Received: 22 October 2024 | Revised: 24 January 2025 | Accepted: 26 February 2025

DOI: 10.1002/trc2.70072

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Biomarkers for neurodegenerative diseases in regulatory decision-making by the European Medicines Agency

Audrey M. M. Hermans[1,2] | **Elisabeth Bakker**[2] | **Viktoriia Starokozhko**[1,2,3] | **Loes den Otter**[1,4] | **André J. A. Elferink**[1,3] | **Angela Bradshaw**[5] | **Lorenzo Guizzaro**[3] | **Peter G. M. Mol**[1,2,3] | **Anna M. G. Pasmooij**[1,6]

[1]Dutch Medicines Evaluation Board (MEB), Utrecht, The Netherlands

[2]Department of Clinical Pharmacy and Pharmacology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[3]European Medicines Agency, Amsterdam, The Netherlands

[4]Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands

[5]Alzheimer Europe, Luxembourg Ville, Luxembourg

[6]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

Correspondence
Audrey Margaretha Maria Hermans, Dutch Medicines Evaluation Board (MEB), Graadt van Roggenweg 500, 3531 AH Utrecht, The Netherlands.
Email: a.hermans@cbg-meb.nl

Funding information
Innovative Medicines Initiative 2 Joint Undertaking, Grant/Award Number: 101034344; European Union's Horizon 2020; Innovative Medicines Initiative, Grant/Award Number: 101034344

Abstract

INTRODUCTION: Biomarkers (BMs) are valuable tools to facilitate early diagnosis of (subtypes of) diseases, improve patient selection and stratification, and detect therapeutic effects or safety concerns. This study explores the extent to which BMs are utilized in the development of treatments for neurodegenerative diseases (NDDs), as well as topics of discussion regarding BMs in regulatory advice- and decision-making processes and sharing of BM-related data.

METHODS: The European Medicines Agency's marketing authorization application (MAA), qualification (QA/QO), and scientific advice (SA) procedures regarding NDDs were screened, and those that mention BMs were analyzed. Data were extracted on the intended disease, BM type, and context of use proposed by applicants. BMs were categorized based on both nature and function.

RESULTS: In total, 105 procedures that discussed BMs were analyzed, 57 SAs (January 2020 to December 2022), 19 QAs/QOs (January 2008 to December 2023), and 29 MAAs (January 1995 to December 2023). The majority involved Alzheimer's disease (AD; $n = 30$), Parkinson's disease (PD; $n = 9$), and multiple sclerosis (MS; $n = 33$). Imaging BMs were the most common type of BMs discussed, and most BMs were used as pharmacodynamic/response measures. The acceptance and role of BMs differed between AD, PD, MS, and other NDDs. In regulatory procedures for AD, for example, diagnostic BMs guiding patient selection were commonly discussed, whereas in MAAs for MS, imaging BMs (particularly lesions) were generally accepted as supportive/secondary endpoints.

DISCUSSION: Despite the established role of certain BMs, mainly imaging BMs for MS, there remains a major need for more precise and reliable BMs to improve diagnostic accuracy and treatment monitoring for NDDs. To implement novel BMs and facilitate development of new treatments and to eventually improve clinical practice, robust

Audrey M. M. Hermans and Elisabeth Bakker share first authorship.

evidence bases showcasing biological plausibility or clear clinical benefits are essential. Collaboration and data-sharing among stakeholders is vital in generating this evidence and enhancing the understanding and management of NDDs.

KEYWORDS
Alzheimer's disease, biomarker, European Medicines Agency, multiple sclerosis, neurodegenerative diseases, Parkinson's disease, precision medicine

Highlights

- The European Medicines Agency's marketing authorization applications and qualification and scientific advice procedures.
- One hundred five procedures were analyzed regarding neurodegenerative diseases that discuss biomarkers.
- We found that acceptance and role of biomarkers differ per disease.
- Biological plausibility/clinical benefits are essential for biomarker implementation.

1 | BACKGROUND

In the field of neurodegenerative diseases (NDDs), including but not limited to Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), there is an urgent need for the development of new treatments, as the prevalence of NDDs is expected to rise significantly with increasing life expectancy.[1] NDDs, defined as "a heterogeneous group of disorders that are characterized by the progressive degeneration of the structure and function of the central nervous system or peripheral nervous system," commonly cause cognitive and motor impairments.[2] Because their epidemiology, symptoms, neuropathology, and neuroimaging features vary,[3] timely diagnosis and monitoring and treatment strategies are often complicated, especially for atypical variants or NDDs in the early stage, where treatment may be most beneficial.[4,5]

Biomarkers (BMs) are imaging features or biological molecules found in blood, other body fluids, or tissues[6] that have emerged as valuable tools that can guide earlier diagnosis of specific NDDs and subtypes, guide earlier detection of therapeutic effects in specific populations, and enhance development and provision of personalized prevention and treatment.[7]

BMs used in clinical development programs generating pivotal evidence for the assessment of new medicines in the European Union must be validated through appropriate studies to be accepted by drug regulators and downstream decision-makers. For example, in the past years, three anti-amyloid monoclonal antibodies intended to treat early AD—*aducanumab*, *donanemab*, and *lecanemab*—were submitted to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The FDA granted authorization to two medicines via its Accelerated Approval program, which allows for earlier authorization of medicines addressing a high unmet need based on what they deem to be a reasonably likely surrogate endpoint,[8,9] in this case, based on their ability to lower amyloid plaque levels in the brain. Although the EMA recognized this ability to lower amyloid plaque levels, aducanumab's authorization was refused because "the link between this effect and clinical improvement had not been established."[10] Lecanemab's accelerated authorization was later converted by the FDA to traditional authorization.[11] Although lecanemab's authorization was initially refused by the EMA because its effect "does not counterbalance the risk of serious adverse events associated with the medicine," lecanemab has recently received a positive opinion for a restricted indication.[12,13] The EMA has an expedited authorization program similar to the FDA's Accelerated Approval program, Conditional Marketing Authorization, which relies on benefit–risk assessment and expires yearly[9]; however, this was not utilized in the cases of aducanemab and lecanemab. Currently, the FDA has also granted traditional authorization to *donanemab*, which at the EMA is still under evaluation.[14] The FDA's decision to authorize these medicines, in contrast to the EMA's initial refusals, has sparked discussion about their differing approaches. Although both agencies generally show a high degree of concordance in marketing authorization decisions (91%–98%),[15] these examples highlight instances where they diverge. The FDA's Accelerated Approval is known to rely more on unmet need and can be based on reasonably likely surrogates of benefit.[16] Of note, the FDA's revised draft guidance regarding drug development for early AD recognizes the use of BM data (e.g., brain amyloid burden, as measured by positron emission tomography) to support the accelerated authorization of these medicines.[17]

Given the debate about BMs in the authorization process of these AD medicines, it is valuable to examine in more detail how BMs are used and discussed in interactions with the EMA. Several procedures exist for drug developers to interact with the EMA's Committee for Medicinal Products for Human use (CHMP) prior to applying for *marketing authorization* (MAA), including *scientific advice* (SA) and *qualification of novel methodologies for medicines development* (QoNM), resulting in *qualification advice* (QA), which may in addition provide a *letter of support* (LoS), or a *qualification opinion* (QO) [18] (see Box 1).

Box. 1. Description of interaction possibilities with the European Medicines Agency (EMA) through scientific advice (SA), qualification of novel methodologies, or innovation task force (ITF) meetings

Through *scientific advice* (SA) procedures, developers can engage with regulators to align development expectations, by posing questions and presenting their plans, after which they receive guidance from the EMA.[1] Additionally, the EMA offers protocol assistance for orphan designated medicines and has established the qualification of novel methodologies (QoNM) for medicine development in 2008, allowing for the assessment and potential endorsement of new methodologies in the context of drug development, such as BMs, by the Committee for Medicinal Products for Human Use (CHMP).[2] Such a qualification procedure can result in a *qualification advice* (QA), in which the CHMP advises on protocols and methods when a methodology is not considered mature enough for qualification yet. In addition to the qualification advice, EMA may issue a *letter of support* (LoS), which becomes publicly available on the EMA website, signaling that the methodology is considered promising for future qualification. If a novel methodology is broadly endorsed by the CHMP, they may issue a *qualification opinion* (QO).[2] Furthermore, it is possible to request an *innovation task force* (ITF) meeting, which functions as a discussion platform for early dialogue. It aims to help in proactively identifying scientific, regulatory, and legal issues of emerging therapies and technologies.[3] An ITF is an informal meeting intended to fill the gap between early-stage research and formal regulatory procedures that involve fees, such as SAs and the QoNM.[3]

[1]European Medicines Agency. Scientific advice and protocol assistance [Internet]. 2023 [Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance.

[2]European Medicines Agency. Qualification of novel methodologies for medicine development [Internet]. 2024 [cited 2024 8th of May]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0.

[3]European Medicines Agency. Supporting Innovation [Internet]. 2024 [Available from: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/supporting-innovation.

RESEARCH IN CONTEXT

1. **Systematic review**: We analyzed the European Medicines Agency's marketing authorisation applications, qualification, and scientific advice procedures related to neurodegenerative diseases (NDDs), focusing on the role of biomarkers (BMs). Key data extracted included the disease, BM type, and context of use.
2. **Interpretation**: Our findings provide the first comprehensive overview of BM use in regulatory decision-making for NDD treatments. This helps inform future BM discovery and validation efforts, offering valuable insights into the current regulatory landscape.
3. **Future directions**: There is a need for more precise and clinically validated BMs for NDDs. Future efforts should prioritize building a robust evidence base, with collaboration and data-sharing across stakeholders being crucial. Initiatives like the European Platform for Neurodegenerative Diseases can accelerate BM discovery and validation, thereby enhancing the development of effective therapies.

Previous publications have explored advances in the field of BMs for NDDs[5] or the use of BMs in the European or global regulatory contexts.[18–21] However, no comprehensive overview is available that details the role of BMs in the development, and European regulatory advice- and decision-making, for NDD treatments. Within the scope of the Innovative Medicines Initiative (IMI)–funded European Platform for Neurodegenerative Diseases (EPND) (see Supplementary Material 1), this study was designed to describe the extent to which BMs are utilized in the development of NDD treatments and to explore topics of discussion around these BMs and sharing of BM-related data within European regulatory advice- and decision-making processes, ultimately informing initiatives for BM discovery and validation for future therapeutic developments.

2 | METHODS

Regulatory dossiers regarding NDD medicines development and authorization submitted to the EMA that mentioned BMs were analyzed. The included MAAs were selected from all MAAs since the establishment of the EMA (January 1995 to December 2023), including refused and withdrawn MAAs. All qualification procedures since initiation of the QoNM procedure were screened for inclusion (January 2008 to December 2023). For feasibility reasons, SAs were selected from 3 recent years (January 2020 to December 2022), since there are more than 750 SAs yearly.[22]

2.1 | Selection of procedures

The units of analysis are MAA, QA/QO/LoS, and SA procedures described in NDD regulatory dossiers. A complete overview of included NDDs, based on the International Classification of Diseases, Eleventh Revision (ICD-11),[23] is provided in the Supplementary Material 2.[23] Each procedure could comprise several (candidate) BMs, either as individual BMs or as part of a panel. Related procedures, such as follow-up procedures, were treated as independent units.

Type of procedure	Dates included	Data obtained from
Marketing Authorisation Application (MAA)	January 1st 1995- December 31st, 2023	EMA website (overview table) (24) Union Register of medicinal products for human use (26)
Qualification of Novel Methodologies for Medicine Development (QA/QO/LoS)	January 1st, 2008 – December 31st, 2023 (i.e. since the introduction of the procedure)	IRIS; internal EMA database EMA website screened (August 2024) (25)
Scientific Advice (SA)	January 1st, 2020 – December 31st, 2022	IRIS; internal EMA database

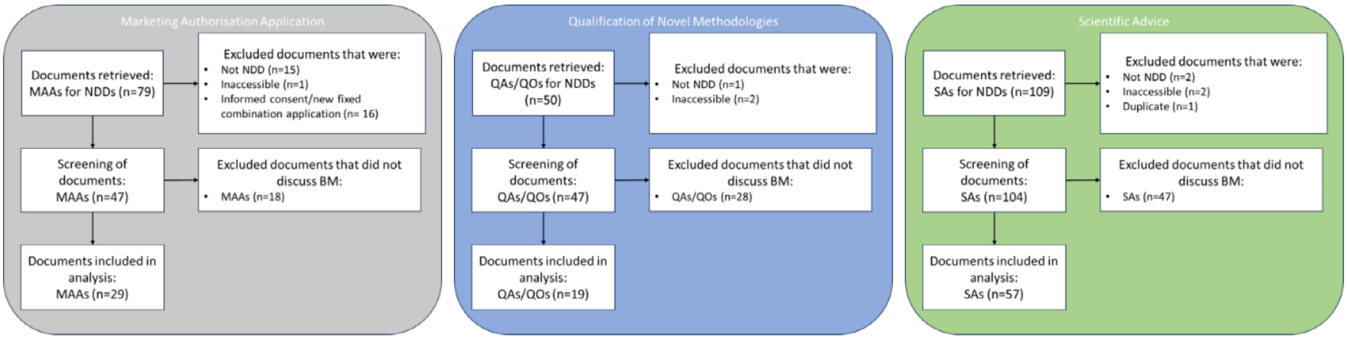

FIGURE 1 Study population and source documents and selection of biomarker-related regulatory documents on NDDs at the EMA. In gray: MAAs, resulting in 29 included documents. In blue: QA/QO procedures, resulting in 19 included documents. In green: SAs, resulting in 57 included documents. EMA, European Medicines Agency; MAA, marketing authorisation applications; NDD, neurodegenerative diseases; SA, scientific advice; QAs/QOs, qualifications.

The documents were retrieved from the EMA's internal database IRIS (QA/QO/LoS, SA) or the EMA website (MAA)[24] (Figure 1). European Public Assessment Reports (EPARs) of the MAAs, as well as the QOs and LoS, are publicly available on the EMA website. The used search strategy is presented in Supplementary Material 3. The identified documents were cross-checked with those provided on the Union Registry (MAA), the EMA website (QOs/LoS), and internal records of all requested QAs/SAs.[25,26] The obtained documents were screened to determine their eligibility for inclusion. Documents were excluded if they were not related to NDDs, or were duplicates, inaccessible, or solely aimed at treating a symptom. Only initial, full MAAs (with a legal basis of Article 8(3)) were included. MAAs concerning generics, informed consent, or new fixed-dose combination applications were excluded. For QAs/QOs and SAs withdrawn before completion of the procedure, it was confirmed that these documents could not be retrieved. In addition, QAs/QOs that aimed to qualify non-BM methodologies—including clinical scores, performance outcomes, patient-reported outcomes, registries and other data platforms, clinical trial methodologies, and statistical or modeling methods—were excluded. The selection process was performed by one researcher (A.M.M.H.) and validated by at least one other researcher (A.M.G.P., E.B., L.d.O., P.G.M.M., V.S.). Disagreements were resolved through discussion until consensus was reached.

2.2 | Data extraction, characterization, and interpretation

For each procedure, several characteristics were extracted, including the NDD (and subtype) for which the medicine was intended, and information regarding sharing and access of data and samples. Additional characteristics were extracted depending on the type of procedure:

1. MAA procedures: Whether SA had been sought before the MAA.
2. Qualification procedures: The outcome of the procedure (QA/QO) and whether it was a follow-up procedure. In the case of a QA, it was reported whether the applicant received an LoS.
3. SA procedures: Whether it was a follow-up procedure.

For all BMs, the following characteristics were extracted: BM type, and context of use (CoU) proposed by the applicant. Each BM was categorized based on its function, according to the EMA's definition of BMs and categories used in previous studies (Table 1).[6,18] In addition, BMs were assigned to the following broad CoU-categories: (1) patient selection, stratification, and/or enrichment; (2) efficacy; and (3) safety. BMs could be assigned to multiple intended CoU, BM-categories, BM-types, and/or diseases.

3 | RESULTS

3.1 | Overview of regulatory documents

The total number of regulatory documents for NDDs within the defined study periods that were identified were 78 MAAs (January 1995 to December 2023), 50 QAs/QOs (January 2008 to December 2023), and 109 SAs (January 2020 to December 2022) (Figures 1 and 2). After the exclusion of documents for various reasons, 44 MAAs, 47 QAs/QOs, and 104 SAs were screened for discussions on BMs. Of those, 29 MAAs, 19 QAs/QOs, and 57 SAs met the inclusion criteria

TABLE 1 Definitions, adapted from the EMA's definition of BMs[6] and the categories used in previous studies.[7,13,15]

BM categories	Definition
• Diagnostic BM	Used to identify individuals with a disease or condition.
• Prognostic BM	Used to identify the likelihood of a clinical event, disease recurrence, or progression.
• Predictive BM	Used to identify the likelihood of a response to exposure to a particular medicine. The response could be a symptomatic benefit, improved survival, or an adverse effect.
• Pharmacodynamic/response BM	Used to show that a (beneficial or harmful) biological response has occurred in an individual after exposure to a medicine.
Biomarker measurement	The method is used to quantify the biomarker.
• Imaging BM	Measurement of the BM through imaging.
• Histopathology BM	Measurement of the BM in biological tissues.
• Physiology BM	Measurement of the BM through physiological responses.
• Soluble BM	Measurement of the BM in biological fluids.
• Genetic BM	Measurement of the BM through DNA sequencing.
• BM panel/algorithm	
BM CoU	
• Patient selection, stratification, and/or enrichment	
• Efficacy ○ Surrogate efficacy/primary endpoint ○ Secondary endpoint ○ Tertiary endpoint (or higher)/Exploratory endpoint	
• Safety	
• Proof of concept	

Abbreviations: BM, biomarker; CoU, context of use; DNA, Deoxyribonucleic Acid; EMA, European Medicines Agency.

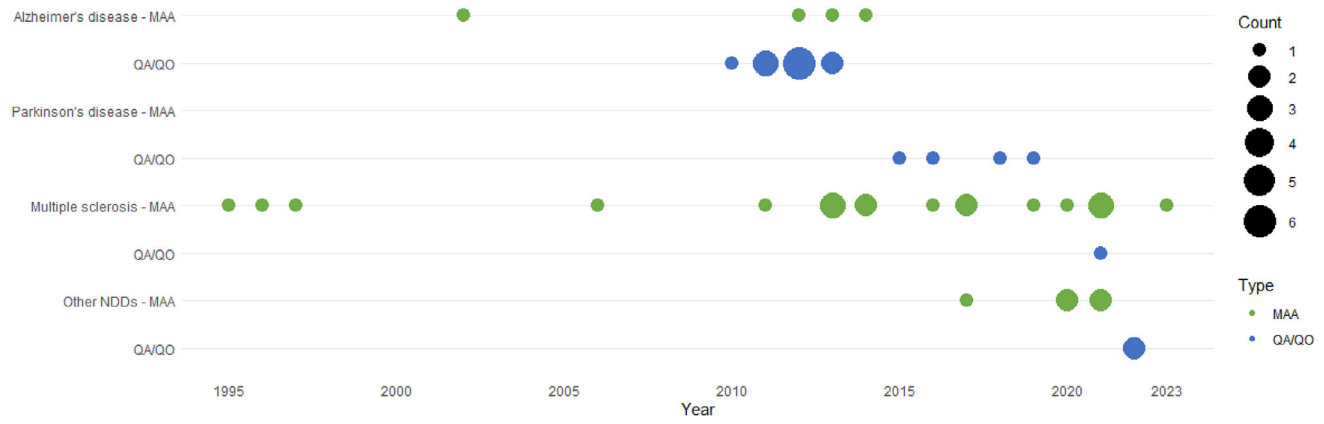

FIGURE 2 Timeline of MAAs and QA/QO procedures discussing BMs related to AD, PD, MS, and other NDDs. In green: MAAs from the establishment of the EMA in 1995 until 2023, focusing on the mentioned diseases. In blue: QAs/QOs since the introduction of the qualification of novel methodologies for medicine development in 2008 until 2023. AD, Alzheimer's disease; BM, biomaker; EMA, European Medicines Agency; MAA, marketing authorisation applications; MS, multiple sclerosis; NDD, neurodegenerative diseases; PD, Parkinson's disease; QA, qualification advise;QO, qualification opinion.

and provided data for analysis (Supplementary Material 4). Although SA was sought prior to the MAA for 19 MAA procedures, none of these SAs were included, as 18 of those were outside of the selected study period for the SAs and one did not mention BMs. For the 19 QAs/QOs, 9 corresponding LoS could be identified. A detailed overview of the data of all included procedures that contain publicly available information is available upon request.

3.2 | AD

The four MAAs in the field of AD that discussed BMs included mainly imaging BMs detecting histopathological changes in the brains of AD patients (Table 2 and Figure 3). Three of the four authorized AD medicines were imaging radiotracers used to measure amyloid beta and tau in the brain, to inform AD diagnosis. However, it was stated

TABLE 2 BMs found for NDDs in the publicly available MAAs, QOs, and LoS.

BMs identified	Year	Procedure	Type	Use	CoU	Ref.
Alzheimer's disease						
Macrolesions	2002	1 MAA	Imaging	Diagnostic	Patient selection, stratification, and/or enrichment	27
Low hippocampal volume	2011	2 QO	Imaging	Diagnostic, Prognostic	Patient selection, stratification, and/or enrichment; Proof of concept	28,29
CSF Aβ1-42 and total tau	2011–2012	2 QO	Soluble	Diagnostic, prognostic	Patient selection, stratification, and/or enrichment	28,30
PET imaging for amyloid beta	2012–2014	3 MAA 2 QO	Imaging	Diagnostic, prognostic, predictive	Other: proof of tracer binding, patient selection, stratification, and/or enrichment	28,31–34
APOE ε4	2012–2013	2 MAA	Genetic	Diagnostic	Patient selection, stratification and/or enrichment	32,33
PD						
Dopamine transporter	2016–2018	1 LoS 1 QO	Imaging	Diagnostic, prognostic	Patient selection, stratification, and/or enrichment	35,36
MS						
Serum neutralizing activity (neutralizing antibodies)	1995	1 MAA	Soluble	Pharmacodynamic/ response	Other	37
Lesions (GdE+, T1, T2	1996–2023	17 MAA	Imaging	Pharmacodynamic/ response	Patient selection, stratification, and/or enrichment Efficacy; (surrogate) efficacy, secondary endpoint, tertiary or exploratory endpoint	38–53
Brain volume	2011–2021	5 MAA	Imaging	Pharmacodynamic/ response	Efficacy; (surrogate) efficacy, secondary endpoint, Safety	44,48–50,54
White blood cell and/or lymphocyte count	2011–2013	2 MAA	Soluble	Diagnostic, pharmacodynamic/ response	Safety, Other	42,54
Interleukin 21	2013	1 MAA	Soluble	Predictive	Safety	39
Brain atrophy	2014	1 MAA	Imaging	Diagnostic, prognostic, pharmacodynamic/ response	Patient selection, stratification, and/or enrichment, Efficacy; secondary endpoint, exploratory or tertiary endpoint	40
Peripheral blood mononuclear cells	2014	1 MAA	Soluble	Pharmacodynamic/ response	Safety	40
Inflammatory markers (CRP, ESR, fibrinogen)	2014	1 MAA	Soluble	Pharmacodynamic/ response	Safety	40
Serum neopterin concentration	2014	1 MAA	Imaging	Pharmacodynamic/ response	Other	47
RNA gene expression profiling & genetic polymorphisms	2014	1 MAA	Genetic	Predictive	Efficacy; exploratory or tertiary endpoint	47
Cytokine/chemokine panel	2014	1 MAA	Soluble	Predictive	Efficacy; exploratory or tertiary endpoint	47
SMA						
SMN protein levels	2017	1 MAA	Soluble	Pharmacodynamic/ response	Efficacy; exploratory or tertiary endpoint	55
SMN gene	2017-2021	3 MAA	Genetic	Diagnostic, prognostic, predictive	Patient selection, stratification, and/or enrichment	55–57

(Continues)

TABLE 2 (Continued)

BMs identified	Year	Procedure	Type	Use	CoU	Ref.
Compound muscle action potential (number of motor neurons)	2017	1 MAA	Physiology	Pharmacodynamic/ response	Efficacy; secondary endpoint	55
ALS						
Lipid peroxide concentration in blood	2019	1 MAA	Soluble	Pharmacodynamic/ response	Efficacy; secondary endpoint, exploratory endpoint	58
Free fatty acid concentration in blood	2019	1 MAA	Soluble	Pharmacodynamic/ response	Efficacy; secondary endpoint, exploratory endpoint	58
MLD						
Arylsulfatase A activity	2020	1 MAA	Soluble	Pharmacodynamic/ response	Efficacy; (surrogate) efficacy	59
ALD						
ALDP-producing cells	2021	1 MAA	Soluble	Pharmacodynamic/ response	Efficacy; exploratory endpoint	60
ABCD1 gene mutation	2021	1 MAA	Genetic	Diagnostic	Patient selection, stratification, and/or enrichment	60
Lesions (GdE)	2021	1 MAA	Imaging	Diagnostic, pharmacodynamic/ response	Patient selection, stratification, and/or enrichment Efficacy; secondary endpoint, exploratory endpoint	60
Various neurodegenerative diseases						
NfL	2022	1 LoS	Soluble	Diagnostic, prognostic, pharmacodynamic/ response	Patient selection, stratification and/or enrichment Efficacy; not specified	61
BrainTale	2023	1 LoS	Imaging	Diagnostic, prognostic, pharmacodynamic/ response	Patient selection, stratification, and/or enrichment Efficacy; not specified	62

Note: A detailed overview of the data of all included procedures that contain publicly available information is available upon request.
Abbreviations: *ABCD1*, adenosine triphosphate binding cassette subfamily D member 1; Aβ, amyloid-β; ALD, adrenoleukodystrophy; ALDP, adrenoleukodystrophy protein; ALS, amyotrophic lateral sclerosis; APOE ε4, apolipoprotein E ε4; BM, biomarker; CoU, context of use; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; GdE, gadolinium-enhancing; LoS, letter of support; MAA, marketing authorisation application; MLD, metachromatic leukodystrophy; MS, multiple sclerosis; NDD, neurodegenerative disease; NFL, neurofilament light chain; PD, Parkinson's disease; PET, positron emission tomography; QO, qualification opinion; RNA, ribonucleic acid; SMA, spinal muscular atrophy; SMN, survival motor neuron.

that these BMs are not sufficient on their own to confirm AD diagnosis. The genetic BM apolipoprotein E (*APOE*) ε4 was used in trials to stratify the population and investigate differences in binding of the radiotracer based on genetic predisposition (Table 2 and Figure 3). In the fourth MAA, macrolesions were used to stratify patients in studies investigating *memantine hydrochloride* for treatment of mild to severe AD and vascular dementia. In three of the previously described procedures, the discussed BMs were included in the benefit–risk discussion of the dossier. For two of the diagnostic tracer MAAs, SA was sought before the MAAs were submitted.

Four of the 12 BM-related qualification procedures resulted in QOs, of which three were follow-up procedures to previous QAs. These four QOs included: (1) PET amyloid imaging for enrichment of predementia AD clinical trials, (2) cerebrospinal fluid (CSF) related BMs (Aβ1-42 and total tau) for selecting patients for amyloid-targeting medicines in early AD, (3) low hippocampal volume by MRI for use in clinical trials in predementia stage of AD, and (4) CSF-related BMs (Aβ1-42 and total tau) for enrichment of trials assessing medicines for mild and moderate AD (Table 2). None of the eight QAs received a LoS.

There were 14 SAs in the field of AD that discussed BMs, of which 6 were follow-up procedures related to four different medicines. Similar to the MAAs and QA/QOs, BMs discussed within these procedures were mainly imaging, soluble, and genetic BMs, mostly for selecting or stratifying trial participants (Figure 3). In two cases, an imaging BM was proposed as an efficacy measure, but the use of this BM as a surrogate for efficacy was not considered justified according to the CHMP.

3.3 | PD

Although there were 13 MAAs for medicines treating PD, none of these dossiers discussed BMs within their main studies.

The four qualification procedures related to PD discussed three diagnostic/stratification and prognostic protein-based imaging BMs,

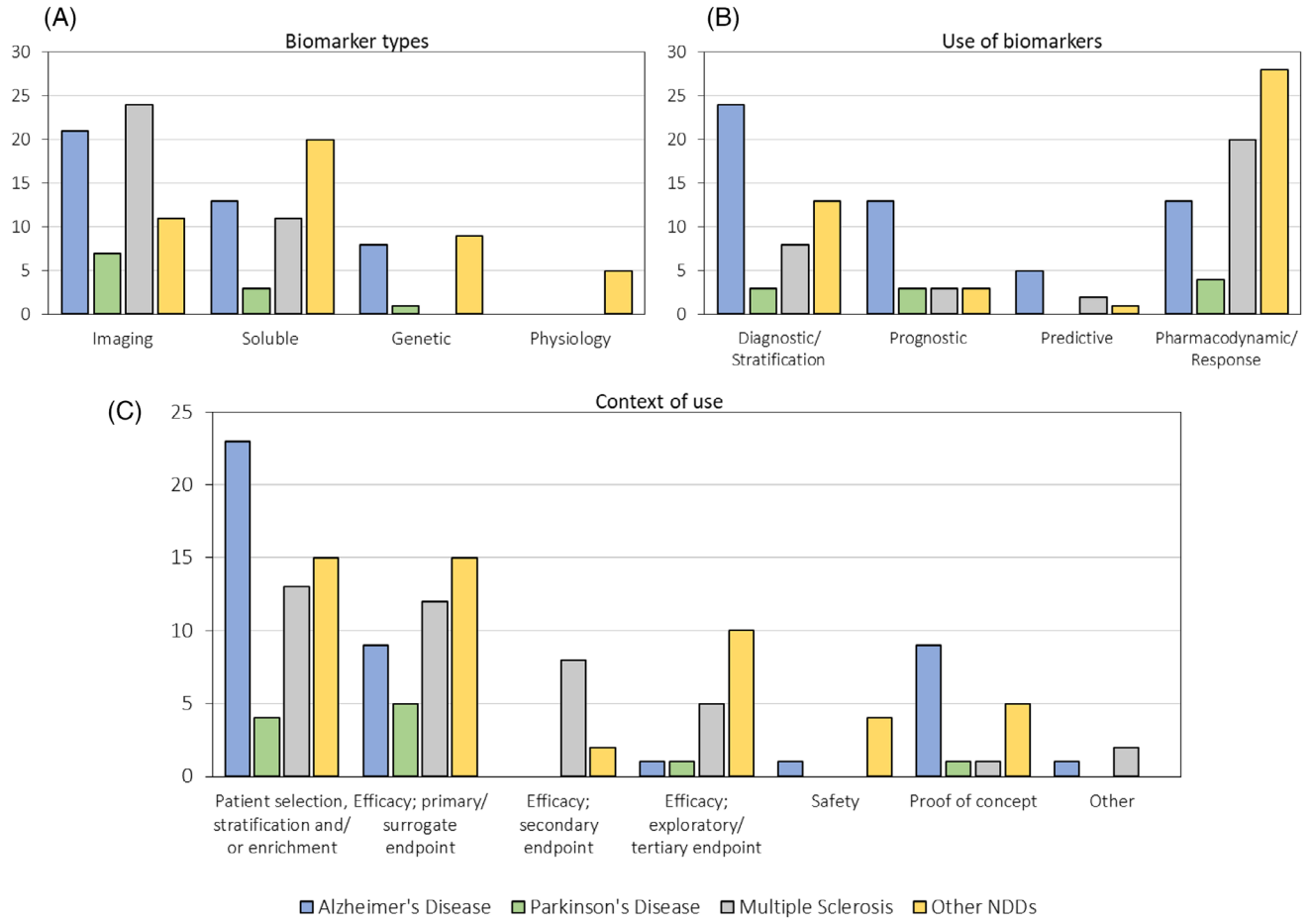

FIGURE 3 Number of regulatory documents (MAAs, qualification procedures and SA procedures) for AD, PD, MS, and other NDDs mentioning different types of BMs (A); use of BMs (B), and contexts of use (C). For AD (blue), the majority of the procedures mentioned imaging BMs ($n = 21$) or BMs used for diagnostic/stratification purposes ($n = 24$), and the most seen CoU was patient selection, stratification, and/or enrichment ($n = 23$). For Parkinson's disease (green), most BMs were imaging BMs ($n = 7$) or BMs used for pharmacodynamic/response purposes ($n = 4$), and the most observed CoU was efficacy as a primary/surrogate endpoint ($n = 5$). For MS (gray), the majority of BMs were imaging BMs ($n = 24$) or BMs used for pharmacodynamic/response purposes ($n = 20$), with the most frequent CoU being patient selection, stratification, and/or enrichment ($n = 13$). Finally, for other NDDs (yellow), the majority of BMs were soluble BMs ($n = 20$) or BMs used for pharmacodynamic/response purposes ($n = 28$), with the most observed CoUs being patient selection, stratification, and/or enrichment ($n = 15$), and efficacy as a primary/surrogate endpoint ($n = 15$). AD, Alzheimer's disease; BM, biomarker; CoU, context of use; MAA, marketing authorisation application; MS, multiple sclerosis; NDD, neurodegenerative diseases; PD, Parkinson's disease; SA, scientific advice.

and one pharmacodynamic protein-based imaging BM used for monitoring disease progression or response (Figure 3). One QA, regarding molecular imaging of dopamine transporters for identifying patients and enriching trials (dopamine transporter single photon emission computed tomography (DAT-SPECT)), resulted in a LoS. The follow-up procedure resulted in a QO (Table 2).

There were five SAs in PD, of which four discussed pharmacodynamic/response BMs and one discussed a genetic predictive BM to select patients with a genetic deficiency (Figure 3).

3.4 | MS

The majority of the BMs mentioned in the 20 MAAs regarding MS were lesions measured by protein-based imaging, including gadolinium-enhancing lesions, and T1 and T2 lesions, used for patient selection or to measure the effect on disease activity (Table 2 and Figure 3). About half of the included procedures also discussed these lesions as diagnostic or prognostic BMs to select and/or stratify patients for MS clinical trials. Other MAAs included soluble BMs, which were mainly pharmacodynamic/response BMs ($n = 12$) to assess safety or efficacy (Figure 3). These included, for example, lymphocyte or B-cell counts ($n = 6$), brain volume ($n = 5$), and neopterin ($n = 1$), used to confirm the recipient has a pharmacodynamic response to treatment based on the mechanism of action. Neutralizing antibodies in serum were sometimes measured ($n = 2$) to analyze whether the response to treatment was different in recipients with and without neutralizing antibodies, and several inflammatory markers were measured for safety reasons ($n = 3$). More specifically, interleukin 21 (IL-21) was measured, since it was considered as a potential predictive

BM of autoimmunity. In this specific dossier, CHMP recommended the applicant to further investigate IL-21, as well as to continue exploring additional potential BMs. BMs measured as secondary, tertiary, or exploratory endpoints included RNA gene-expression profiling BMs, a cytokine/chemokine panel, and neurofilament light chain (NfL). The first two were considered to be predictive of treatment response (*peginterferon beta-1a*). NfL was included as a secondary endpoint in the MAA of *ofatumumab*, since it was "hypothesized to be a putative BM to indicate treatment response and to predict disability worsening in patients with MS". In 18 of the 20 MAAs, BMs were considered by the CHMP of such relevance that they were also included in the benefit–risk discussion of the dossier. For fourteen of the included MAAs SA was sought before the MAA.

One qualification procedure was included, discussing a protein-based soluble BM to use as a prognostic BM or to measure efficacy response, which did not result in a QO (Figure 3).

In the selected study period, there were 12 SAs within the field of MS discussing BMs. Two of those were follow-up procedures, both related to the same medicine. Four SAs discussed diagnostic and/or stratification imaging BMs. The eight other BMs were suggested for pharmacodynamic/response purposes (Figure 3). These also included nine imaging, efficacy BMs, and four soluble, efficacy BMs, one of those included as a tertiary or exploratory endpoint.

3.5 | Other NDDs

Other NDDs for which MAAs existed that discussed BMs (n = 6) included adrenoleukodystrophy, spinal muscular atrophy (SMA), ALS, and metachromatic leukodystrophy. These discussions on BMs included four diagnostic/stratification BMs, six pharmacodynamic/response BMs, and one used for both (Figure 3). Most were soluble BMs (n = 5), followed by genetic (n = 4), imaging (n = 1), and functional BMs (n = 1), used mainly to measure efficacy (n = 6) or select patients (n = 5). In addition, BMs included two secondary endpoints, four tertiary or exploratory endpoints, and one safety measure (Table 2 and Figure 3). In five procedures, the discussed BMs were included in the benefit–risk discussion of the dossier. For five MAAs, SA was sought.

Two qualification procedures on other NDDs were included, one concerned a BM panel and one a single BM. Both were initial QAs that resulted in LoS, of which the first was the BrainTale platform, combining several dynamic imaging BMs for use as, for example, a diagnostic, disease staging, prognostic, or response to treatment (surrogate) BM (Table 2 and Figure 3). BrainTale is a digital tool for studying white matter in NDDs known to be linked to white matter alterations (e.g., leukodystrophies). The other BM was NfL, proposed as a BM of axonal damage for disease staging, to monitor disease activity, and to assess treatment responses in various pediatric neurological diseases, including SMA, neuronal ceroid lipofuscinoses 1 and 2, MS, metachromatic leukodystrophy, and mitochondrial encephalopathy (Table 2).

There were 26 SAs for other NDDs discussing BMs. Five of those were follow-up procedures. The main diseases within these 24 SAs were ALS (n = 8), SMA (n = 4), and Huntington's disease (HD) (n = 4).

3.6 | Sharing of data and samples

Information about sharing of and/or access to data and samples was not discussed in any of the included MAAs and SAs. Only the single included QA on MS discussed this topic, which related to standardizing sample collection and assay validation for the BM to ultimately qualify the BM. However, the use of publicly accessible data and intending the sharing of tools was mentioned in multiple QAs/QOs. Five of the AD procedures used publicly available data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Two AD procedures mentioned that they intended to provide a tool for diagnosis and risk assessment with the data they gathered. Four of the procedures on PD mentioned the use of public data from the Parkinson's Disease Progressive Markers Initiative (PPMI). Of interest, in one initial and one follow-up QA on PD it was mentioned by the applicant that a LoS issued by the EMA could allow the sharing of information on the BM.

4 | DISCUSSION

This analysis provides a broad perspective on the role of BMs within European regulatory procedures for NDDs. The acceptance and role of BMs differ between NDDs. The number of included MAAs discussing BMs was highest for MS (n = 20). For PD, only a few MAAs were identified, none discussing BMs. Early interaction was sought most frequently in AD, with 12 qualification procedures discussing the use of novel BMs to assist in AD diagnosis, of which 4 resulted in a QO. The majority of SAs discussing BMs (n = 24) were in the context of NDDs other than AD, PD, or MS. Most BMs within the procedures were imaging and soluble BMs used for patient selection or to assess efficacy, the latter driven primarily by the high number of MS MAAs.

Our results should be seen in the context of a rapidly changing landscape, where NDDs are being redefined as biological constructs, including their presymptomatic phases. For example, imaging BMs have been advancing rapidly in recent years and have been providing valuable information for diagnosis or monitoring of several NDDs in a minimally invasive manner.[63] This is reflected by our results, showing that imaging BMs were used predominantly within the studied dossiers, especially in the field of MS followed by soluble BMs, which were most dominant within the field of AD (Table 2). According to the EMA MS guideline, these magnetic resonance imaging (MRI) outcomes are even sufficient to establish clinical similarity for the authorization of biosimilars.[64] In addition, according to CHMP assessment, for example, in a variation application of *teriflunomide*, it is justified to use these outcomes for extrapolation to pediatric indications.[65] Although their use seems relatively established within the regulatory dossiers and gadolinium-enhancing lesions and T2 lesions are considered a crucial part of the widely accepted diagnostic criteria, a need remains for more accurate, reliable, objective, and trackable BMs to prevent

misdiagnosis and to improve monitoring of MS and its treatments.[66] Several novel imaging and soluble BMs are currently being investigated, including a cytokine/chemokine panel, BMs related to RNA gene expression, and NfL, which were also described in included MAAs as secondary, tertiary, or exploratory endpoints.

In the MAA of MS treatment, *ofatumumab* NfL was studied as a secondary endpoint. In addition, the CHMP issued an LoS for the use of NfL to monitor disease activity in various pediatric NDDs. This BM, used mainly as an indicator for neuron axonal damage, is included as an endpoint in 28 trials currently registered in the EU Clinical Trials Information System (CTIS) (including for AD, ALS, MS, and HD),[67] and has been used as a secondary outcome in studies assessed by the FDA and EMA for authorization of *tofersen*, a recently-authorized, novel treatment for a rare genetic form of ALS. Both authorities have indicated that more evidence is needed to establish the prognostic and predictive value of NfL in ALS and other NDDs, and that NfL cannot be considered a validated surrogate endpoint for NDDs, despite the biological plausibility.[68] The FDA, in the setting of unmet need, however, labeled NfL as a reasonably likely surrogate endpoint for superoxide dismutase type 1 (SOD1) ALS and granted Accelerated Approval.[16] In the EU, the majority of CHMP considered that in this rare setting with an important unmet need, the totality of the evidence was adequate to support authorization. This evidence included the NfL data, *tofersen*'s plausible mechanism of action, demonstrated SOD1 target engagement, and numerical improvement on the ALS Functional Rating Scale Revised (ALS-FRS-R).[69] Some members disagreed and requested additional information to be generated post (conditional) authorization.[68]

Also noteworthy is the use of integrated staging systems in PD and HD, with alpha-synuclein as measured by seed amplification assays playing a key role in PD.[70,71] The FDA has recently issued an LoS encouraging further studies of a novel method to amplify alpha-synuclein in CSF, to detect at-risk populations and enrich clinical trial populations.[72] In addition, the LoS encourages sharing patient-level data from clinical trials and natural history studies to enable confidence in the use of alpha-synuclein in CSF as a BM in drug development.

Also outside of the study inclusion time frame, in June 2024, CHMP adopted the QO for Centiloid Unit (CL) used to quantify brain amyloid for the enrichment of clinical trials. This methodology enables a tracer-independent standardized approach to quantitatively measure amyloid in the brain, for which the three F-18 PET tracers [^{18}F] florbetapir, [^{18}F] florbetaben, [^{18}F] flutemetamol, which were also identified in our study, are currently authorized.[73] In addition, [^{11}C]PiB, although not authorized for this indication, is used widely for evidence generation and repeatedly mentioned in the identified QOs. The CL QO stated that "it is agreed that a quantitative measurement such as CL might provide valuable additional information for the consistent inclusion of patients for AD targeted therapies and possibly also to identify the optimal window for therapeutic intervention." It also stated that it could potentially serve as a tool for monitoring and follow-up in future treatments, but that its clinical utility would rely on clinical data produced for such treatments and that, since it remains debatable if reducing amyloid beta leads to meaningful clinical benefits, using it as a surrogate BM or for monitoring treatment response is still premature.[73] Even more recently, [^{18}F] flortaucipir has been authorized as the first PET tracer in the EU for the detection of tau neurofibrillary tangles.[74] There is a growing body of literature supporting the utility of blood-based BMs in AD, with guidance on the preferred characteristics of these tests recently published by the World Health Organization.[75] For example, phosphorylated tau (p-tau) is described as a leading blood BM candidate, as it demonstrated superior diagnostic accuracy and disease specificity compared to other candidates.[76] Blood-based BMs such as amyloid, tau, and immunological markers could be helpful as early diagnostic tests to select patients who are likely to benefit from treatments and to monitor treatment effects.[77] Yet, at the same time, the researchers recognize that correlation between the BM and clinical change is essential.[77] Furthermore, as long as the BM is not fully validated, the impact of the BM on clinical endpoints remains key for regulators. Therefore, early interaction with regulators through SAs or QoNM is of added value on the road to European marketing authorization.

The above-mentioned examples illustrate that understanding of the disease mechanisms and implications of the quantities measured by each BM in such mechanisms form the basis for regulators' trust in using BMs. For AD, ALS, and other NDDs, further research on the disease mechanisms is much needed. However, even if the disease mechanism is not fully elucidated, evidence for the relation between a BM and the clinical outcome, sufficiently validated in appropriate studies, could contribute to the evidence base supporting regulatory acceptance of its use as a surrogate for clinical outcome. For example, if robust evidence on the correlation of amyloid reduction with meaningful clinical benefit had been available, it might have contributed to the evidence base supporting the AD treatments, of which one was withdrawn after re-examination and second refusal by the EMA (*aducanemab*), and the other received a positive opinion for a restricted indication at the time of writing after initial refusal (*lecanemab*).[12,13,78] In addition to mechanistic understanding, regulators require data confirming suitability for a given CoU.

The standardization of measurements, such as CL, promotes data harmonization, which in turn contributes to building a sufficient evidence base for novel NDD BMs and, eventually, treatments. This data harmonization can be enhanced by data sharing between different stakeholders in the field of NDDs. From the regulatory side, the public availability of QOs and LoS is a way for the EMA to encourage data sharing on ongoing developments, promoting further advancements while ensuring quality by being open to scientific review and discussion.[79] In addition, a summary of the most important data that form the evidence base in MAAs is published in EPARs on the EMA website. Regulatory agencies, including the EMA, aim to promote sharing of data and knowledge, as stated in their EMA Regulatory Science to 2025 Strategic Reflection. For this purpose, the EMA aims to drive a data sharing culture to foster open science that is mutually beneficial for all stakeholders. Publicly available data from ADNI and PPMI have been used in BM-related qualification procedures for AD and PD, which shows that the data sharing can be valuable for BM development in NDDs. This aim is shared by EPND (Supplementary Material 1), which seeks to accelerate BM discovery for NDDs to address the

need, for example, enabling earlier diagnosis, improved selection of patient populations, and better disease monitoring and monitoring of treatment effects.

Although this study provides valuable insights that may help achieve the abovementioned goals, the results of this study should be seen in view of some limitations. Performance outcomes, of which some could be considered digital BMs, were not included in this study, since these are beyond the scope of the used definition of BMs. However, for some NDDs, such as PD, they may be of great interest to, for example, establish efficacy or monitor disease progression. This led to an underrepresentation of the current developments in the field of PD. Another limitation of the study is that the content of SAs due to their confidentiality cannot be disclosed other than on a high-level aggregated manner. The risk of bias introduced by this type of data selection, extraction, and analyses was mitigated through data validation by multiple researchers to minimize subjectivity.

In conclusion, this study offers an overview of different approaches to BM utilization across regulatory procedures within the rapidly changing landscape of NDDs. Despite the established role of some BMs in regulatory dossiers and clinical guidelines, there remains a significant need for more precise and reliable BMs. To successfully implement novel BMs in the field of NDDs, leading to new authorized treatments, a robust evidence base is required, including demonstration of strong biological plausibility or a clear correlation of the change in BM with meaningful clinical benefits. With the increasing experience in developing and evaluating BMs, the ongoing redefinition of NDDs as clinical–biological constructs, and the exchange of knowledge through the multiple existing interaction opportunities (Box 1), regulators and researchers should establish sets of requirements for each possible CoU. Such a framework, together with continued collaboration and data harmonization and data-sharing among stakeholders will be pivotal in transforming our understanding and management of these complex disorders.

ACKNOWLEDGMENTS

We sincerely thank Falk Ehmann (European Medicines Agency) for his valuable input and feedback and Stefan Verweij (Dutch Medicines Evaluation Board) for his indispensable help with creating one of the figures. This work was supported by funding from the Innovative Medicines Initiative (IMI) 2 Joint Undertaking (JU) under grant agreement number 101034344 (European Platform for Neurodegenerative Diseases). The IMI JU receives support from the European Union's Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations.

CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

The data of the LoS, MAA, and QO procedures can be shared upon request. The data of the SA and QA procedures are confidential in nature and therefore cannot be shared.

CONSENT STATEMENT

This study is not considered a human subject research study and we confirm that consent was not necessary, for the reasons described as follows: we processed and analyzed documents that do not contain any personal data.

DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations with which the authors are affiliated.

ORCID


Audrey M. M. Hermans https://orcid.org/0000-0003-0952-767X

REFERENCES

1. Zheng JC, Chen S. Translational Neurodegeneration in the era of fast growing international brain research. *Transl Neurodegener*. 2022;11(1):1.
2. Nature portfolio. Neurodegenerative diseases. 2022. https://www.nature.com/subjects/neurodegenerative-diseases
3. Sobański M, Zacharzewska-Gondek A, Waliszewska-Prosół M, Sąsiadek MJ, Zimny A, Bladowska J. A review of neuroimaging in rare neurodegenerative diseases. *Dement Geriatr Cogn Disord*. 2020;49(6):544-556.
4. Gómez-Río M, Caballero MM, Gorriz Saez JM, Mínguez-Castellanos A. Diagnosis of neurodegenerative diseases: the clinical approach. *Curr Alzheimer Res*. 2016;13(5):469-474.
5. Hansson O. Biomarkers for neurodegenerative diseases. *Nat Med*. 2021;27(6):954-963.
6. European Medicines Agency. Biomarker. https://www.ema.europa.eu/en/glossary/biomarker#:~:text=A%20biological%20molecule%20found%20in,novel%20methodologies%20for%20medicine%20development%27
7. Knowles LLW, Bubela T. Paving the road to personalized medicine: recommendations on regulatory, intellectual property and reimbursement challenges. *J Law Biosci*. 2017;4(3):453-506.
8. U.S. Food and Drug Administration. Accelerated approval program. U.S. Food and Drug Administration; 2024. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program
9. Mehta GU, de Claro RA, Pazdur R. Accelerated approval is not conditional approval: insights from international expedited approval programs. *JAMA Oncol*. 2022;8(3):335-336.
10. European Medicines Agency. Refusal of the marketing authorisation for Aduhelm (aducanumab). European Medicines Agency; 2021.
11. U.S. Food and Drug Administration. FDA converts novel alzheimer's disease treatment to traditional approval: action follows confirmatory trial to verify clinical benefit. U.S. Food and Drug Administration; 2023. https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval
12. European Medicines Agency. Refusal of the marketing authorisation for Leqembi (lecanemab). 2024.
13. European Medicines Agency. Lecanemab. European Medicines Agency; 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/leqembi
14. Alzheimer Europe. FDA grants traditional approval to donanemab for the treatment of early Alzheimer's disease. Alzheimer Europe; 2023. https://www.alzheimer-europe.org/news/fda-grants-traditional-approval-donanemab-treatment-early-alzheimers-disease?language_content_entity=en

15. Kashoki M, Hanaizi Z, Yordanova S, et al. A comparison of EMA and FDA decisions for new drug marketing applications 2014–2016: concordance, discordance, and why. *Clin Pharmacol Ther*. 2020;107(1):195-202.
16. U.S. Food and Drug Administration. CDER drug and biologic accelerated approvals based on a surrogate endpoint. U.S. Food and Drug Administration; 2024.
17. U.S. Food and Drug Administration. Early Alzheimer's disease: developing drugs for treatment—guidance for industry. U.S. Food and Drug Administration; 2024.
18. Bakker E, Hendrikse NM, Ehmann F, et al. Biomarker qualification at the European Medicines Agency: a review of biomarker qualification procedures from 2008 to 2020. *Clin Pharmacol Ther*. 2022;112(1):69-80.
19. Gromova M, Vaggelas A, Dallmann G, Seimetz D. Biomarkers: opportunities and challenges for drug development in the current regulatory landscape. *Biomark Insights*. 2020;15:1177271920974652.
20. Bakker E, Starokozhko V, Kraaijvanger JWM, Heerspink HJL, Mol PGM. Precision medicine in regulatory decision making: Biomarkers used for patient selection in European Public Assessment Reports from 2018 to 2020. *Clin Transl Sci*. 2023;16(11):2394-2412.
21. Orellana García LP, Ehmann F, Hines PA, Ritzhaupt A, Brand A. Biomarker and companion diagnostics—a review of medicinal products approved by the European Medicines Agency. *Front Med*. 2021;8:753187.
22. European Medicines Agency. 2023 annual report of the European Medicines Agency. European Medicines Agency; 2024.
23. WHO. International classification of diseases, eleventh revision (ICD-11), neurology speciality linearization. WHO; 2019/2021. Accessed September 13, 2024. https://icd.who.int/dev11/l-neuro/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1954798891
24. European Medicines Agency. Download medicine data. European Medicines Agency; 2024. https://www.ema.europa.eu/en/medicines/download-medicine-data
25. Opinions and letters of support on the qualification of novel methodologies for medicine development. European Medicines Agency; 2024. Accessed August 21, 2024. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance/opinions-letters-support-qualification-novel-methodologies-medicine-development
26. European Commission. Union Register of medicinal products for human use. European Commission; 2024.
27. European Medicines Agency. Assessment report: Axura. European Medicines Agency; 2002.
28. European Medicines Agency. Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for the use of CSF AB 1-42 and t-tau and/or PET-amyloid imaging (positive/negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer's disease. European Medicines Agency; 2012.
29. European Medicines Agency. Qualification opinion of low hippocampal volume (atrophy) by MRI for use in clinical trials for regulatory purpose—in pre-dementia stage of Alzheimer's disease. European Medicines Agency; 2011.
30. European Medicines Agency. Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: cerebro—spinal fluid related biomarkers for drugs affecting amyloid burden. European Medicines Agency; 2011.
31. European Medicines Agency. Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for BMS-708163. European Medicines Agency; 2011.
32. European Medicines Agency. Assessment report: Amyvid. European Medicines Agency; 2013.
33. European Medicines Agency. Assessment report: Neuraceq. European Medicines Agency; 2013.
34. European Medicines Agency. Assessment report: Vizamyl. European Medicines Agency; 2014.
35. European Medicines Agency. Letter of support for molecular imaging of the dopamine transporter biomarker as an enrichment biomarker for clinical trials for early Parkinson's disease. European Medicines Agency; 2016.
36. European Medicines Agency. Qualification opinion on dopamine transporter imaging as an enrichment biomarker for Parkinson's disease clinical trials in patients with early Parkinsonian symptoms. European Medicines Agency; 2018.
37. European Medicines Agency. Assessment report: Betaferon vials. European Medicines Agency; 1995.
38. European Medicines Agency. Assessment report: AUBAGIO. European Medicines Agency; 2013.
39. European Medicines Agency. Assessment report: Lemtrada. European Medicines Agency; 2013.
40. European Medicines Agency. Assessment report: Nerventra—refusal report. European Medicines Agency; 2014.
41. European Medicines Agency. Assessment report: Ponvory. European Medicines Agency; 2021.
42. European Medicines Agency. Assessment report: Tecfidera. European Medicines Agency; 2013.
43. European Medicines Agency. Assessment report: Vumerity. European Medicines Agency; 2021.
44. European Medicines Agency. Assessment report: Zinbryta. European Medicines Agency; 2016.
45. European Medicines Agency. Assessment report: Tysabri. European Medicines Agency; 2006.
46. European Medicines Agency. Assessment report: Rebif. European Medicines Agency; 1997.
47. European Medicines Agency. Assessment report: Plegridy. European Medicines Agency; 2014.
48. European Medicines Agency. Assessment report: Ocrevus. European Medicines Agency; 2017.
49. European Medicines Agency. Assessment report: Kesimpta. European Medicines Agency; 2021.
50. European Medicines Agency. Assessment report: Mayzent. European Medicines Agency; 2019.
51. European Medicines Agency. Assessment report: Briumvi. European Medicines Agency; 2023.
52. European Medicines Agency. Assessment report: Mavenclad. European Medicines Agency; 2017.
53. European Medicines Agency. Assessment report: Zeposia. European Medicines Agency; 2020.
54. European Medicines Agency. Assessment report: Gilenya. European Medicines Agency; 2011.
55. European Medicines Agency. Assessment report: Spinraza. European Medicines Agency; 2017.
56. European Medicines Agency. Assessment report: Zolgensma. European Medicines Agency; 2020.
57. European Medicines Agency. Assessment report: Evrysdi. European Medicines Agency; 2021.
58. European Medicines Agency. Withdrawal assessment report: Radicava. European Medicines Agency; 2019.
59. European Medicines Agency. Assessment report: Libmeldy. European Medicines Agency; 2020.
60. European Medicines Agency. Assessment report: Skysona. European Medicines Agency; 2021.
61. European Medicines Agency. Letter of support of Neurofilament light in childhood neurological diseases. European Medicines Agency; 2022.
62. European Medicines Agency. Letter of support for Braintale platforms. European Medicines Agency; 2023.
63. Selvam S, Ayyavoo V. Biomarkers in neurodegenerative diseases: a broad overview. *Explor Neuroprot Ther*. 2024;4(2):119-147.

64. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. European Medicines Agency; 2015.
65. European Medicines Agency. Assessment report: AUBAGIO. European Medicines Agency; 2013.
66. Gill AJ, Schorr EM, Gadani SP, Calabresi PA. Emerging imaging and liquid biomarkers in multiple sclerosis. *Eur J Immunol*. 2023;53(8):2250228.
67. European Medicines Agency. Search for clinical trials. https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en
68. Mullard A. NfL makes regulatory debut as neurodegenerative disease biomarker. *Nat Rev Drug Discov*. 2023;22(6):431-434.
69. European Medicines Agency. New treatment for rare motor neurone disease recommended for approval. European Medicines Agency; 2024 https://www.ema.europa.eu/en/news/new-treatment-rare-motor-neurone-disease-recommended-approval
70. Simuni T, Chahine LM, Poston K, et al. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. *Lancet Neurol*. 2024;23(2):178-190.
71. Tabrizi SJ, Schobel S, Gantman EC, et al. A biological classification of Huntington's disease: the Integrated Staging System. *Lancet Neurol*. 2022;21(7):632-644.
72. U.S. Food and Drug Administration. Letter of support critical path institute critical path for Parkinson's consortium. U.S. Food and Drug Administration; 2024.
73. European Medicines Agency. Qualification opinion for Centiloid measure of Amyloid PET to quantify brain amyloid deposition. European Medicines Agency; 2024.
74. European Medicines Agency. Assessment report: Tauvid. European Medicines Agency; 2024.
75. World Health Organisation (WHO). WHO publishes preferred product characteristics for blood tests for Alzheimer disease. WHO; 2024 https://www.who.int/news/item/23-10-2024-who-publishes-preferred-product-characteristics-for-blood-tests-for-alzheimer-disease
76. Ashton NJ, Brum WS, Di Molfetta G, et al. Diagnostic accuracy of a plasma phosphorylated tau 217 immunoassay for Alzheimer disease pathology. *JAMA Neurol*. 2024;81(3):255-263.
77. Padala SP, Newhouse PA. Blood-based biomarkers in Alzheimer's disease: a mini-review. *Metab Brain Dis*. 2023;38(1):185-193.
78. European Medicines Agency. Withdrawal assessment report Aduhelm. European Medicines Agency; 2021.
79. European Medicines Agency. Qualification of novel methodologies for medicine development. European Medicines Agency; 2024 Accessed May 8, 2024. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hermans AMM, Bakker E, Starokozhko V, et al. Biomarkers for neurodegenerative diseases in regulatory decision-making by the European Medicines Agency. *Alzheimer's Dement*. 2025;11:e70072. https://doi.org/10.1002/trc2.70072