ADVANCING ADOPTION OF NOVEL SAFETY BIOMARKERS INTO DRUG DEVELOPMENT THROUGH VOLUNTARY SUBMISSION OF DATA AT FDA, EMA, AND PMDA

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Abstract

Background and objective: Recently established channels for FDA, EMA, and PMDA to receive and evaluate scientific data supporting novel tools for use in drug development are now defined in guidances. Termed "regulatory qualification," these pathways are intended to drive scientific consensus on the specific utility of novel tools.

As these pathways begin to be utilized, it is important to ask: how do we evaluate the effectiveness and efficiency of regulatory qualification to drive applications of novel tools, e.g. biomarkers, clinical outcome assessments, quantitative disease models, in drug development?

***Methods*:** As a first stage of addressing this question, the qualification procedure, volume and types of submissions to each global regulatory agency with an established, formal qualification guidance were summarized and compared.

Results: From 2008-present, FDA, EMA, and PMDA have collectively qualified 16 unique biomarkers for use in safety assessment and therapeutic development for Alzheimer's disease. While the regulatory qualification procedure is similar among the three ICH agencies, some significant aspects such as whether a fee is collected and how regulatory review teams are constructed, impact the efficiency and resources needed to qualify new tools.

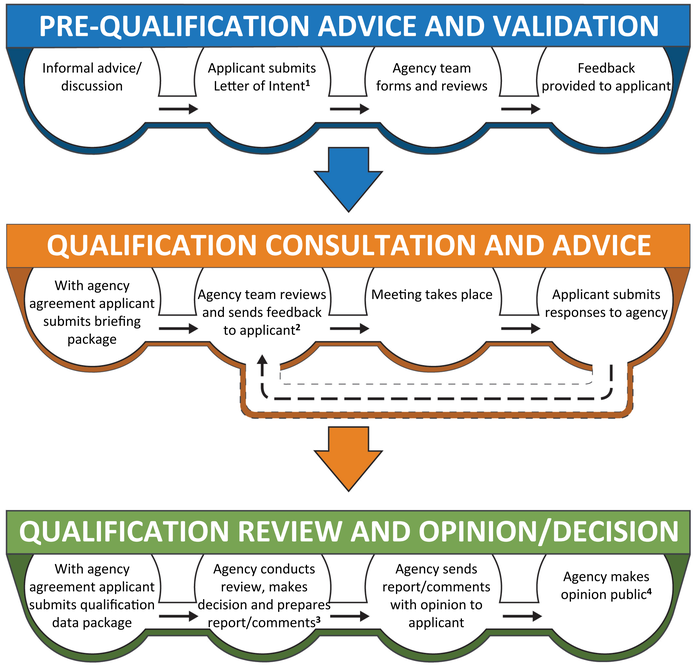
Conclusions: Two major challenges in assessing success of qualification are 1) no mechanism to track use of qualified tools in drug development programs currently exists, and 2) the cumulative time from qualification of a new tool to implementation for developmental compound to new drug approval and measuring patient benefit is long - likely a minimum of 5-7 years.

Results

	FDA	EMA	PMDA
Guidance documents	Draft Guidance for Industry: Qualification Process for Drug Development Tools	Qualification of novel methodologies for drug development: Guidance to applicants	Special scientific consultation regarding biomarker qualification
Reference website	http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0	http://www.pmda.go.jp/operations/shonin/info/consult/file/0302070-betten4.pdf (Japanese only)
Phases of qualification	Pre-initiation discussion Consultation and Advice Review	Committee for Medicinal Products for Human Use (CHMP) Qualification Advice and CHMP Qualification Opinion	Pre-qualification Qualification
Review team	Biomarker Qualification Review Team (BQRT): comprised of staff from therapeutic divisions at CDER. Chaired by one individual.	Qualification Team: Appointed by CHMP, led by Coordinator, comprised from EMA experts' network	Qualification Review Team, PMDA Omics Project team (POPT): comprised of experts from various divisions (e.g. New drug, GCP, device) at PMDA. Will use external experts if appropriate.
Public consultation period?	No.	Yes for Qualification Opinion. EMA qualification report posted for public comment prior to final opinion.	No.
Scope of acceptable biomarker requests	Any drug development tool for clinical or nonclinical context of use including imaging but NOT drug/diagnostic co-development. CDRH handles approval of devices.	Innovative drug development methods and tools for clinical or nonclinical context of use including imaging.	Any biomarker for clinical or nonclinical context of use including imaging but NOT an individual drug/diagnostic development program.
Fee[1]	None.	77,900 Euros (approx. 94,721 USD) for initial Advice or Opinion 38,900 Euros (approx. 47,299 USD) for follow-up Advice or Opinion	3,028,400 YEN (approx. 38,775 USD) for qualification 921,900 YEN for follow-up advice to 1) 1,111,000 YEN for evaluation of qualification strategy and protocols 403,100 YEN for follow-up advice to 3)
Regulatory product	Formal regulatory opinion issued in form of DDT qualification recommendations and supporting documentation will be made publically available on FDA website with notice of availability published in federal register.	Formal CHMP Qualification Opinion issued in form of letter to sponsor and EMA-drafted report made publically available on EMA website.	Formal Qualification Opinion issued in form of letter to sponsor and PMDA-drafted report containing overall summary from sponsor made publically available on PMDA website.

Table 1. Comparison of the process for qualification of drug development tools at FDA, EMA, and PMDA

Figure 1. A generalized figure of phases of drug development tool/biomarker qualification common to all three ICH agencies. Steps for each specific procedure are contained in the respective agencies' guidance.



(1) Specific forms and timelines for review vary by Agency, see Table 1
(2) EMA utilizes Scientific Advice procedure with CHMP/SAWP
(3) EMA utilizes Scientific Opinion procedure with CHMP/SAWP; FDA may utilize an Advisory Committee if appropriate
(4) PMDA process allows applicant to comment on report prior to publication; EMA undergoes public consultation phase after applicant is allowed to comment on opinion

		INITIATION STAGE	CONSULTATION AND ADVICE STAGE	REVIEW STAGE	QUALIFIED
FDA	biomarkers	3	13	1	3
	COAs[1]	15	18	2	0
	animal models	0	0	0	0
EMA	biomarkers	0	18	0	6
	COAs	0	5	1	0
PMDA	biomarkers	0	2	0	1

Table 2. Volume of drug development tool qualification projects at regulatory agencies. Multiple biomarkers packaged within a single qualification submission (e.g. the seven nonclinical nephrotoxicity biomarkers qualified by FDA (2009), EMA (2010) and PMDA (2011)) are counted as a single project. FDA terminology is imperfectly adapted here for all three agencies. The start of the Consultation and Advice Stage is herein defined as when the Letter of Intent is accepted and a Briefing Package requested from the sponsor.
[1]COA: clinical outcomes assessment

DRUG DEVELOPMENT TOOL(S)	CONTEXT OF USE (COU)	HEALTH AUTHORITIES WHERE QUALIFIED	QUALIFICATION SPONSOR	REF(S)
Urinary renal biomarkers (Kim-1, albumin, total protein, B-2 microglobulin, cystatin C, clusterin, trefoil factor-3)	**NONCLINICAL:** Biomarkers are acceptable for voluntary use in nonclinical drug development for the detection of acute drug-induced nephrotoxicity, either tubular or glomerular with associated tubular involvement. They provide additional and complementary information to BUN and serum creatinine to correlate with histopathological alterations. **CLINICAL:** The use of these renal biomarkers in clinical trials may be considered on a case-by-case basis in order to gather further data to qualify their usefulness in monitoring drug-induced renal toxicity in man.	FDA, EMA, PMDA	Critical Path Institute's Predictive Safety Testing Consortium	1, 2, 3, 4
Urinary renal biomarkers (clusterin, RPA-1, a-GST (EMA only))	Urinary Clusterin is a biomarker that may be used by Applicants to detect acute drug-induced renal tubule alterations, particularly when regeneration is present, in male rats and can be included along with traditional clinical chemistry markers and histopathology in GLP toxicology studies which are used to support renal safety in clinical trials. RPA-1 is qualified for the same context of use as stated above, but is specific to the collecting duct in kidney. **EMA only:** The data may support the use of urinary α-GST in detecting proximal tubule injury in male rats.	FDA, EMA	Health and Environmental Science Institute's Committee on Biomarkers of Nephrotoxicity	5, 6, 7
CSF biomarkers for Alzheimer's disease (Ab_{1-42}, total tau, phosphorylated tau)	In patients with MCI as evaluated by Dubois criteria, a positive CSF biomarker signature based on a low Ab_{1-42} and a high T-tau can help predict evolution to AD-dementia type and is useful for clinical trial enrichment for drugs affecting amyloid burden in Alzheimer's disease.	EMA	Bristol Myers Squibb	8
Volumetric imaging of hippocampal volume for Alzheimer's disease	Low hippocampal volume (HV), as measured by MRI and considered as a dichotomized variable (low volume or not), may be used along with clinical criteria to help enrich recruitment into clinical trials aimed at studying drugs potentially slowing the progress/conversion to AD dementia. Low HV might be considered a marker of progression to dementia in subjects with cognitive deficit compatible with predementia stage of AD (Dubois, 2007), for the purposes of enriching a clinical trial population. However, neither the actual value of low HV to accurately predict rate of such progression in the referred subjects nor the relative value of other biomarkers have been reported.	EMA	Critical Path Institute's Coalition Against Major Disease	9
PET amyloid imaging in Alzheimer's disease	Amyloid related positive/negative PET signal qualifies to identify patients with clinical diagnosis of predementia AD who are at increased risk to have an underlying AD neuropathology for the purposes of enriching a clinical trial population. However, neither the actual value of PET (+) or (-) to accurately predict rate of such progression to dementia in the referred subjects nor the relative value of other biomarkers have been reported. Thus, we recommended to follow-up these patients until clinical diagnosis of Mild AD is made.	EMA	Bristol Myers Squibb	10
Circulating cardiac troponins T and I	Serum/plasma cardiac troponin T and I are biomarkers of cardiac morphological damage and are useful for specific purposes in nonclinical safety assessment.	FDA	O' Brien, Regan, York, and Jacobsen	11

Table 3. Currently qualified biomarkers at FDA, EMA, and PMDA. Some context of use (COU) statements have been paraphrased as needed for brevity. In some instances where a DDT submission was reviewed by multiple agencies, the qualified context of use differs slightly (e.g. ILSI/HESI nephrotoxicity biomarkers, FDA and EMA, 2010). The approved COU is available online from each agency.

Conclusions

- Qualification of new safety biomarkers and other drug development tools by regulatory agencies and subsequent adoption by drug developers is anticipated to speed therapeutic development for patients in need, build scientific consensus as to the usefulness and readiness of novel tools for understanding disease and therapeutic development, and decrease uncertainty between the regulators and sponsors regarding their appropriate application. However, the return on investment in qualifying new tools must be demonstrated for such a resource-intensive process.
- Next steps must determine whether regulatory qualification has promoted the adoption of new tools into their intended use, and how impactful these new tools are for assessing drug safety, efficacy, quality and/or performance.
- A pharmacoeconomic analysis to establish the return on investment for qualification is of high value and in planning stages.

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