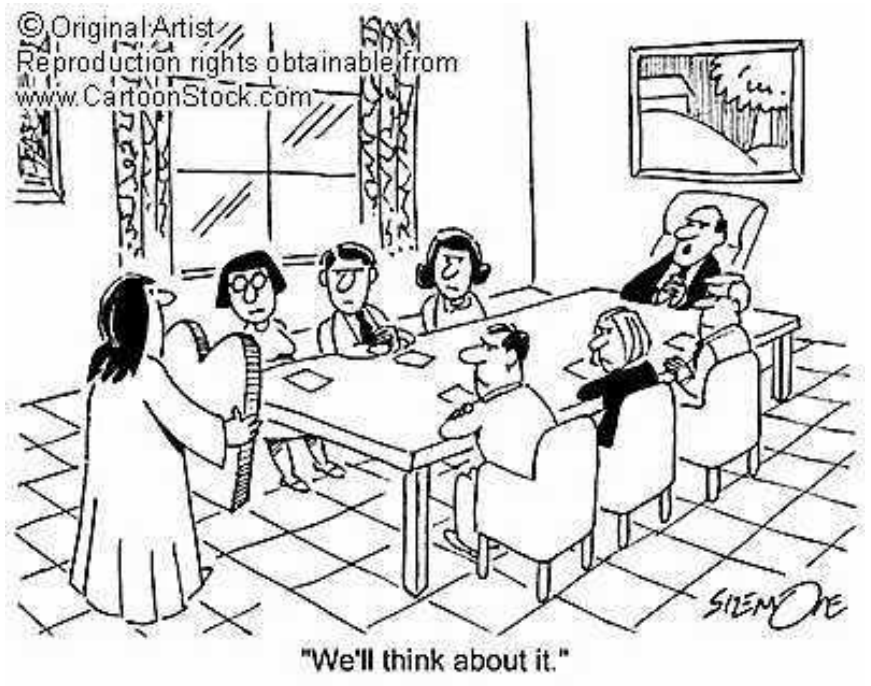
Paediatric Committee **PDCO**

Committee for Veterinary Medicinal Products **CVMP**

Committee for Orphan Medicinal Products **COMP**

# The regulatory framework

## For each step in the procedure: guidelines!


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

Guideline purpose:
To enable adequate benefit-risk assessment

# 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)*

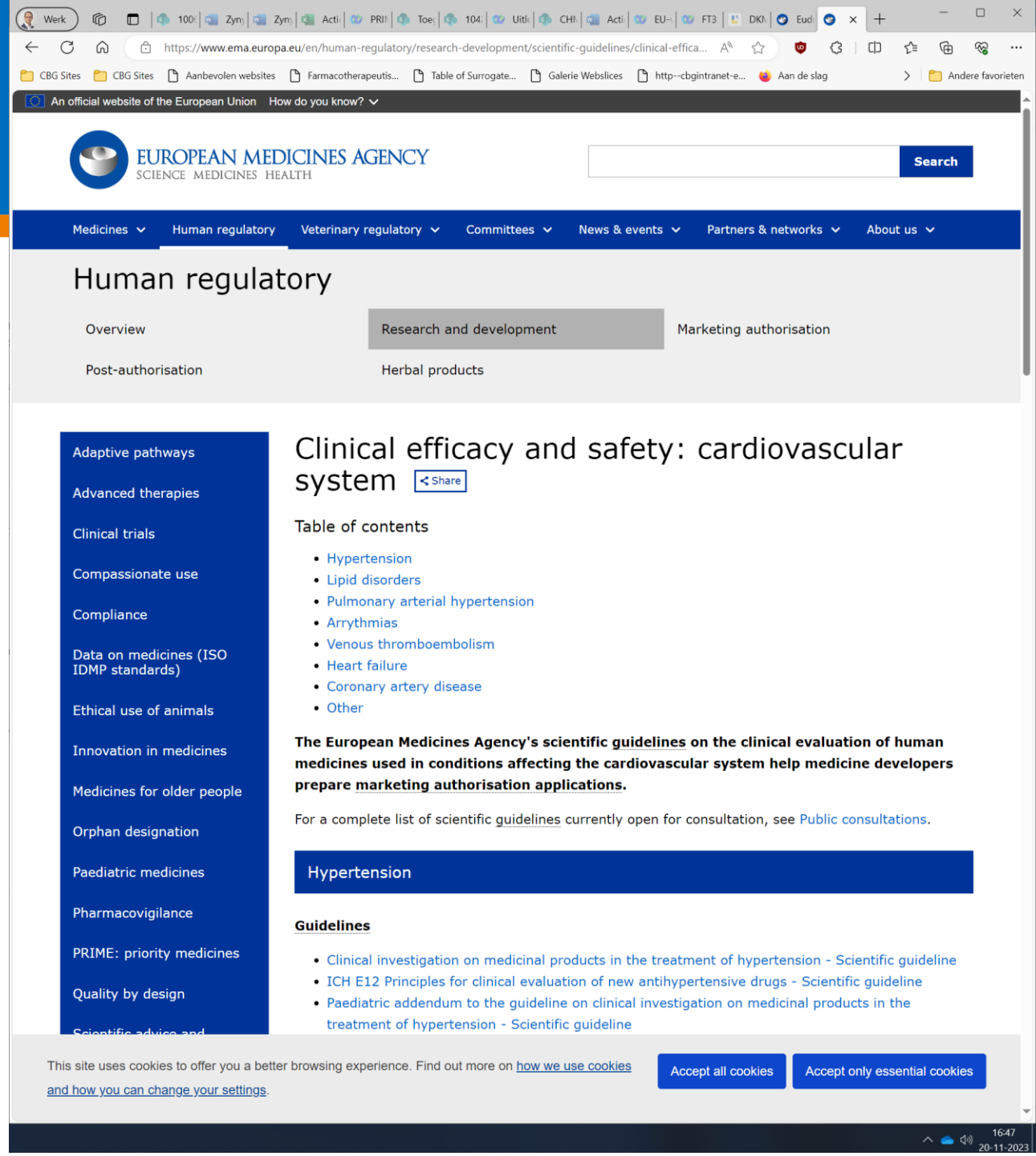
But not,

HDL-c

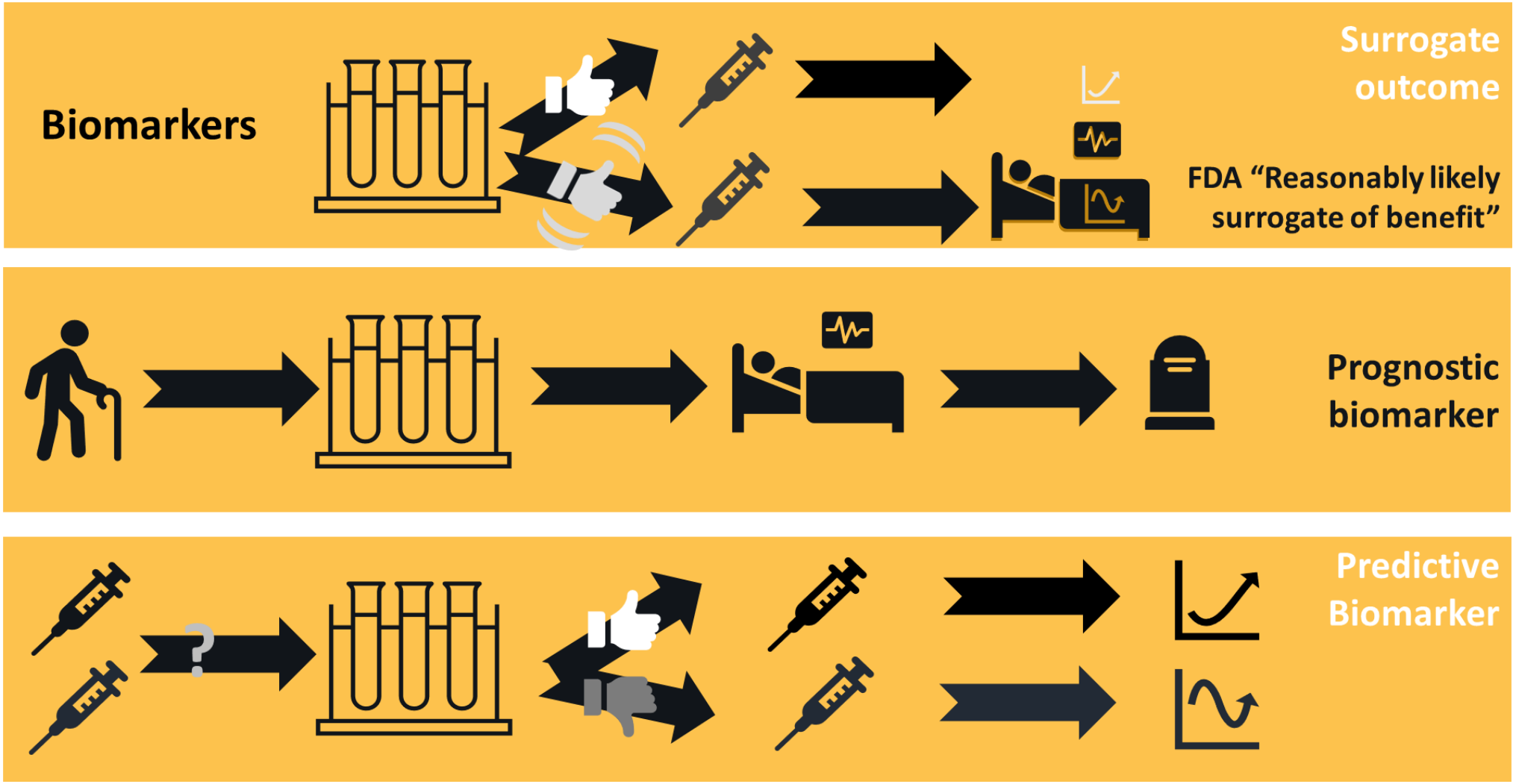
BNP or NT-proBNP

PVR (PAH)





# Biomarkers


Biomarkers
Surrogate outcome
FDA "Reasonably likely surrogate of benefit"
Prognostic biomarker
Predictive Biomarker

UPPSALA UNIVERSITET

# 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

Elisabeth Bakker[1,†], Natalie M. Hendrikse[2,†], Falk Ehmann[2], Daniëlla S. van der Meer[1,3], Jordi Llinares Garcia[2,†], Thorsten Vetter[2], Viktoriia Starokozhko[1,3] and Peter G.M. Mol[1,3,4,*]

Received: 22 July 2023 | Revised: 22 July 2023 | Accepted: 21 August 2023

doi:10.1111/cts.13641

ARTICLE

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

Elisabeth Bakker[1] | Viktoriia Starokozhko[1,2] | Jet W. M. Kraaijvanger[2,3] | Hiddo J. L. Heerspink[1] | Peter G. M. Mol[1,2]

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doi: 10.3389/fphar.2021.662642

OPEN ACCESS

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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

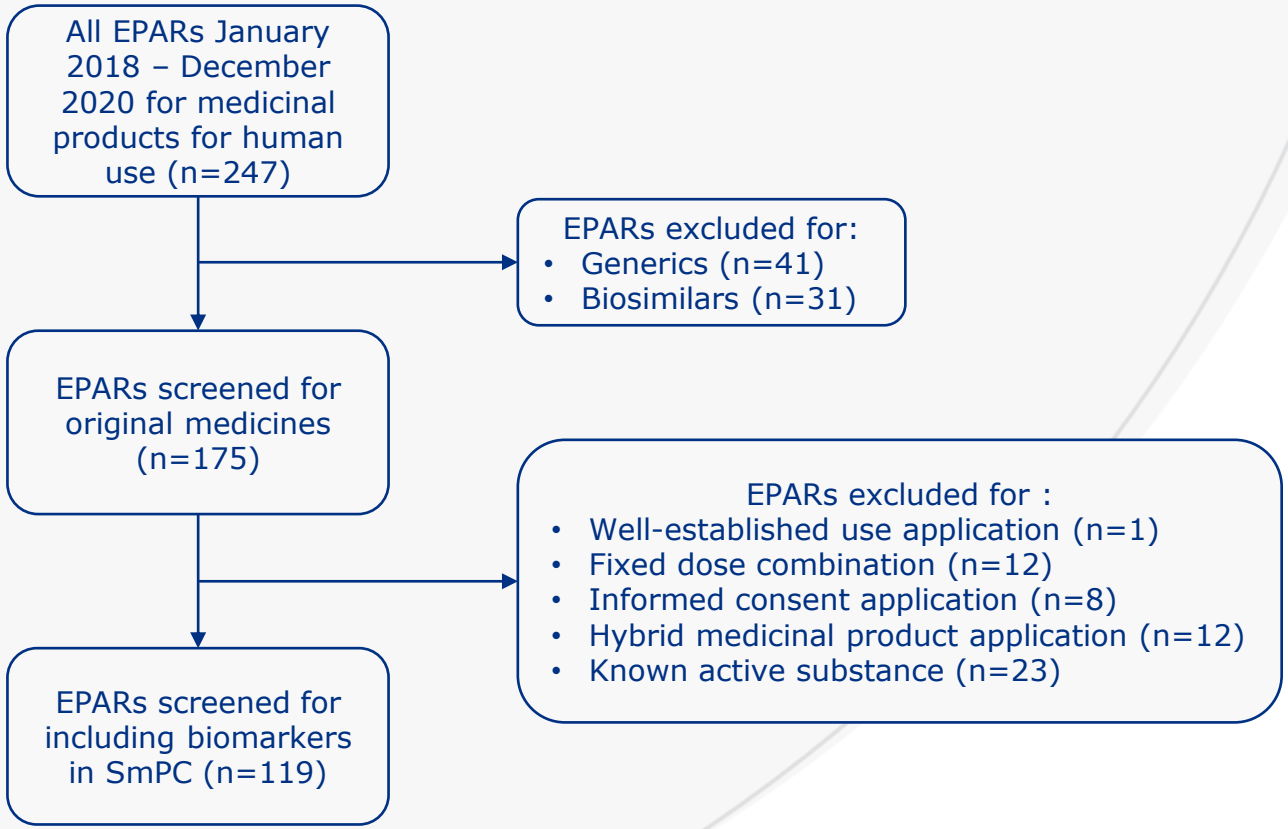
*Elisabeth Bakker[1†], Peter G. M. Mol[1,2,3†], João Nabais[4,5†], Thorsten Vetter[6], Matthias Kretzler[7†], John J. Nolan[8†], Gert Mayer[9†], Anna K. Sundgren[10†], Hiddo J. L. Heerspink[1†], Anja Schiel[3,11], Sieta T. de Vries[1†], Maria F. Gomez[12†], Friedrich Schulze[13], Dick de Zeeuw[1†] and Michelle J. Pena[1*†] 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

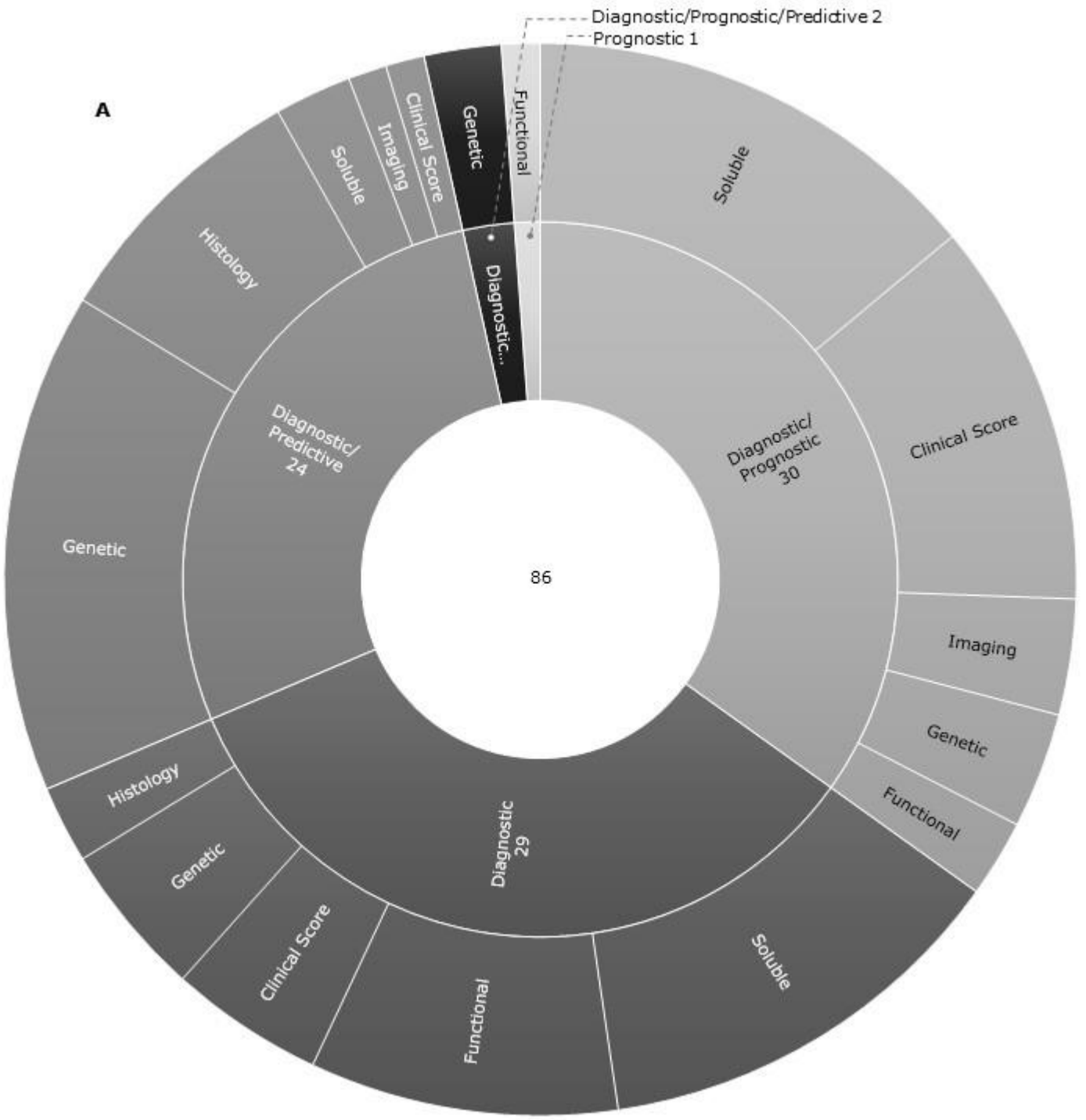
**Precision medicine in regulatory decision making: Biomarkers used for patient selection in European Public Assessment Reports from 2018 to 2020**

Elisabeth Bakker[1] | Viktoriia Starokozhko[1,2] | Jet W. M. Kraaijvanger[2,3] | Hiddo J. L. Heerspink[1] | Peter G. M. Mol[1,2]



# 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

BEAT DKD

umcg

# 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 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 |

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

# e-GFR slope

## Qualification Opinion as agreed by CHMP

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

### *Agreed Context of Use (CoU)*

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

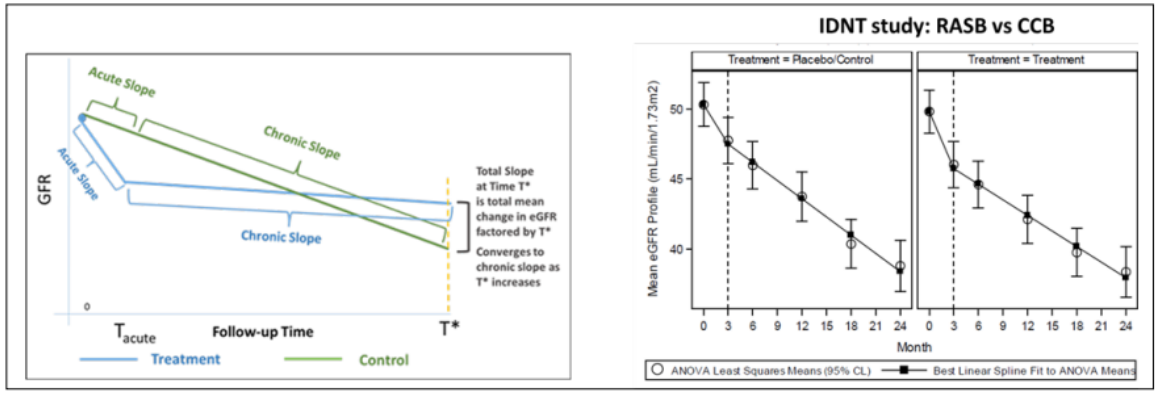



**Figure R3: GFR slope by treatment arm.** Left panel hypothetical example and right panel demonstration in an example study. eGFR, Estimated glomerular filtration rate; GFR, Glomerular filtration rate; RCT, Randomized controlled trial; T, Time.



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 |

# Qualification of Novel Methodologies



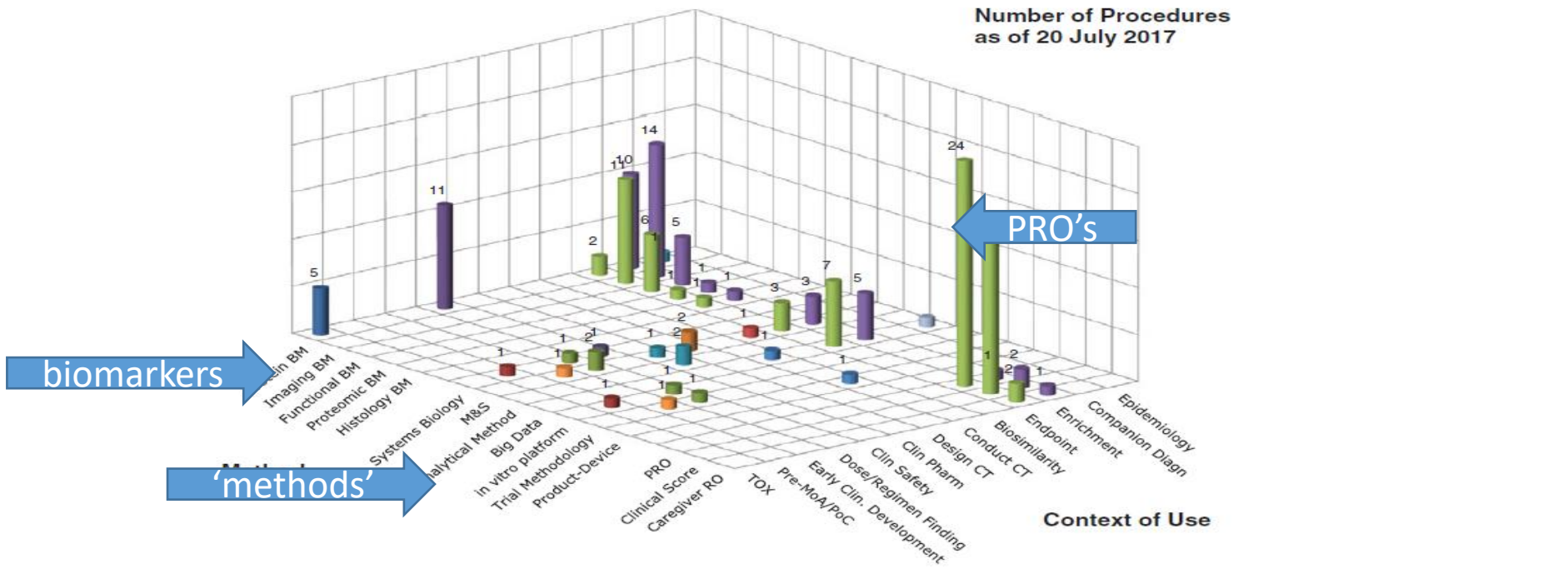



**FIGURE 1** Scope of qualification of novel methodologies applications at the European medicines agency. The novel methodology (method) and their intended use (Context of Use) that were submitted to the Scientific Advice Working Party of the European Medicines Agency up to July 20, 2017 are presented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

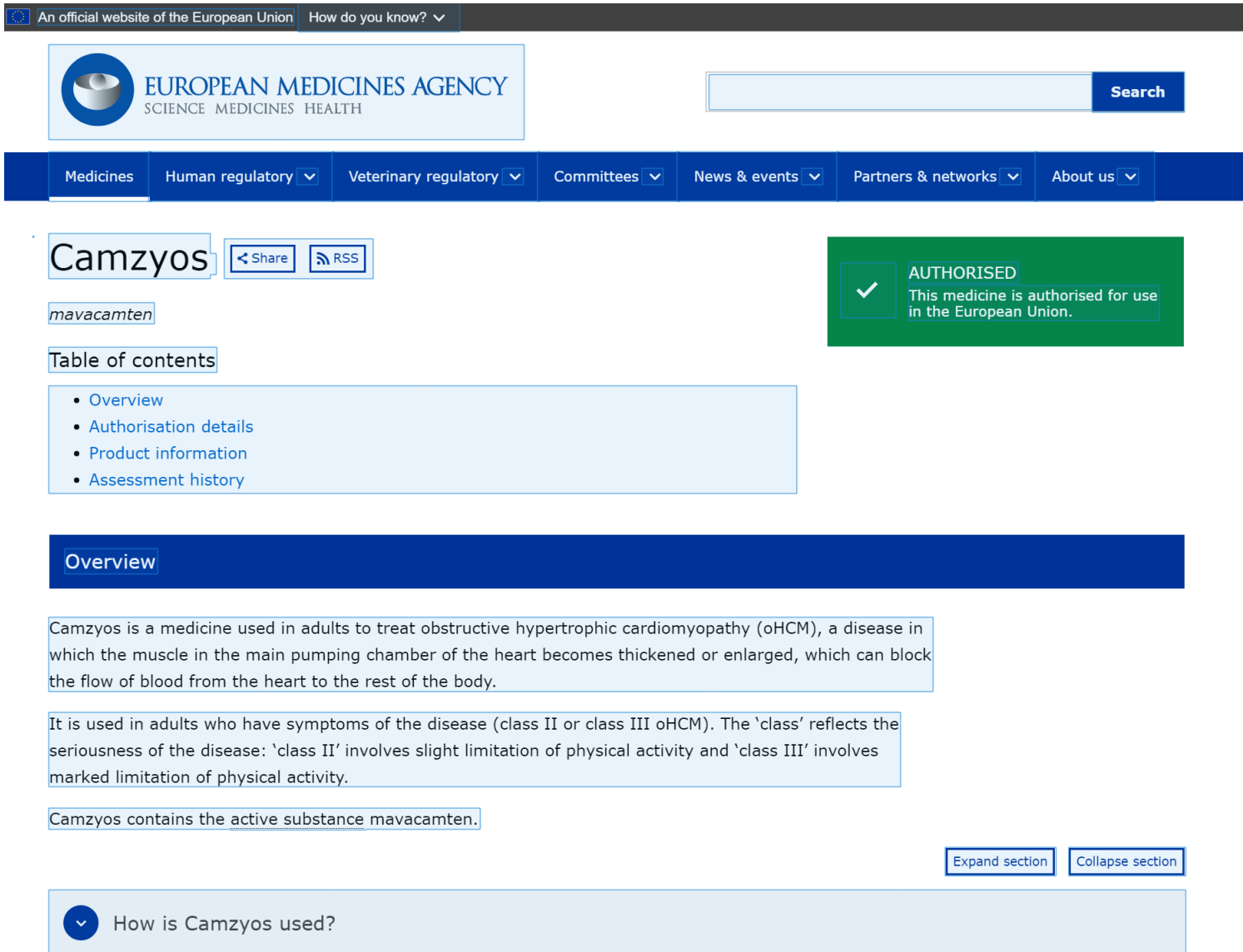
Mol, P.G. et al. Diabetes Obes Metab. 2018

# Mavecamten

*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**)"*



# Mavecamten (II)

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."*

# Mavecamten (III)

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."*

# Conclusion

- 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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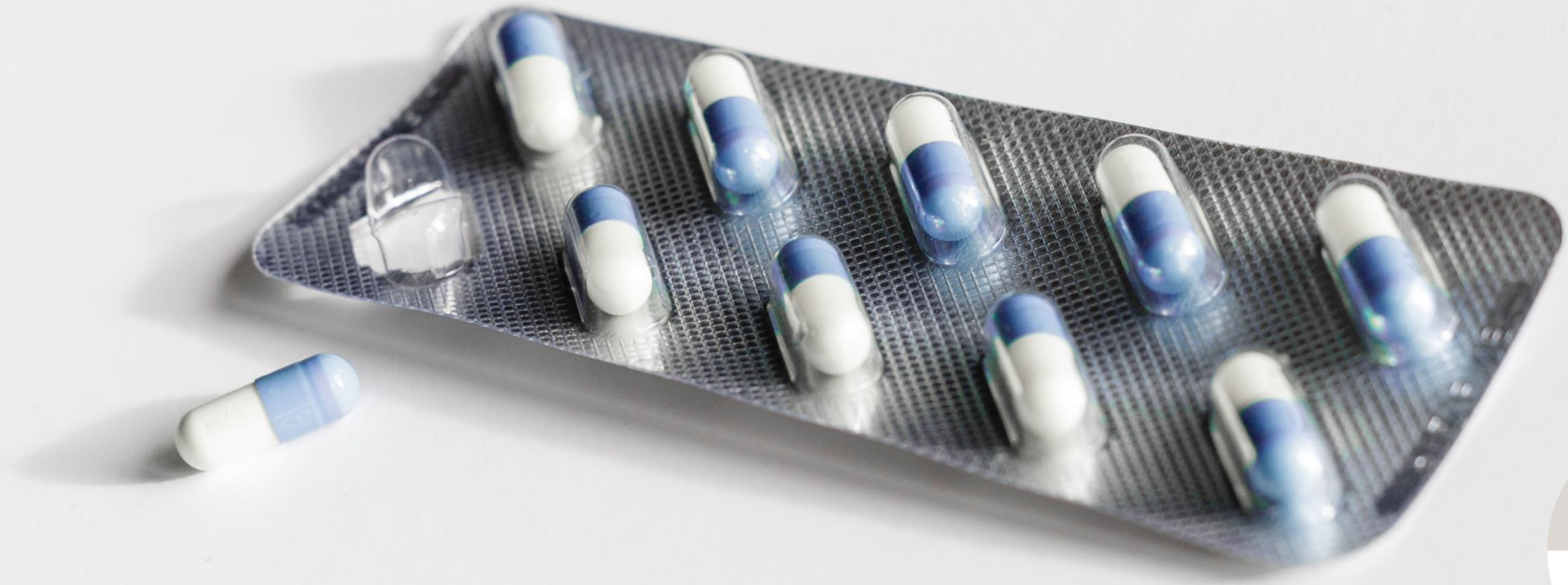

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