nature REVIEWS RHEUMATOLOGY

SUPPLEMENTARY INFORMATION

In format as provided by the authors

Biomarkers as drug development tools: discovery, validation, qualification and use

Virginia B. Kraus

https://doi.org/10.1038/s41584-018-0005-9

Supplementary Table S1 | **FDA and EMA qualified biomarkers.**

General Area	**Submitter**	**Biomarker(s) Qualified for Specific Contexts of Use**	**Issuance / Adopted Date with Link (FDA) or Document Number (EMA) to Specific Guidance**	**Application**
FDA				
Nonclinical Safety	Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary biomarkers: Albumin, β2-Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil factor-3	4/14/2008 Drug-induced Nephrotoxicity Biomarkers	Detection of acute drug-induced nephrotoxicity in rats and can be included along with traditional clinical chemistry markers and histopathology in toxicology studies; KIM-1, Albumin, Clusterin and Trefoil Factor-3 can be included as biomarkers of drug-induced acute kidney tubular alterations in Good Laboratory Practice (GLP) rat studies used to support clinical trials. Total Protein, β2 Microglobulin and Cystatin C can be included as biomarkers of acute drug-induced glomerular alterations/damage and/or impairment of kidney tubular re-absorption in GLP rat

				studies used to support clinical trials.
Nonclinical Safety	International Life Sciences Institute (ILSI)/ Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group	Urinary biomarkers: Clusterin, Renal Papillary Antigen (RPA-1)	9/22/2010 Drug-induced Nephrotoxicity Biomarkers	Clusterin: detection of acute drug-induced renal tubule alterations, particularly when regeneration is present (urinary clusterin) or particularly in the collecting duct (RPA-1), in male rats when used in conjunction with traditional clinical chemistry markers and histopathology in GLP toxicology studies for drugs for which there is previous preclinical evidence of drug induced nephrotoxicity or where it is likely given the experience with other members of the pharmacologic class.; may use these biomarkers to determine more conservative NOAELs for estimating starting doses in the initial human clinical trial of a drug that displays nonclinical nephrotoxicity as determined by histopathology.
Nonclinical Safety	PJ O'Brien, WJ Reagan, MJ York and MC Jacobsen	Serum/plasma biomarkers: Cardiac troponins T (cTnT) and I (cTnI)	2/23/2012 Drug-induced Cardiotoxicity Biomarkers	When there is previous indication of cardiac structural damage with a particular drug, cardiac troponin testing can help estimate a lowest toxic dose or a

				highest non-toxic dose to help choose doses for human testing. In safety assessment studies in rats and dogs, to help determine a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL)
Clinical Diagnostic	Mycoses Study Group	Serum/bronchoalveolar lavage fluid biomarker: Galactomannan	11/14/2015 Patient selection biomarker for enrollment in Invasive Aspergillosis (IA) clinical trials	Treatments for invasive aspergillosis (IA), qualified as a sole microbiological criterion to classify patients as having probable IA; for enrollment in, and analysis of, clinical trials conducted to evaluate the efficacy and safety of drugs for the treatment of IA; restricted to patients with hematologic malignancies or recipients of hematopoietic stem cell transplant
Clinical Prognostic	Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)	Plasma biomarker: Fibrinogen	9/14/2016 Prognostic biomarker for enrichment of clinical trials in Chronic Obstruction Pulmonary Disease	Interventional clinical trials of patients with chronic obstructive pulmonary disease (COPD) at high risk for exacerbations and/or all-cause mortality; measured at baseline, as a prognostic biomarker to select patients with COPD at high risk for

			(COPD)	exacerbations and/or all-cause mortality for inclusion in interventional clinical trials. This biomarker should be considered with other demographic and clinical characteristics, including a prior history of COPD exacerbations, as an enrichment factor in these trials. Plasma fibrinogen can be used as an enrichment factor, in addition to standard inclusion/exclusion criteria, in COPD clinical trials with endpoints of COPD exacerbation and/or all-cause mortality
Clinical Prognostic	Polycystic Kidney Disease Outcomes Consortium	Imaging Biomarker: Total Kidney Volume (TKV, sum of volume of the left and right kidneys)	9/15/2016 Prognostic biomarker for enrichment of clinical trials in Autosomal Dominant Polycystic Kidney Disease	Treatment of autosomal dominant polycystic kidney disease: measured at baseline, as a prognostic enrichment biomarker to select patients with ADPKD at high risk for a *progressive decline* in renal function (defined as a confirmed 30% decline in the patient's estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient's age and

				baseline eGFR as an enrichment factor in these trials.
EMA				
Preclinical and Clinical Safety	International Life Sciences Institute (ILSI)/ Health and Environmental Sciences Institute (HESI),	Renal toxicity: Urinary renal Papillary Antigen (RPA-1) and clusterin	10/21/2010 (WC500099359)	To detect acute drug-induced renal tubule alterations in male rats, particularly in the collecting duct RPA-1) or when regeneration is present (clusterin); both biomarkers can be included along with traditional clinical chemistry markers and histopathology in toxicology studies to support renal safety in clinical trials.
Clinical Diagnostic	Bristol-Myers Squibb	Cerebrospinal fluid biomarkers of amyloid burden: Aß1-42 and total tau	4/14/2011 (WC500106357)	Identification of predementia stage of Alzheimer's disease for selection of patients for trials in early disease
Clinical Diagnostic	Critical Path Institute (C-Path) Coalition Against Major Diseases (CAMD) Biomarker Working Group	Low hippocampal volume (atrophy) by magnetic-resonance imaging	11/17/2011 (WC500118737)	Low hippocampal volume (atrophy) for clinical trial selection of individuals with high likelihood of early prodromal Alzheimer's disease
Clinical Diagnostic	Bristol-Myers Squibb	Cerebrospinal fluid biomarkers for	2/16/2012 (WC500125019)	Selection for trial enrichment of individuals with mild and moderate

		Alzheimer's Disease: amyloid beta 1-42, T-tau, and/or positron-emission-tomography amyloid imaging		Alzheimer's disease; additional biomarker
Clinical prognostic	Critical Path Global, Ltd	Trial endpoint ADAS-Cog	9/19/2013 (WC500151309)	Longitudinal data driven model for describing changes in cognition in patients with mild and moderate Alzheimer's Disease
Clinical trial dose selection	Novartis	Multiple comparison procedure modelling (MCP-Mod)	1/23/2014 (WC500161027)	MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies to provide a more solid basis for all subsequent dose selection strategies and decisions.
Clinical trial pharmacokinetic simulation	Critical Path to TB Drug Regimens (CPTR)	In-vitro hollow-fibre-system model of tuberculosis (HSF-TB)	1/22/2015 (WC500181899)	In vitro system to optimize drug regimens and dose selection to maximize the bactericidal effect rates and minimize the emergence of resistance to Mycobacterium tuberculosis
Clinical Prognostic	Polycystic Kidney Disease Outcome Consortium (PKDOC)	Total kidney volume by MRI, CT or US (with patient age and	10/22/2015 (WC500196569)	Selection of individuals with autosomal dominant polycystic kidney disease at the greatest risk for a substantial decline in

	of the Critical Path Institute	glomerular filtration rate)		renal function
Clinical Diagnostic and Efficacy of Intervention	Copyrighted to Hospital for Sick Children, Toronto	Pediatric Ulcerative Colitis Activity Index (PUCAI)	12/17/2015 (WC500200026)	Non-invasive 6 patient-reported item index for selection of individuals for trials and for use as a primary outcome measure in clinical trials
Clinical Diagnostic	Proteus Digital Health, Inc	Ingestible sensor	12/17/2015 (WC500201943)	Class IIa medical device for measuring medication adherence and associated physiological responses

Data on FDA and EMA qualified biomarkers available at:
https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/biomarkerqualificationprogram/ucm535383.htm
and
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0

MRI-magnetic resonance imaging, CT=computed tomography, US=ultrasound