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REVIEW

US, EU, and Japanese Regulatory Guidelines for Development of Drugs for Treatment of Alzheimer's Disease: Implications for Global Drug Development

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Drug development guidelines from regulatory authorities provide important information to sponsors on requirements for clinical evidence needed to support approval of new drugs. In the field of Alzheimer's disease (AD), recently published guidelines are available from EU, US, and Japanese regulatory authorities. In this review, these three guidelines are compared and discussed with emphasis on the recommendations provided for demonstration of efficacy in pivotal clinical trials conducted in predementia stages of AD. Similarities and differences are highlighted, and impact for global drug development is discussed in the context of the new International Conference on Harmonization E17 guideline on multiregional clinical trials. The AD field is characterized by significant challenges as, to date, no drug approval precedence exists in predementia AD despite numerous and ambitious efforts to slow the progression of the disease by pharmacologic intervention. Despite these uncertainties regulatory authorities across regions have blazed a trail for proactive multistakeholder collaboration, involvement, and continuous dialogue, setting a positive example on how to foster a supportive environment for development of new and meaningful treatments for patients with AD globally.

Regulatory agencies, such as the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Chinese National Medical Products Administration (NMPA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), play a central role in advancing new therapeutic drug development. The partnership between regulators and pharmaceutical sponsors is key to discussing and aligning expectations for evidence generation, facilitating innovative development approaches, and eventually ensuring timely availability of new treatments for patients globally.

These and other regulatory agencies contribute to harmonization of global regulatory requirements via bilateral collaborations as well as by active membership of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The mission of the ICH is to facilitate global harmonization of drug development to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner.[1] The recently adopted ICH E17 guideline on *General principles for planning and design of Multi-Regional Clinical Trials* is an excellent example hereof as the principles described in the guideline could facilitate earlier access to new therapeutic drugs worldwide.[2]

In addition, several regulatory agencies supplement the scientific and technical ICH guidelines by publishing their own recommendations for drug development within specific therapeutic areas. These guidelines are highly valued information sources for sponsors to understand the individual regulatory agency's thinking on drug development within a given therapeutic area and constitute a great starting point for the dialogue between sponsors and regulators. In addition, transparency in relation to regulatory decisions is critical for understanding the basis for approval of new therapeutic drugs.

To support drug development in Alzheimer's disease (AD), regulatory therapeutic guidelines have been issued by three major agencies (i.e., the EMA,[3] the FDA (draft),[4] and the PMDA (interim report; of note, the Ministry of Health, Labour, and Welfare (MHLW) officially issues the regulatory guidelines and the final approval of new therapeutic drugs in Japan, but in this review—due to simplicity—we refer to the PMDA, which is the agency responsible for reviewing drug and medical device applications).[5] To our knowledge, no AD guideline is available from the NMPA or other regulatory agencies to date. AD is an age-related neurodegenerative disease with pathophysiological changes starting and evolving many years before the appearance of clinical symptoms and onset of dementia.[6] The disease is now recognized as a continuum progressing seamlessly from preclinical and prodromal AD (the disease stage preceding AD dementia is referred to as prodromal AD or mild cognitive impairment (MCI) due to AD depending on the research diagnostic criteria applied. For the purpose of this review, we apply the "prodromal AD" terminology on a conceptual level, i.e., without favoring one or the other definition of this disease stage) to the dementia stages entailing mild, moderate, and severe AD.[6] In 2013, the number of people living with dementia was

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estimated to be ~ 44 million globally. This figure was projected to increase to > 75 million in 2030 and 135 million in 2050, mainly driven by population aging.[7] With AD accounting for an estimated 60–80% of cases of dementia,[8] the need for effective treatments that could ideally delay or slow the progression becomes increasingly urgent. The improved scientific understanding of the disease biology, as well as the ability to diagnose patients before clinical symptoms manifest have led to a surge in a quest for new therapies that target the underlying pathophysiological changes in the predementia stages of AD.[9] Substantial political focus and public funding as well as concerted undertakings from industry, academia, and regulators, including public-private-partnerships, are invested in this endeavor. Yet, symptomatic drugs that target the dementia stages remain the only available pharmaceutical treatment option for patients with AD. Although a fixed dose combination of the previously approved symptomatic drugs donepezil and memantine was approved by the FDA in 2014, no novel therapeutic drugs have reached the patients since the FDA and EMA approval of memantine in the beginning of the 2000s[10,11] (followed by PMDA approval in 2011[12]).

Demonstrating a drug effect in the predementia stages of AD is significantly more complex compared with establishing a symptomatic effect in the advanced disease stages,[3–5,13] where clinical symptoms are clearly manifested. A main challenge for AD drug development is the lack of biomarkers that will accurately predict and detect the (clinical) progression of AD. Such biomarkers could enable not only smaller and shorter clinical trials in the slowly progressing predementia stages but also allow reliable demonstration of an effect on the underlying pathophysiological processes. To add to the complexity, the role of β-amyloid, which is a key pathological hallmark of this multifactorial disorder, has been challenged by the recurrent failure of amyloid-targeting therapies. This includes observations that treatment with BACE-inhibitors may even accelerate clinical decline in the prodromal AD stages.[14,15] However, it was recently announced that the amyloid-targeting monoclonal antibody aducanumab demonstrated efficacy in patients with prodromal and mild AD, and that the sponsor is planning to submit an application for marketing authorization to the FDA.[16] As such, AD drug development is a continuously evolving field of research in which certain recommendations may be outdated already by the time regulatory guidelines are published.

Regulatory recommendations and requirements outlined in disease-specific and general regulatory guidelines have an important impact on global drug development in AD and other disease areas. We therefore performed a review specifically of the current therapeutic development guidelines for AD issued by the EMA Committee for Medicinal Products for Human use (CHMP), the FDA, and the PMDA. We address key aspects of the regulatory AD guidelines with main focus on recommendations for demonstration of efficacy in confirmatory trials in predementia AD. Finally, we discuss challenges in the context of global drug development and the recent ICH E17 guidance on planning and design of multiregional clinical trials.

REGULATORY GUIDELINES FOR THE CLINICAL DEVELOPMENT OF DRUGS FOR TREATMENT OF AD

AD guideline development and scope of current guidelines

Drug development for AD has been addressed in CHMP and FDA guidelines for years with consecutive revisions reflecting the evolving scientific understanding and the consequent focus on developing drugs targeting progressively earlier stages of the disease. The first CHMP guideline pertaining to AD and other dementias was adopted in 2008.[17] A CHMP discussion paper from 2014[18] formed the basis for development of the current revision of the guideline (focusing on AD specifically), which came into effect in September 2018.[3] The initial *FDA Guidelines for the Clinical Evaluation of Antidementia Drugs*[19] from 1990 focused mainly on development of symptomatic treatments for Alzheimer's dementia. In 2013, the FDA published the first draft guideline (the FDA typically applies the terminology "guidance"; for simplicity, we refer to "guidelines" for all three agencies in this review) for drug development in early AD (i.e., the predementia stages of AD).[20] The current version of the FDA draft guideline[4] was published in February 2018. The Japanese PMDA guideline was published in the form of an interim report in October 2017 and outlines issues to be considered or resolved for development of drugs for treatment of AD (**Table 1**).[5] The regulatory agencies have taken different approaches to the development of the current AD guidelines. This includes the extent to which multistakeholder interaction has been part of the process (**Table 1**).

The guidelines vary in terms of the general scope and the topics addressed (i.e., disease stages and treatment concepts for which recommendations are provided (**Tables 1** and **2**). In fact, it may be argued that the three guidelines to a large extent nicely complement each other, even if some discrepancies exist. In general, the CHMP guideline has a wider scope compared with the FDA and PMDA guidelines. The CHMP guideline applies to the full AD continuum covering preventive, disease-modifying, and symptomatic treatments, as well as recommendations for targeting specific behavioral and psychiatric symptoms. It provides considerations on efficacy, safety, biostatistics, monotherapy, and combination therapy. The FDA guideline focuses on demonstration of efficacy in the early AD stages and the PMDA guideline mainly provides considerations on disease-modifying approaches targeting prodromal AD and AD dementia (**Table 2**).

For the purpose of this review, we make no inference of how any given drug effect may translate into label indication claims. Instead, we apply the term "disease-modifying" only in a conceptual context (i.e., referring to drugs that are intended to mediate an enduring clinical effect through targeting the pathophysiological processes underlying the disease).

Definition of target patient population: Diagnostic criteria and disease staging

As AD is a multifactorial, heterogenous disorder that progresses on a continuum without clearly demarcated disease stages,[6] defining a homogenous target population comes

Table 1 General guideline information including terminology and definitions

	CHMP 2018	FDA 2018 (draft)	PMDA 2017 (interim report)
Title	Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease	Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry	Issues to Consider in the Clinical Evaluation and Development of Drugs for Alzheimer's Disease
Aim	To provide guidance for the evaluation of any medicinal product for treatment across the AD continuum	Intended to serve as a focus for continued discussions among representatives of the FDA Division of Neurology Products in CDER or the Office of Tissues and Advanced Therapies in CBER, pharmaceutical sponsors, the scientific community, and the public	To present issues to be considered or resolved in conducting effective clinical studies of disease-modifying AD drugs
Guideline terminology applied to imply a disease-modifying treatment effect	Disease modification Prevention of symptomatic disease Slowing or delay of clinical decline	Persistent effect on disease course Alter the course of AD through a direct effect on the underlying disease pathology	Disease modification
Definition of a symptomatic drug or treatment effect	Treatment effect that does not change the overall course of the disease	N/A	Medical agents that improve the clinical symptoms of AD, but cannot inhibit the progression of the disease
Definition of a disease-modifying drug or treatment effect	Slowing or arrest of symptom progression and evidence of delay in the underlying neuropathological process	Permanently altering the course of AD through a direct effect on the underlying disease pathophysiology; effect persists in the absence of continued exposure to the drug	Medical agents that delay neurodegeneration and neuronal cell death by acting on the pathological mechanism of AD and, as a result, inhibit the progression of clinical symptoms
Guideline development: External stakeholder interaction	Several multi-stakeholder interactions; publication of CHMP discussion paper; EMA workshop[44] with FDA, PMDA, patient organizations, academia, healthcare professionals, and industry participation; draft guideline released for public consultation leading to final, current guideline	Guideline authored by FDA Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Current draft guideline distributed for public consultation	Guideline developed in collaboration between the University of Tokyo Hospital, PMDA, and MHLW. No known solicitation of input from the public

AD, Alzheimer's disease; CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; CHMP, Committee for Medicinal Products for Human use; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MHLW, Ministry of Health, Labour, and Welfare; N/A, not applicable; PMDA, Pharmaceuticals and Medical Devices Agency.

with inherent challenges. In addition, the lack of (or subtle) clinical symptoms in predementia disease stages add to the complexity of identifying a target patient population that is likely to progress during the course of a clinical trial. Even so, the CHMP, the FDA, and the PMDA guidelines all recognize the importance of early intervention targeting the pathological features that cause the disease.

The development of two main sets of research diagnostic criteria (i.e., the International Working Group (IWG)[21] and the National Institute on Aging and the Alzheimer's Association (NIA-AA)[22] criteria) have resulted in a major shift toward a biological definition of the disease. Consequently, diagnosis of AD is now possible before the onset of clinical symptoms, paving the way for inclusion of patients with predementia AD in clinical trials. Both criteria acknowledge the progression of AD along a continuum without clearly demarcated stages and, in overall terms, describe disease progression from preclinical through the dementia stages. However, notable differences do exist, of which one is in the definition of prodromal AD (IWG terminology) vs. MCI due to AD (National Institute on Aging-Alzheimer's Association (NIA-AA) terminology).[23]

Although this allows for a potential identification of patients at earlier disease stages, the constant evolution of the science poses challenges for drug development. As such, none of the regulatory guidelines endorse a specific set of diagnostic criteria (**Table 3**). The PMDA guideline even discusses hypothetical consequences of a potential difference between the diagnostic criteria used to define the clinical trial population and those that could be established in the future. This could be triggered by the extensive treatment duration needed to demonstrate efficacy in the earliest, slowly progressing stages of the disease, meaning that several years may pass from the initiation of the pivotal clinical trials to the submission of a marketing authorization application. In addition, changes in the scientific and medical environment (e.g., advances in understanding of the disease biology; potential validation of biomarkers for diagnosis, target engagement, or detection of disease progression; or changes to standard of care including availability of new treatment options) may compromise study conduct impacting the validity and medical relevance of the findings. Such discrepancy could lead to evidence from clinical trials being insufficient for drug approval.[5] Regulatory flexibility and continuous dialogue will be

Table 2 Scope of regulatory AD drug development guidelines

		CHMP 2018	FDA 2018 (draft)	PMDA 2017 (interim report)
Disease stages	Preclinical AD	X	X	(X)
	Prodromal AD/MCI due to AD	X	X	X
	AD dementia	X	O	X
Treatment goals	Prevention	X	O	O
	Disease modification	X	X	X
	Symptomatic treatment	X	O	O
	Behavioral and psychiatric symptoms	X	O	O
Specific AD subgroups	Familial AD	(X)	O	O
	ApoE4 Ɛ4 homozygotes	(X)	O	X
Treatment concept	Monotherapy	X	X	X
	Adjunctive therapy	X	O	O
	Combination therapy (co-development)	X	O	O
Clinical development phases	Phase I: Safety; tolerability; PK/PD	X	O	X
	Phase II: Exploratory efficacy; dose finding	X	O	X
	Phase III: Pivotal trials	X	X	X
Miscellaneous	Clinical trial design	X	X	X
	Efficacy	X	X	X
	Safety	X	O	(X)
	General statistical considerations	X	O	O
	Clinical meaningfulness	X	X	X
	Expedited regulatory pathways	O	X	O
	Regional requirements	O	O	X

AD, Alzheimer's disease; CHMP, Committee for Medicinal Products for Human use; FDA, US Food and Drug Administration; PK/PD, pharmacokinetic/pharmacodynamic; PMDA, Pharmaceuticals and Medical Devices Agency.
X, topic in scope of guideline; O, topic not included in guideline; (X), topic mentioned or discussed, but without recommendations.

Table 3 Diagnostic criteria, disease staging, and clinical trial inclusion criteria

	CHMP 2018	FDA 2018 (draft)	PMDA 2017 (interim report)
Diagnostic criteria	• Both IWG and NIA-AA criteria accepted for diagnosis of AD for research and trial enrichment purposes, although they are "not fully validated and undergo constant refinement" • Emphasizes that prodromal AD (IWG) and MCI due to AD (NIA-AA) may lead to different study populations • Specific recommendations are kept open	• Recommends use of "current consensus diagnostic criteria" [i.e., current at time of approval]; no specific criteria mentioned	• No consensus on applicable diagnostic criteria • IWG and NIA-AA are discussed
Disease staging	• Preclinical AD, prodromal AD (or MCI due to AD), mild, moderate and severe AD. • Operationally defined stages of disease are not clearly demarcated • Selection of patients with early AD for long-term interventional trials is complex and should not be unnecessarily subdivided if not justified from a clinical viewpoint; subjects with prodromal and mild AD may be studied together	• Conceptual stages proposed to guide end points selection • Predementia stages divided in stage 1 (asymptomatic with pathophysiological changes), 2 (+ neuropsychological changes), and 3 (+ detectable functional impairment) • Stages 4, 5, and 6 (mild, moderate, and severe AD) • AD stage to be specified for inclusion and as anticipated at time of primary outcome assessment	• Preclinical AD, prodromal AD (or MCI due to AD), mild, moderate and severe AD
Inclusion criteria	• Enrichment strategies are recommended to identify and characterize patients at high risk to develop clinical AD during the trial • Importance of defining a homogenous patient population with a defined rate of progression highlighted	• Enrollment should be based on current consensus diagnostic criteria, with focus on objective tests and, when appropriate, history and physical examination, to determine the presence of AD, and to exclude other conditions that can mimic AD	• Prodromal AD: inclusion criteria should be specified using appropriate cognitive test results, evidence of Aβ deposition, neurodegeneration BMs etc.

Aβ, β-amyloid; AD, Alzheimer's disease; BM, biomarker; CHMP, Committee for Medicinal Products for Human use; MCI, mild cognitive impairment; FDA, US Food and Drug Administration; IWG, International Working Group research diagnostic criteria for AD; NIA-AA, National Institute of Aging-Alzheimer's Association research diagnostic criteria for AD.

essential to accommodate for these risks to ensure sponsors are not discouraged from conducting clinical research in the earliest stages of the disease.

For the AD disease stages, the CHMP and PMDA guidelines are aligned with the definitions and terminology of the IWG and NIA-AA research diagnostic criteria that were current as per the date of the guidelines.[24,25] The FDA guideline takes a more timeless approach by referring to the use of "*current consensus diagnostic criteria*" for enrollment of patients into clinical trials. The FDA proposes a set of conceptual categories from stages 1 (asymptomatic) through 6 (severe AD dementia; **Table 3**) for the purpose of selecting end points for clinical trials (discussed below). However, according to our interpretation, the specific diagnostic recommendations could very well be integrated with the more pragmatic FDA approach as schematically illustrated in **Figure 1**.

The role of biomarkers in AD drug development

At present, no biomarkers have been demonstrated to reliably predict the clinical outcome of an AD intervention. Yet, the importance of biomarkers is recognized by all three agencies in the context of enrichment and definition of the patient population as well as measures of disease progression (**Table 4**); especially in the predementia stages, where clinical symptoms are absent or subtle. However, the guidelines differ in the level of detail provided and the nature of the recommendations put forward. This diversity, in part, reflects that our understanding of the disease biology, including the link between the pathophysiological changes and clinical progression, is still uncertain.

Again, the FDA guideline takes a more conceptual approach compared with the CHMP and PMDA guidelines and does not provide any recommendations for choice of specific biomarkers for patient identification and measurement of treatment outcome. Regardless, the FDA encourages sponsors to include biomarker outcome measures in clinical trials and state that the findings will be "*interpreted in the context of the state of the scientific evidence at the time of a future marketing application*."[20]

For patient selection, both the FDA and the PMDA guidelines highlight the potential need to co-develop companion diagnostics for identification of the patients who will be eligible for treatment in clinical practice if biomarkers are applied for identification or enrichment of patients for clinical trials (**Table 4**). The guidelines do not provide directions on how the indicated patient population should be defined in the product label. Future regulatory approvals will reveal if the exact diagnostic biomarkers used for

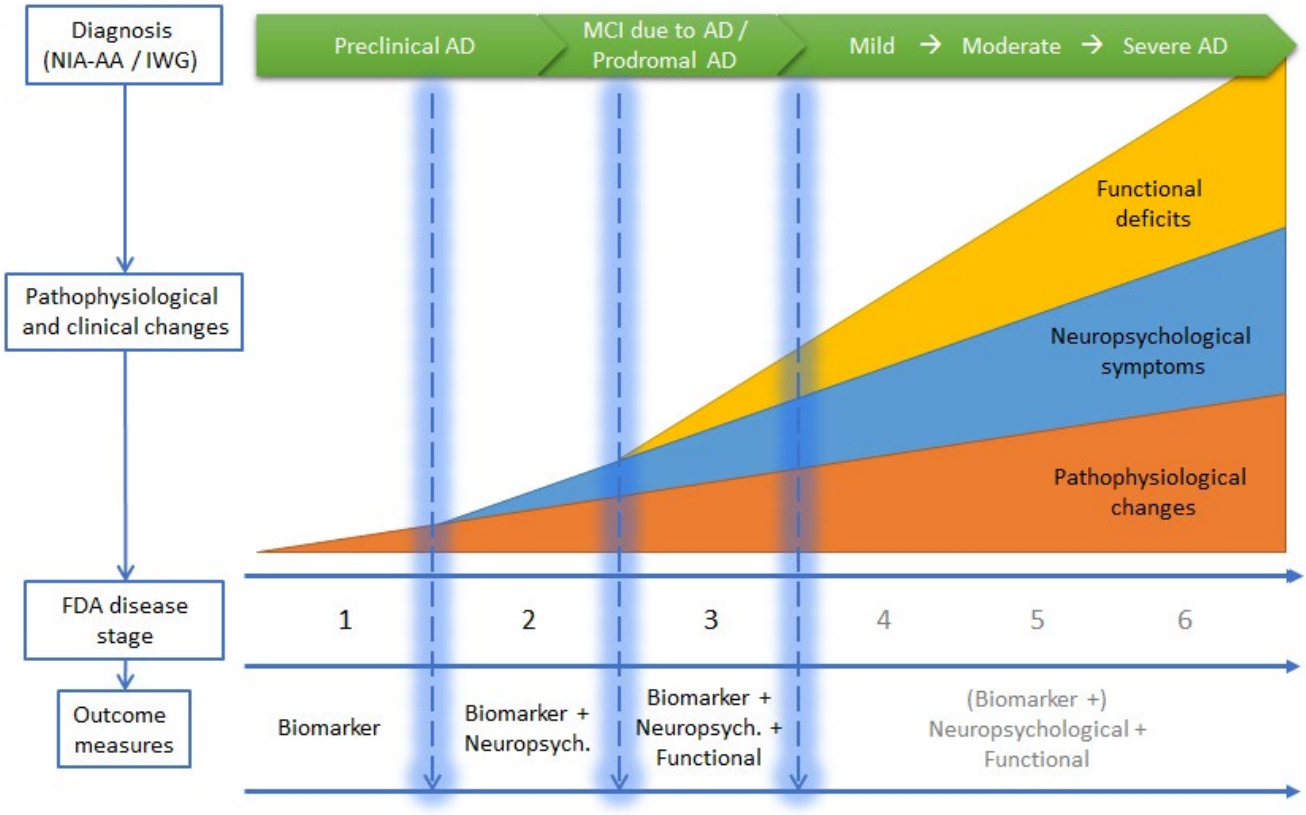

Figure 1 Schematic interpretation of relation between Alzheimer's disease (AD) diagnosis, definition of US Food and Drug Administration (FDA) disease stage and selection of outcome measures. Patients are diagnosed and potentially further enriched for trial inclusion; according to the presence of pathophysiological, neuropsychological, and functional changes, patients are categorized into FDA stages 1, 2, or 3; the FDA stage is used to guide the nature of outcomes needed for the clinical trial, taking into account the anticipated FDA stage at the time of primary outcome assessment. IWG, International Working Group; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging and the Alzheimer's Association.

Table 4 Role of biomarkers in AD drug development

	CHMP 2018	FDA 2018 (draft)	PMDA 2017 (interim report)
General	• Dedicated section on role and type of BMs • No BMs endorsed over others • Advised to measure total Tau or phospho-Tau in addition to Aβ42	• No dedicated section on BMs	• Dedicated section on use of BMs • Central laboratory measurement required for CSF BMs to reduce variability
Patient selection and enrichment	• CSF, MRI, and PET imaging BMs qualified for enrichment of study population (however, context of use remains to be qualified in preclinical AD) • Define risk factors, e.g., vascular or metabolic	• No specific BMs recommended • If BM evidence needed to define the indicated population, need to discuss potential need for companion diagnostics	• Need to predefine handling of patients who are + on e.g., a CSF BM and – on imaging BM • BMs used for patient selection in clinical trials may be required for selection of the right patients in clinical practice (companion diagnostics)
Disease progression	• The value and qualification of several BMs has been progressing considerably and some may be used as primary end point in PoM/PoP studies • Refers to hippocampal atrophy (MRI) and cortical hypometabolism (FDG PET) as potentially valuable for measuring disease progression • Highlights that the disease trajectory may also be influenced by non-BM related factors (i.e., cognitive reserve, comorbidities etc)	• No consensus on BMs that would be appropriate to support clinical findings • Encourages analyzing BMs independently, (although prespecified); findings will be interpreted in the context of the state of the scientific evidence at the time of approval	• Desirable to evaluate BMs as much as possible as secondary end points to confirm target engagement and investigate clinical/BM end point relationship • BMs included on an exploratory basis; not accepted as surrogate end points in confirmatory studies
Genetic BMs	• ApoE ε4 status may be used as one of the means of enrichment in a clinical trial population. Generalizability to be justified if only patients with this specific genotype are included without data in non-carriers	• No recommendations	• Obtaining information on ApoE genotypes is desirable to allow for subgroup analyses

Aβ, β-amyloid; AD, Alheimer's disease; BM, biomarker; CHMP, Committee for Medicinal Products for Human use; CSF, cerebrospinal fluid; FDA, US Food and Drug Administration; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; PMDA, PMDA, Pharmaceuticals and Medical Devices Agency; PoM, proof of mechanism; PoP, proof of principle.

inclusion of patients in the clinical trials will have to be specified in the label, or whether the regulatory authorities will allow for more conceptual label descriptions to accommodate future advances in the diagnostic biomarker field.

In terms of outcome measures, ideally, correlating changes in all measurable entities would mutually support the meaningfulness of the overall treatment effect. That is, a correlation of pathophysiological, neurophysiological, and functional measures, as applicable depending on the specific disease stage(s) in question. All three regulatory guidelines emphasize that no progression biomarkers are currently available that will reliably reflect clinical progression. The CHMP and PMDA guidelines discuss the role of progression biomarkers in the context of demonstrating a relationship between clinical treatment effect and changes in the underlying pathophysiology. The FDA takes a more holistic view without explicitly focusing on whether disease modification is demonstrated or not; in fact, the FDA guideline does not use this terminology (**Table 1**).

In light of the current understanding of the underlying disease biology, a potential progression biomarker would at least need to show some degree of correlation with the change in clinical symptoms to support the overall weight of evidence. Any other effect of treatment on a claimed progression biomarker would be difficult to interpret. This is not least due to conflicting evidence, as exemplified by the recent findings that BACE inhibitor mediated reduction in amyloid load unexpectedly resulted in clinical worsening in patients with prodromal AD.[14,15] In contrast, monoclonal antibody-mediated amyloid removal may result in clinical improvement in patients with prodromal/mild AD.[16]

Efficacy outcome measures

Although the choice of outcome measures that will reliably detect a clinically meaningful change during the course of a clinical trial is a key challenge in AD drug development, a detailed discussion is beyond the scope of this paper. Nevertheless, each of the three regulatory guidelines provides considerations on outcome measures required for each of the targeted disease stages that are in scope of the individual guidelines (**Table 5**). The EMA and the PMDA divide their end point considerations according to preclinical AD (CHMP guideline only), prodromal AD/AD due to MCI, and AD dementia. In contrast, the FDA proposes a conceptual framework to guide the nature of outcome measures recommended for clinical trials based on the measurable pathophysiological, neuropsychological, and functional changes pertaining to each disease stage (**Table 5**; **Figure 1**).

In general, there are no established clinical or biomarker outcome measures for use in the early stages of the disease, and none of the guidelines endorse any specific end points over others. Hence, a sound scientific rationale and justification for the use of any set of outcome measures remains important to support the clinical meaningfulness of the (expected) change in response to treatment.

Table 5 Outcome measures

	CHMP 2018	FDA 2018 (draft)	PMDA 2017 (interim report)
		Prodromal AD[a]	
General	• Acknowledges that progression of functional deficits will be very slow → feasibility issues → acceptable to investigate only functional domains specifically impaired in prodromal AD • Functional measure: Constructing more sensitive item scoring for MCI-specific scales and/or investigating only domains shown to be impaired consistently in MCI due to AD, could be the way forward	• Important to demonstrate effect on the subtle impairments in daily functioning • Encourages the development of novel approaches to the integrated evaluation of subtle functional deficits that arise from early cognitive impairment (e.g., facility with financial transactions, adequacy of social conversation)	• No established efficacy end points • The end point should clearly show the clinical meaningfulness of performing early intervention in AD • May also be possible to develop a new rating scale suitable for the assessment of patients with MCI
Primary end point(s)	• Co-primary cognitive + functional end points or single composite (cognition/function) end point	• Independent assessment of cognitive effect + daily function or a single integrated cognitive/functional scale, or • Time to a clinically meaningful event	• Time to onset of dementia, or • Single composite (cognition/function) end point may be acceptable
Secondary end points	• Cognition, function, instrumental activities, executive functions and HRQOL	• No specific recommendations • At present, insufficient information on which to base a hierarchical structuring of a series of BMs as secondary outcome measures	• Evaluation of the length of time until onset of AD dementia • Proportion of patients developing AD dementia • Neurodegeneration BMs
		Preclinical AD[a]	
General	• No gold standard to assessment of treatment effect • Until a BM is qualified as a reliable surrogate measure of treatment effect, patients should be followed up for a sufficient time to capture relevant cognitive changes	• If patients transition to next stage during the trial, the principles applicable to outcome assessment for that stage would apply • A large effect size and/or a pattern of treatment effects seen across multiple individual biomarker (and for stage 2, neuropsychological) measures would increase the persuasiveness of the findings	N/A
Primary end point(s)	• New sensitive neuropsychological measures not yet validated → not endorsed as sole primary end point • For prevention trials: Prevention of cognitive impairment (since no BM can yet be considered a valid surrogate end point)	Stage 2 • Sensitive measures of neuropsychological performance may provide adequate support for a full approval or AA depending on clinical meaningfulness, or • Time to a clinically meaningful event • Alternatively allow patients to transition to stage 3 →stage 3 outcome measures Stage 1 • BM may serve as basis for AA if reasonably likely to predict clinical benefit (at present, none are), or • Time to a clinically meaningful event • Alternatively allow patients to transition to stage 2 →stage 2 outcome measures	N/A
Secondary end points	• Time to event analysis could support relevance of primary measure; event must be of clear clinical importance (e.g., onset of cognitive impairment)	• At present, insufficient information on which to base a hierarchical structuring of a series of BMs as secondary outcome measures • Stage 2: Effect on clinical outcome measures to be supported by similarly persuasive progression BM effects	N/A

AA, Accelerated Approval; AD, Alzheimer's disease; BM, biomarker; CHMP, Committee for Medicinal Products for Human use; FDA, US Food and Drug Administration; HRQOL, health-related quality of life; MCI, mild cognitive impairment; N/A, not applicable; PMDA, Pharmaceuticals and Medical Devices Agency.
[a]Similar to FDA stage 3. [b]Similar to FDA stages 1 and 2.

Traditionally, for AD dementia trials, efficacy should be demonstrated not only on a primary cognitive end point but also on a coprimary daily function or global outcome measure. As explained in the 1990 FDA guidelines, the aim of this dual outcome assessment strategy was to ensure that the drug exerts its effect on "*the 'core' phenomena of dementia*" (performance based or cognitive instrument) and that the effect is clinically meaningful.[19] In the 2018 FDA early AD guideline,

this dichotomous approach is discussed at a conceptual level and the idea that an effect on cognition in its entirety is not clinically relevant *per se* is challenged; the FDA argues that the questionable clinical relevance of a given change on a neuropsychological measure is linked to the assessment method itself (e.g., small changes in specific cognitive domains as measured by "*sensitive neuropsychological tests that are capable of detecting changes of uncertain clinical meaningfulness*"), not to the entity of cognition. A large effect size and/or effect across measures of diverse cognitive domains will be supportive of a clinically meaningful effect.[4]

Regardless, the need to confirm the clinical meaningfulness of a given drug effect by inclusion of a measure of daily function or a global measure remains a requirement put forward by all three current guidelines for those disease stages where functional impairment appears (**Table 5**). However, the guidelines also agree that in the prodromal AD stage an integrated cognitive/functional scale may serve as a single primary end point (**Table 5**).

Alternatively, or as a supportive measure, demonstration of a delay in time to a clinically meaningful event (e.g., time to onset of dementia) could inherently be clinically relevant (**Table 5**).

As we interpret the FDA guideline, diverse biomarker, neuropsychological, and functional or global measures as applicable all contribute to the totality of the evidence and could strengthen the perception of a given effect of treatment as being clinically meaningful.

Opportunities for expedited regulatory approval pathways

The FDA Accelerated Approval is a provisional approval pathway that allows for a trade-off between the uncertainty linked to reliance on a surrogate or intermediate clinical outcome measure deemed reasonably likely to predict a clinical benefit and early patient access. It is reserved for drugs intended to treat serious or life-threatening conditions and requires postapproval confirmation of the clinical benefit.[26,27] The FDA AD guideline highlights the opportunity for an Accelerated Approval based on primary biomarker measures of pathophysiological changes in the earliest asymptomatic stages (stage 1) and based on a primary cognitive end point supported by additional secondary measures of neuropsychological and pathophysiological changes in the early symptomatic stages where functional impairment is still absent (stage 2; **Table 5**). Although the FDA emphasizes that there is not yet sufficient evidence to support any biomarker as reasonably likely to predict a clinical benefit, the fact that the agency is open to discuss approval based on biomarker or intermediate clinical end points is very welcome in the context of AD.

The CHMP and PMDA guidelines do not include any considerations on the use of provisional approval pathways. Of note, the Japanese Conditional Approval pathway was only introduced 7 months after the date of the PMDA AD guidelines.[28] Although the scope of the EMA Conditional Marketing Authorization[29] and the PMDA Conditional Approval[28] is fundamentally different from the FDA Accelerated Approval, the applicability of these pathways have been discussed jointly by the FDA, the EMA, and the PMDA regulators. (Regulatory panel debate as part of the November 2018 Alzheimer's Association Research Roundtable meeting on preclinical AD. https://www.alz.org/research/for_researchers/partnerships/research_roundtable).

Trial design for confirmatory trials in predementia AD: Monotherapy and combination therapy

Both the CHMP and PMDA guidelines focus on the need to demonstrate that a clinical effect is accompanied by a change in the underlying pathophysiology to confirm a disease-modifying effect of the drug (**Table 6**). The CHMP recommends that the study should be "*enhanced with a phase of delayed start*" to ideally show that a difference in response is maintained between patients who were initiated on placebo and active treatment. The PMDA does not provide any recommendations other than encouraging sponsors to seek consultation with the agency on this issue. In contrast, the FDA guideline places comparably less emphasis on the role of biomarker end points and focuses on the randomized start design for demonstrating a "*persistent effect on disease course*" (**Table 6**).

In early disease stages where symptoms are subtle, the CHMP proposes the use of a time to event approach as an alternative to the delayed start trial design. In the absence of validated biomarker outcome parameters, the CHMP, however, notes that innovative trial designs may support evidence of change in the disease course and may serve as an alternative treatment goal "*in case interpretation of relevant biomarker changes is unclear.*"[3]

In addition, only the CHMP guideline addresses prevention trial design specifically (**Table 6**) as well as considerations on combining disease-modifying therapies targeting different pathways.[3] Codevelopment or combination therapy is not addressed in the FDA AD guideline, but concepts described in the FDA guideline on "*Codevelopment of Two or More New Investigational Drugs for Use in Combination*"[30] are to some extent relevant to development of combination therapies in AD. Also, the meeting report from the Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) annual US FDA/Alzheimer's Disease Allies meetings in 2012 and 2013 mentions that "*the participation of officials from FDA and EMA in these meetings demonstrates regulators' interest in working with researchers and drug developers to ensure that trials of combination therapies are designed to be as effective and efficient as possible.*"[31] The challenges conferred by adding such a layer of complexity to AD drug development include, but are not limited to: interpretation of study results, especially if a primarily disease-modifying drug candidate is studied in combination with a symptomatic treatment; feasibility of inclusion of two monotherapy arms in addition to a combination and a placebo arm in clinical studies; need for rigorous dose selection studies; and lack of reliable biomarker end points that could improve dose-finding and confirmatory clinical trial feasibility. Further dialogue among sponsors, regulators, and other stakeholders with the aim of facilitating codevelopment in AD would be desirable, as targeting multiple pathophysiological pathways may be the

Table 6 Pivotal trial design

	CHMP 2018	FDA 2018 (draft)	PMDA 2017 (interim report)
Replicability of confirmatory data: Number of pivotal studies needed	• Two PhIII studies needed, preferably in two adjacent disease stages	Not discussed	• MCI: A single pivotal trial may be acceptable if, e.g., multiple dose groups demonstrate significant robust efficacy + dose-response relationship • MCI + AD dementia: A single global PhIII study in each stage may be mutually supportive
Trial design	• Slowing of clinical decline + effect on validated BMs reflecting key pathophysiological aspects • Placebo-controlled as no other disease-modifying products are approved • Ideally, efficacy to be demonstrated in two trials at two different stages • Study should be enhanced with a delayed start phase • Alternatively: Time to event design → inherent clinical relevance in delaying time to onset of dementia • If interpretation of BM changes is unclear, evidence of change in the disease course supported by innovative study design could be an alternative treatment goal	• Randomized start design recommended to demonstrate a 'persistent effect on the disease course' • BMs may provide supportive evidence, but the effects on BMs in AD are not sufficiently well understood to provide evidence of a persistent effect on disease course	• Demonstration that the drug improves the clinical symptoms + evaluation of suppression of the pathophysiological progression of AD by using biomarkers • For use of randomized withdrawal design, consultation with PMDA is recommended
Prevention trials	• Placebo controlled trials in enriched populations • Require large samples and long follow up, typically ≥ 3 years • Scientific information to provide a firm regulatory framework for prevention trials is lacking	No specific recommendations	N/A

AD, Alzheimer's disease; BM, biomarker; CHMP, Committee for Medicinal Products for Human use; FDA, US Food and Drug Administration; MCI, mild cognitive impairment; N/A, not applicable; PMDA, Pharmaceuticals and Medical Devices Agency.

way forward to obtain a clinically meaningful treatment effect in predementia AD.

Demonstrating a clinically meaningful treatment effect

The clinical meaningfulness of the effect of a new treatment is an important aspect of the regulatory benefit/risk assessment.[32,33] Yet, there is no consensus definition of what a clinically meaningful effect size or outcome parameter is.[34,35] It is clear that demonstrating a clinically meaningful effect is particularly challenging in the predementia stages, as neuropsychological symptoms and functional impairment are absent or relatively subtle.[13] All three regulatory guidelines address the concept of clinical meaningfulness but to varying extents and in different contexts (**Table 7**). The PMDA guideline primarily discusses this topic in the context of the role of functional measures in supporting the clinical meaningfulness of changes on cognitive measures.[5] The CHMP guideline more systematically addresses clinical meaningfulness; the guideline recognizes the inherent clinical relevance of delaying time to onset of dementia, and recommends a range of secondary measures, including analysis of time to a meaningful event to support the meaningfulness of the primary outcome.[3] Finally, the FDA AD guideline lines up with the FDA's efforts to promote patient-focused drug development,[36] focusing on a meaningful treatment effect rather than whether the treatment might be disease-modifying or not.[4]

The three guidelines agree that it is necessary to demonstrate an effect on functional outcome in the prodromal AD stage (where subtle functional impairment is present) to confirm the clinical meaningfulness of changes on neuropsychological measures (**Tables 5** and **7**). However, they also acknowledge that current measures of functional decline may not be suitable for detecting the specific and subtle functional changes at the prodromal AD stage. Although the agencies, therefore, encourage development of new measures, the FDA and the CHMP guidelines also point to the possibility of measuring only the specific functional domains known to be impaired in the early stages of cognitive impairment (**Table 5**).

Clearly, interaction between regulators and sponsors will be needed to agree on how to design the pivotal clinical trials to demonstrate that the effect of a new drug is clinically meaningful to the patients. Future approvals of drugs targeting the predementia stages of AD should bring insights into how the clinical meaningfulness is assessed and if this assessment is influenced by whether the treatment is claimed to be disease-modifying and/or symptomatic.

Distinguishing between symptomatic and disease-modifying treatments

In terms of definition of a disease-modifying treatment effect and the terminology used to describe such effect,

Table 7 Considerations on clinical meaningfulness

	CHMP 2018	FDA 2018 (draft)	PMDA 2017 (interim report)
General	• New instruments have to demonstrate the capability to measure a relevant clinical construct • Inherent clinical relevance in delaying time to onset of dementia	• Comprehensive discussion of clinical meaningfulness concern being linked to methods of cognitive assessment, not to the entity of cognition itself	• No specific recommendations
Prodromal AD	• It is necessary to demonstrate the clinical relevance of the results (also when patients with prodromal and mild AD are studied together) • Range of different secondary measures to be included to establish that the demonstrated effects of treatment are clinically relevant	• Need to demonstrate meaningful functional benefit to support clinical meaningfulness of an effect on a sensitive measure of neuropsychological performance of uncertain independent clinical meaning	• End point should clearly show the clinical meaningfulness of early intervention • Composite scale: clinical meaningfulness should be demonstrated based on association of scores & AD progression • Data from appropriate longitudinal studies may be helpful
Preclinical AD	Time to event analysis could support relevance of primary outcome; event should be of clear clinical importance	Stage 2 • Difficult to establish a clinically meaningful effect during course of a trial; allow patients to transition to stage 3 or show effect across multiple mutually supportive end points Stage 1 • A clinically meaningful benefit cannot be measured in stage 1 because there is no clinical impairment to assess	N/A

AD, Alzheimer's disease; CHMP, Committee for Medicinal Products for Human use; FDA, US Food and Drug Administration; N/A, not applicable; PMDA, Pharmaceuticals and Medical Devices Agency.

subtle but imperative differences exist between the three regulatory guidelines (**Table 1**). Whereas the CHMP and PMDA guidelines clearly distinguish between symptomatic and disease-modifying treatments, the FDA guideline does not explicitly distinguish between the two.[4] In addition, the FDA has abandoned the use of the term "disease modification" in the current guideline as opposed to earlier versions,[37] and now only mentions a persistent effect on the disease course in this context. Rather, the FDA guideline focuses on demonstrating an effect on the changes (be it functional, neuropsychiatric, or pathophysiological only) that can be measured at the given disease stage and ideally supporting the clinical meaningfulness by demonstration of persuasive effects across different outcomes measures.[4]

The reduced emphasis on disease modification is in line with arguments put forward (e.g., by Doody[38] and supported by FDA and EMA authors); Broich and Kozauer argue that regardless of whether a treatment may be symptomatic or disease-modifying, focus should be on demonstrating a meaningful benefit to patients rather than data requirements for supporting a potential label claim.[13]

At present, distinguishing between symptomatic and disease-modifying approaches may not be imperative in AD drug development, as disease-modifying therapies are mainly in development for treatment of predementia stages for which no symptomatic therapies are currently approved. From a methodological point of view, this leaves plenty of room for development of disease-modifying drugs for treatment of AD. This is as opposed to Parkinson's disease (PD) where disease-modifying drug development efforts target the same or overlapping disease stages as those for which effective symptomatic treatments are already available. As a result, there is a very narrow window for demonstration of short-term meaningful clinical improvement on top of what is already offered by standard of care in PD. As placebo-controlled trials would not be ethically feasible in populations where effective symptomatic therapies are approved, very large trials would be needed to demonstrate a statistically significant effect of adjunctive treatment with a new disease-modifying drug. Alternatively, trials of several years' duration would be needed to demonstrate a delay in disease progression. In general, there is a need to acknowledge that disease-modifying drugs for these multifactorial neurodegenerative disorders are likely to exert a modest acute effect that will increase and potentially only become meaningful after an extended treatment duration.

Development of symptomatic treatments

The majority of ongoing drug development efforts target the underlying pathophysiological process in the early stages of AD.[9] In contrast, relatively few attempts are made to develop more efficient symptomatic therapies for treatment of patients with AD dementia, and most of these aim at treating specific behavioral or psychiatric symptoms.[9] This disposition is reflected in the scope of the guidelines with only the CHMP specifically addressing development of symptomatic treatments (**Table 2**). Although symptomatic drug development in AD will mostly be applicable to AD dementia, the considerations discussed below are also relevant for the more advanced predementia stages.

In addition to the recommendations for development of symptomatic drugs for treatment of AD in general, the CHMP acknowledges the high prevalence and burden of behavioral and psychiatric symptoms of dementia (BPSD)

and how some of these symptoms are more prevalent at the early stages of the disease. Accordingly, developing drugs that target single or clusters of symptoms of BPSD should be "*justified by a strong rationale and would depend on the drug mechanism of action.*" Another key issue put forward by the guideline is pseudospecificity (i.e., focus on artificially narrow claims (reference is made to Laughren 2003[39] for definition and discussion of the concept of pseudospecificity).[3]

In the context of BPSD, we welcome regulatory considerations for a so-called trans-diagnostic approach to development of drugs for treatment of common behavioral and/or psychiatric symptoms that present across neurodegenerative disorders. An example of such approach is pimavanserin, which is in development for treatment of dementia-related psychosis (i.e., psychosis across a range of different forms of dementia). Of note, pimavanserin is already approved by the FDA for treatment of hallucinations and delusions associated with PD psychosis.[40] The sponsor has announced plans to discuss submission of a supplementary new drug application for the dementia-related psychosis indication[41] for which the FDA has granted Breakthrough Therapy Designation. The outcome of these FDA discussions may set new precedence.

In line with the main focus of this review, efforts should continue to reach the ultimate goal of preventing the progress to symptomatic stages of this devastating disease. Nonetheless, effective management of the symptomatic manifestation of AD remains an urgent need for the millions of people who suffer from AD as well as for their caregivers. Therefore, regulatory guidance on symptomatic AD drug development, including BPSD, would be welcomed.

Considerations on global AD drug development

It is acknowledged that a range of guidelines apply to drug development regardless of therapeutic area and that their application is implicit. However, given the challenges described above, AD drug development needs to be approached in a global context. Therefore, this section focuses on the recently adopted ICH E17 guideline and the recommendations put forward in the regulatory AD guidelines that specifically have an impact on global AD drug development.

The ICH E17 guideline describes the general principles for the planning and design of multiregional clinical trials (MRCTs) under a single study protocol to support concurrent marketing approvals of new therapeutic drugs across countries and regions.[2] For such MRCTs, the potential impact of intrinsic and extrinsic factors needs to be identified early applying the principles outlined for the bridging or extrapolation of foreign clinical data in the ICH E5 guideline *Ethnic Factors in the Acceptability of Foreign Clinical Data*.[42]

The PMDA guideline is the only of the three regulatory guidelines on AD that explicitly addresses MRCTs and extrapolation of foreign clinical data, albeit in the context of AD dementia. Regardless of whether a global or a bridging development strategy is pursued, the PMDA guideline recommends inclusion of Japanese patients from an early stage of development.[5] For dose-finding, it requires studying a minimum of two doses using clinical outcome measures that should show reproducibility between global and Japanese patients (the latter included as part of a global or separate Japanese dose-finding study).[5] In contrast, the CHMP guideline endorses use of biomarkers as primary end points at least in the context of proof of principle studies, although collection of clinical data is also encouraged.[3] The FDA guideline does not provide recommendations for the exploratory phase of drug development.[4]

Although insufficient dose-finding prior to phase III could arguably be one of numerous causes of the high attrition rate in AD drug development,[43] showing a dose-response relationship using clinical outcome measures, let alone demonstrating potential regional differences, would require substantial additional investments in terms of time and funding. Hence, meeting the PMDA dose-finding requirements would be a major challenge for global AD drug development. Particularly in the early, slowly progressing stages of AD, long-duration trials are required to observe a clinical effect compared with placebo. Therefore, we argue that trade-offs will have to be made to allow dependence on biomarker end points for estimating dose-finding as well as similarities and differences between ethnic groups, even if biomarkers that are validated for these purposes in AD are not yet available. Hence, early exploration of various biomarker end points in phase Ib/IIa may help inform decisions on global development, including whether to conduct MRCTs vs. regional randomized control trials. Furthermore, the ICH E17 guideline opens for the possibility to use different dosing regimens within the same MRCT if ethnic differences exist.[2]

For confirmatory trials, the PMDA guideline requires that consistency is shown for both primary end points and secondary biomarker end points for both the Japanese and the overall study population. The ICH E17 guideline defines consistency as a "*lack of clinically relevant differences*" and recommends the use of descriptive statistics, graphical displays, and/or model-based estimations to inform regulatory decision making.[2]

If scientifically justified, the ICH E17 allows for prespecified pooling of data across regions (e.g., by geographic or regulatory region) or subpopulations (e.g., by genotype) to help provide flexibility in sample size allocation and to support regulatory decision making. In addition, prespecified region-specific statistical analysis plans tailored to meet the individual requirements of the regulatory authorities are supported if needed.[2] These principles offer important regulatory and operational flexibility for global drug development, especially if data from (M)RCTs could permit extrapolation of the treatment effect to diverse populations supporting approvals globally regardless of whether the regional data originate from one or more MRCTs. We suggest that, in theory, an example of such a scenario in AD could be to perform two mutually supportive MRCTs, each conducted in different countries and targeting adjacent disease stages (e.g., one in prodromal AD and one in mild AD) with the aim of supporting regulatory approval for treatment of prodromal and mild AD in all involved regions. In this scenario, the replicability of the clinical results would be confirmed by data from different regions and different disease stages.

Such flexibility, in combination with regulatory alignment across regions on key elements, such as the diagnostic criteria used for patient identification, clinical trial design, and choice of outcome measures, could facilitate more timely, global availability of new therapeutic drugs. However, the

planning phase will evidently be longer especially if any major differences between regional requirements need to be addressed and aligned with regulatory authorities.

CONCLUSIONS

Although this review outlines a series of similarities and differences among the EMA, the FDA, and the PMDA guidelines for clinical development of drugs for treatment of AD, overall the positions of these agencies nicely complement each other and provide valuable directions for sponsors who are planning a global drug development program. However, at the time of writing, successful development and approval of effective predementia AD treatments is still awaited to contextualize the recommendations provided in the current regulatory AD guidelines.

The challenges pertaining to AD drug development include (but are not limited to) poor disease biology understanding, lack of reliable diagnostic, prognostic and progression biomarkers, patient population heterogeneity, and deficiency of sensitive, yet meaningful clinical outcome measures. These challenges are equally relevant across many central nervous system (CNS) disorders. Therefore, increased public health and regulatory focus as well as publication of disease-specific drug development guidelines is welcome not only within AD, but for neurologic and psychiatric disorders in general. In addition, revisiting the current eligibility criteria of expedited pathways that offer a formalized closer collaboration with regulatory authorities (such as the FDA Breakthrough Therapy Designation and similar expedited pathways offered by other regulatory authorities) to better accommodate promising CNS drugs could potentially help alleviating the therapeutic stagnation observed in many of these disorders.

Importantly, the regulatory agencies continuously demonstrate their willingness to enter into dialogue with sponsors, experts, and other agencies through workshops, guideline consultations, and participation in public-private platforms. In particular, at least within drug development for CNS disorders, the AD area constitutes one of the most positive examples of regulatory agencies securing multistakeholder involvement to discuss regulatory challenges in an area of high medical need. We encourage continuation and further extension of this constructive dialogue to facilitate AD drug development and ultimately provide meaningful treatments to help the millions of patients and their caregivers.

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