Biomarkers: Opportunities and Challenges for Drug Development in the Current Regulatory Landscape

Mariya Gromova, Annegret Vaggelas, Gabriele Dallmann and Diane Seimetz

Biopharma Excellence GmbH, Munich, Germany.

Biomarker Insights
Volume 15: 1–15

DOI: 10.1177/1177271920974652
SAGE

ABSTRACT: Biomarkers are widely used at every stage of drug discovery and development. Utilisation of biomarkers has a potential to make drug discovery, development and approval processes more efficient. An overview of the current global regulatory landscape is presented in this article with particular emphasis on the validation and qualification of biomarkers, as well as legal framework for companion diagnostics. Furthermore, this article shows how the number of approved drugs with at least 1 biomarker used during development (biomarker acceptance) is affected by the recent advances in the biomarker regulations. More than half of analysed approvals were supported by biomarker data and there has been a slight increase in acceptance of biomarkers in recent years, even though the growth is not continuous. For certain pharmacotherapeutic groups, approvals with biomarkers are more common than without. Examples include immunosuppressants, immunostimulants, drugs used in diabetes, antithrombotic drugs, antineoplastic agents and antivirals. As a conclusion, potential benefits, challenges and opportunities of using biomarkers in drug discovery and development in the current regulatory landscape are summarised and discussed.

KEYWORDS: Biomarker, EMA, FDA, regulatory landscape, qualification, companion diagnostics, drug development, drug approval

RECEIVED: October 11, 2020. **ACCEPTED:** October 25, 2020.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

CORRESPONDING AUTHOR: Mariya Gromova, Biopharma Excellence GmbH c/o Munich Technology Center Agnes-Pockels-Bogen 1 80992 Munich, Germany. Email: gromova@biopharma-excellence.com

Introduction

Biomarkers have been used for centuries as indicators of human health or for the diagnosis of pathological conditions. One of the oldest biomarkers used to diagnose certain illnesses was the arterial pulse, which was already documented in ancient Chinese, Indian, Egyptian and Greek medicine.[1] This was followed by blood pressure experiments, which were conducted for the first time in the middle of the 18th century.[2] Arterial pulse, blood pressure and many other biomarkers, such as body temperature and quantification of various blood components (eg, cholesterol levels), have now become an essential part of modern healthcare globally.

In general, the term 'biomarker' refers to a biological parameter that can be measured or quantified accurately and reproducibly. This term is incredibly diverse and includes physiological parameters (eg, diastolic pressure) as well as molecular (eg, liver enzymes, blood glycose), histologic and imaging characteristics (eg, angiography).[3] Nowadays, biomarkers are widely used in diagnostics, to ensure safety of treatment and to guide clinical decisions. Furthermore, since the beginning of the 21st century, biomarkers have gained prominence in drug discovery, development and approval processes, as described in Figure 1. Development of suitable biomarker can contribute to understanding the mechanism of action of a drug, selecting right patients for a clinical trial, monitoring and prediction of toxicity issues and guiding regulatory as well as drug development decisions. Furthermore, biomarkers facilitate more adaptive development paradigm, meaning that the traditional clinical phase 1, phase 2 and phase 3 designs are likely to become less important. Consequently, the regulatory strategies will need to be adapted.[4] All of this has a potential to make development more sustainable, to improve quality and safety of a drug, to reduce development costs and to accelerate the approval process significantly.

The aims of this article are (1) to present an overview of the current global regulatory landscape for biomarkers, (2) to evaluate how it affects the number of approved drugs with at least 1 biomarker used during development (ie, biomarker acceptance) in the European Union (EU) and the United States of America (US) and (3) to describe potential benefits and challenges of using biomarkers in drug development.

Biomarker Definitions and Classification

To date there is no standardised definition of the term biomarker. European Medicines Agency (EMA) defines a biomarker as 'biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals'.[5] In the Biomarkers, EndpointS and other Tools (BEST) Resource glossary, a biomarker is 'a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. [. . .] A biomarker is not an assessment of how an individual feels, functions, or survives', a category of measure known as clinical outcome assessment (COA).[6] BEST Resource was developed in 2016 by the Food and Drug Administration – National Institutes of Health (FDA-NIH) Biomarker Working Group and its main aim is to clarify and harmonise terminology and thus speed up the research, development and testing on novel methodologies, in particular biomarkers. According to the BEST Resource glossary, each biomarker belongs to 1 of 7 defined categories, described in Table 1.

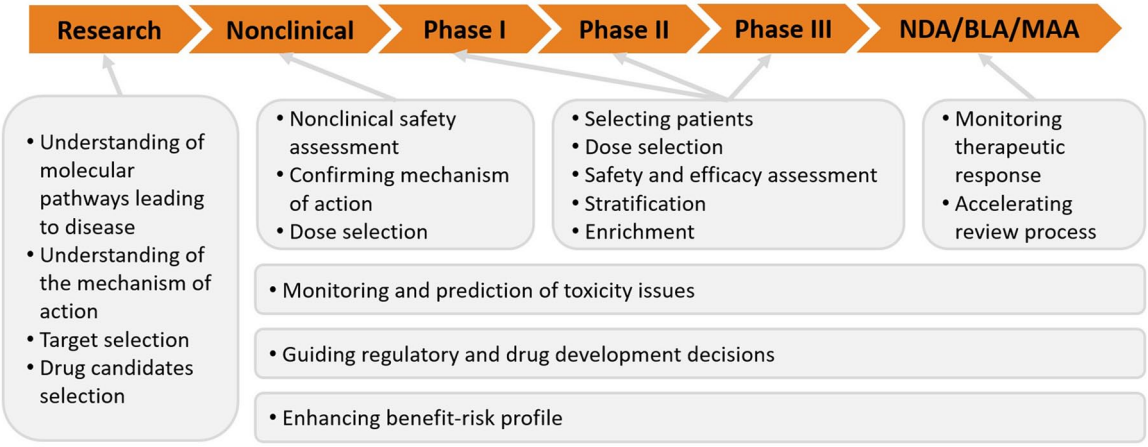

Figure 1. Drug discovery and development processes with a potential to benefit from biomarkers phase I, II and III refer to clinical trial phases. NDA, new drug application (FDA); BLA, biological license application (FDA); MAA, marketing authorisation application (EU).

Table 1. Biomarkers categories according to BEST Resource glossary.

BIOMARKER CATEGORY	DESCRIPTION	EXAMPLE
Diagnostic	A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease	Sweat chloride may be used as a diagnostic biomarker to confirm cystic fibrosis[8]
Monitoring	A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent	Monoclonal protein (M protein) level in blood may be used as a monitoring biomarker to evaluate whether individuals diagnosed with monoclonal gammopathy of undetermined significance (MGUS) are showing signs of progressing to other disorders, including some types of blood cancer which may require treatment[9]
Pharmacodynamic/ response	A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent	Serum LDL cholesterol may be used as a pharmacodynamic/response biomarker when evaluating patients with hypercholesterolemia, to assess response to a lipid-lowering agent or dietary changes[10]
Predictive	A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favourable or unfavourable effect from exposure to a medical product or an environmental agent	BReast CAncer genes 1 and 2 (BRCA1/2) mutations may be used as predictive biomarkers when evaluating women with platinum-sensitive ovarian cancer, to identify patients likely to respond to poly (ADP-ribose) polymerase (PARP) inhibitors[11]
Prognostic	A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest	BReast CAncer genes 1 and 2 (BRCA1/2) mutations may be used as prognostic biomarkers when evaluating women with breast cancer, to assess the likelihood of a second breast cancer[12]
Safety	A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect	Serum creatinine may be used as a safety biomarker when evaluating patients on drugs that affect kidney function to monitor for nephrotoxicity[13]
Susceptibility/risk	A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition	Apolipoprotein E (APOE) gene variations may be used as susceptibility/risk biomarkers to identify individuals with a predisposition to develop Alzheimer's disease[14]

It is also possible that a biomarker belongs to several categories, but only given that enough evidence is generated for each category.[7] This is the case with BReast CAncer genes 1 and 2 (BRCA1/2) mutations that can be used as both predictive and prognostic biomarkers (Table 1).

BEST Resource also covers definition of surrogacy and underlines that not every biomarker can be a surrogate endpoint. A surrogate marker is a 'laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy'.[15] On the contrary, the majority of known biomarkers lack sufficient data to prove the direct relation between the level of a biomarker and the clinical outcome,

that is, the change in the biomarker does not necessary explain the change in the clinical outcome.[7] There are also other more sophisticated biomarker categories that are not covered by BEST Resource glossary, for example, digital biomarkers.[7]

Current Regulatory Landscape for Biomarkers

In the majority of cases biomarkers are currently studied and evaluated as part of drug development programme, that is, linked to a particular drug development. As both drug development and biomarker development are extremely cost- and time-intensive, it might be challenging for a sponsor to develop both simultaneously.[16] The current regulatory landscape for biomarkers progresses rapidly, with ongoing developments for both publicly reported biomarkers and biomarkers used in individual development programmes. There is a tendency though to promote availability of public data on biomarkers, which aids cost reduction and resource optimisation for both drug developers and regulatory agencies.

Rapid development of regulations in biomarkers field began in early 21st century and is closely linked to the development of the 'personalised medicine' concept involving delivery of tailored therapy to a particular patient, based on his genetic and epigenetic information. ICH E15 Guideline[17] was published in 2006 and defines pharmacogenomics (PGx, study of variations of DNA and RNA characteristics as related to drug response) and pharmacogenetics (PGt, study of variations in DNA sequence as related to drug response). Genomic biomarkers are DNA or RNA characteristics that are a crucial part of drug development and essential for successful regulatory approval.[18,19] Examples of the use of genomic biomarkers in drug development include:

- understanding of the mechanistic basis for lack of efficacy, occurrence of adverse drug reactions or drug-drug interactions,
- clarifying differences in response in clinical trials as well as differences in pharmacokinetic (PK) and pharmacodynamic (PD) parameters,
- enrichment and stratification in clinical trials to facilitate accelerated development.[19]

Numerous PGx and PGt related guidelines are available from both EMA and FDA.[20-27] This article will describe in detail the regulatory framework applicable for the biomarker qualification in the European Union (EU) and the United States of America (US). It will also address the regulatory systems to be followed in both regions for placing on the market of companion diagnostic (CDx) assays that are utilised to test predictive biomarkers.

Biomarker validation and qualification

One of the main challenges in the biomarker field is to distinguish between a potential biomarker and a reliable biomarker that can be universally used to guide important clinical and commercial decisions. Scientific justification behind biomarkers and interpretation of biomarker measurements are not always reliable and appropriate. As a response to the increasing need to address quality and suitability of biomarkers, concepts of biomarker qualification and validation have been developed.[28] Biomarker validation refers to the validation of analytical assays, that is, assessment of performance characteristics, such as, for example, precision, accuracy, detection limit and robustness. Biomarkers qualification, on the other hand, is providing evidence that biomarker is linked with a certain biological process and clinical endpoint.[29,30]

The fact that development of better evaluation tools and biomarkers in particular was named a top priority of the FDA's Critical Path Opportunities Report in 2006 underlined the importance of defining biomarkers validation and qualification processes.[31] Joint effort of FDA, EMA and Predictive Safety Testing Consortium's (PSTC) Nephrotoxicity Working Group created the pilot process for biomarker qualification. As a result, 7 renal safety biomarkers have been qualified for limited use in nonclinical and clinical development in 2010.[28,32] The first qualification of renal safety biomarkers has not only become a basis for the still evolving biomarkers qualification procedure, but also emphasised the willingness of agencies to collaborate in this area. The following sections will focus on the biomarker qualification procedures in the EU and the US.

Biomarker qualification in the EU. A voluntary procedure for qualification of biomarkers has been developed by EMA and is described in the EMA guidance for applicants 'Qualification of novel methodologies for drug development'.[33] Novel methodologies include not only biomarkers, but also clinical outcome assessments, symptom scales, animal models, statistical methods etc. The Scientific Advice Working Party (SAWP) and Committee for Medicinal Products for Human Use (CHMP) are both involved in the qualification of novel methodologies, which can lead to 2 possible outcomes: CHMP Qualification Advice or CHMP Qualification opinion.[34]

The procedure for EMA novel methodologies qualification is depicted in Figure 2, and starts with the submission of a Letter of Intent (LOI) and a draft dossier at Day-60. At this stage, it is not compulsory to decide which pathway to follow, that is, qualification opinion or qualification advice. EMA validation procedure follows shortly after initial submission, similar to the process utilised in the Scientific Advice procedure.[33] Furthermore, a qualification team (QT) is usually appointed during the first weeks after initial application. The core QT consists of at least 5 members, that is, 1 to 2 coordinators (SAWP or CHMP) and at least 4 subject experts. Subject experts are chosen based on the context of use of the technology of interest (eg, translational research, nonclinical safety testing etc.), technology platform (eg, genomics, proteomics etc.) and additional needs for this particular project (ie, statisticians, experts in particular therapeutic area).[34] Subject experts

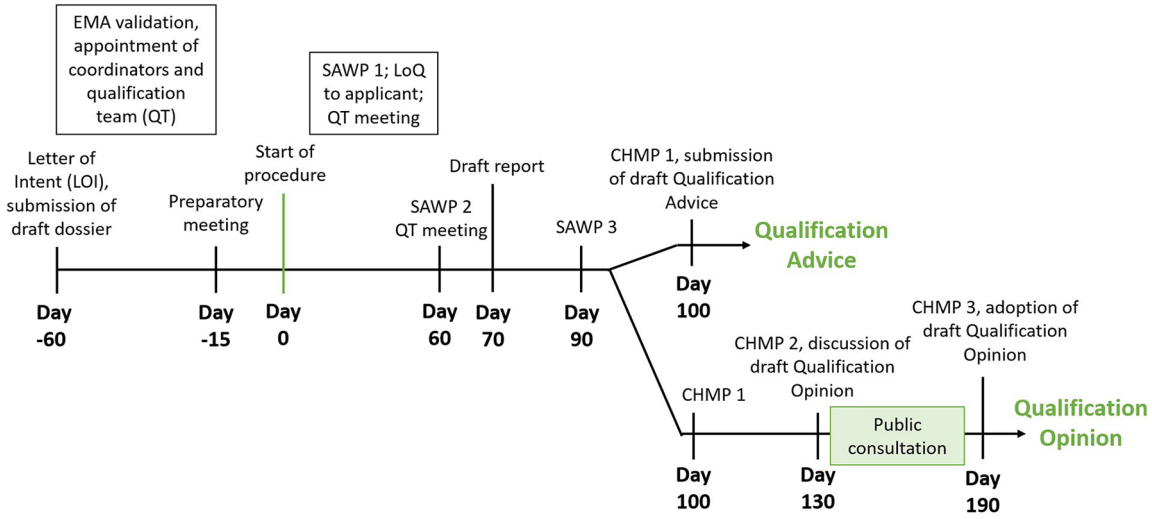

Figure 2. EMA novel methodologies qualification procedure. QT, qualification team; LoQ, list of questions; LOI, Letter of Intent; SAWP, scientific advice working party; CHMP, Committee for Medicinal Products for Human Use; Figure created based on the information provided in EMA guidance to applicants 'Qualification of novel methodologies for drug development'.[33]

can be members of CHMP, SAWP, other EMA working parties or European experts' network. When the QT is determined, the procedure starts at Day 0 followed by extensive discussion during QT meetings, SAWP meetings and meetings with the applicant. During this timeframe, a List of Questions (LoQ) to the applicant is issued and discussed. As the result, at Day 70, a draft report is issued. Moreover, at Day 90 SAWP issues a recommendation on whether to follow the qualification opinion or advice pathway, based on the type of request and available data. For the qualification advice pathway, CHMP adopts the qualification advice for future studies during the first CHMP Meeting at Day 100.[33] Alternatively, if enough information is available, a draft qualification opinion will be issued, discussed and adopted during the first and the second CHMP meetings (Day 100 and 130). After adoption by CHMP, the qualification opinion is always released for a 6-week public consultation period to collect opinions of the scientific community. Following this, the CHMP Qualification opinion is adopted and published on the EMA website 15 days later. EMA and CHMP may then organise qualification workshops to familiarise interested parties with the qualified methodology.[33]

Overall, the procedure for the qualification advice and opinion lasts 160 days and 250 calendar days, respectively. Clock-stops may be requested during the procedure and will further extend the timeline. Possible outcomes of the above-described procedure are summarised in Figure 3. 'CHMP Qualification Advice on future protocols and methods for further method development towards qualification' is usually issued for candidate novel methodologies when more data are needed to support the proposed context of use.[33] As soon as more/better quality data is collected, the CHMP Qualification opinion may be requested. CHMP Qualification Advice is confidential, as opposed to the CHMP Qualification opinion, which is publicly available. When the CHMP Qualification Advice is issued, EMA may propose a Letter of support for novel methodologies, which is also publicly available and aims to encourage data sharing and thus to facilitate future studies.[33]

To maximise a chance of scientific consensus, EMA allows and encourages involvement of non-EU regulatory agencies in parallel qualification procedure. This is facilitated by the existing confidentiality agreement between the FDA/PMDA and the EMA. An option to submit a joint Letter of Intent (LOI) to EMA and FDA was introduced in December 2014 and has been recently discontinued. At present, it is the responsibility of the applicant to ensure that other agencies are informed about the parallel qualification before the start of EMA qualification procedure.[33] EMA qualification procedure is associated with fees, similar to Scientific Advice fees.

Biomarker qualification in the US. Depending on the chosen strategy, data for each biomarker can either be reviewed as part of regulatory submissions for the drug under development (ie, IND/NDA/BLA) or in a separate qualification procedure. Following qualification, biomarker-related data is made public and can be used for development of multiple drugs.[35] Qualification of biomarkers implies FDA's agreement that a particular biomarker and its proposed context of use (COU) can be used in drug development and for regulatory submissions without FDA having to reconfirm its suitability.[36] COU is crucial for biomarker qualification and consists of BEST biomarker category and the intended use in drug development, for example, 'Safety biomarker for the detection of acute drug induced renal tubule alterations in male rats'.[37]

In the US, biomarkers can currently be qualified using the Center For Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP) that is described within the 'Drug Development Tools' (DDTs) Program. DDTs are methods,

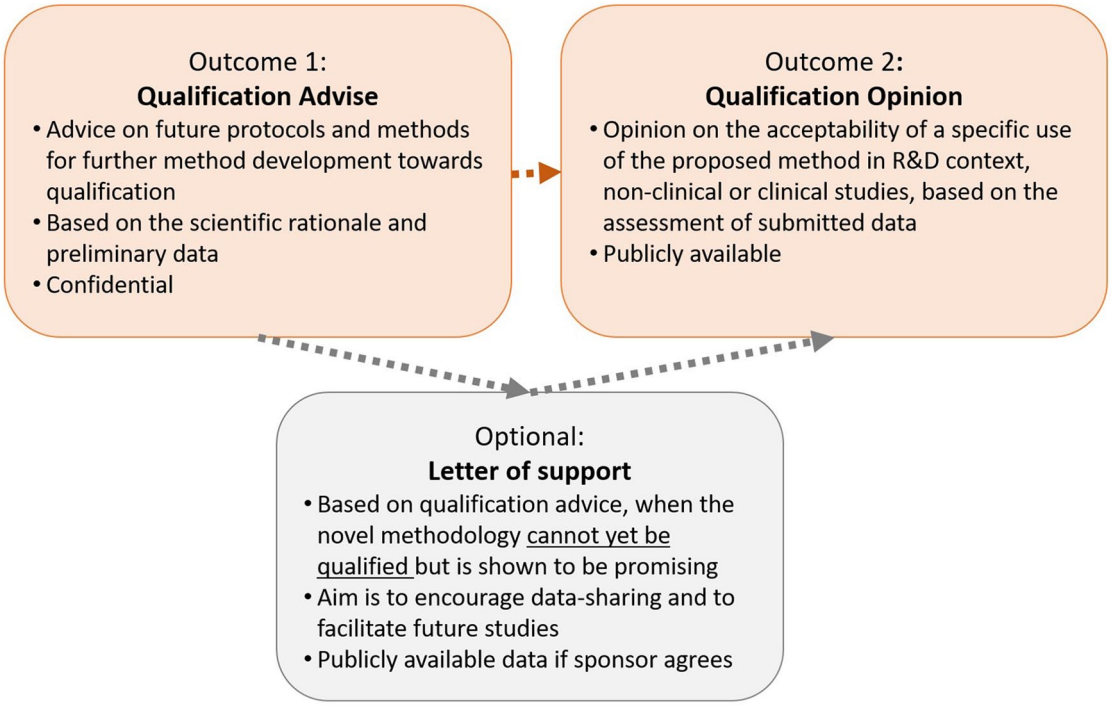

Figure 3. Possible outcomes of the EMA Novel Methodologies Qualification procedure. Figure created based on the information provided in EMA guidance to applicants 'Qualification of novel methodologies for drug development'.[33]

materials, or measures that have the potential to facilitate drug development[36] and include not only biomarkers, but also clinical outcome assessments (COA), animal models etc. There are no fees for a BQP procedure. Development of DDTs is described in the draft guidance 'Qualification process for drug development tools' that was issued by FDA in January 2014 and was replaced by the draft guidance with the same name in December 2019 to incorporate requirements outlined in Section 3011 of the 21st Century Cures Act of 2016, that is, addition of the new section 507, Qualification of Drug Development Tools (DDTs), to the Federal Food, Drug and Cosmetic Act (FD&C Act). When finalised, this guidance will describe 'CDER and CBER's (Center for Biologics Evaluation and Research) current thinking on taxonomy for biomarkers and other drug development tools (DDTs)'.[38] The taxonomy of biomarkers and other DDTs described in this guidance is based on the BEST Resource glossary. In addition to DDTs Program, there is also a 'Medical Device Development Tools' (MDDTs) Program that includes biomarker tests, that is, lab tests used to detect biomarkers and is described in a separate FDA Guidance.[39]

Normally each biomarker should be submitted separately for a qualification unless several biomarkers are intended to be combined in a particular way to represent a single COU. BQP is a 3-stage process, as illustrated in Figure 4. Each stage consists of initial assessment by FDA, comprehensive review and DDT Committee evaluation.[38]

The amount of data and the expected level of details increases gradually during the process and is described in Table 2. The completion of each stage is determined by the issue of Determination Letter: *accept* or *not accept* for LOI and QP stages; and *qualified* or *not qualified* for FQP stage. For LOI and QP stages, the application will only proceed to the next stage in case of receipt of an *accept* Determination Letter.

BQP and other DDT qualification projects are usually complex and require an interdisciplinary approach as well as dedicated financial investments. To aid biomarker qualification, FDA issued a draft guidance for industry and FDA staff entitled 'Biomarker Qualification: Evidentiary Framework' in 2018. This guidance provides recommendations on general considerations to address when developing a biomarker for qualification and describes the evidentiary framework that should be used when determining the level of details required for successful qualification.[40] The evidentiary framework requires a detailed description of the need assessment, proposed COU and benefit-risk assessment for a particular biomarker. Extensive collaborations are accepted and promoted by FDA. The assessment of DDTs and corresponding COUs is performed by subject matter experts (SMEs), that is, internal FDA staff and external specialists focusing on the required area. SMEs then contribute to the list of considerations and recommendations to the DDT Committee.[35] FDA also encourages collaborations and data sharing between single entities developing biomarkers to facilitate and accelerate the DDT development process, for example, by establishing public-private partnerships.

FDA qualification procedure is free of charge, as opposed to EMA. Both FDA and EMA underline the importance of interdisciplinary collaboration and extensive communication between the applicant(s) and the agencies.

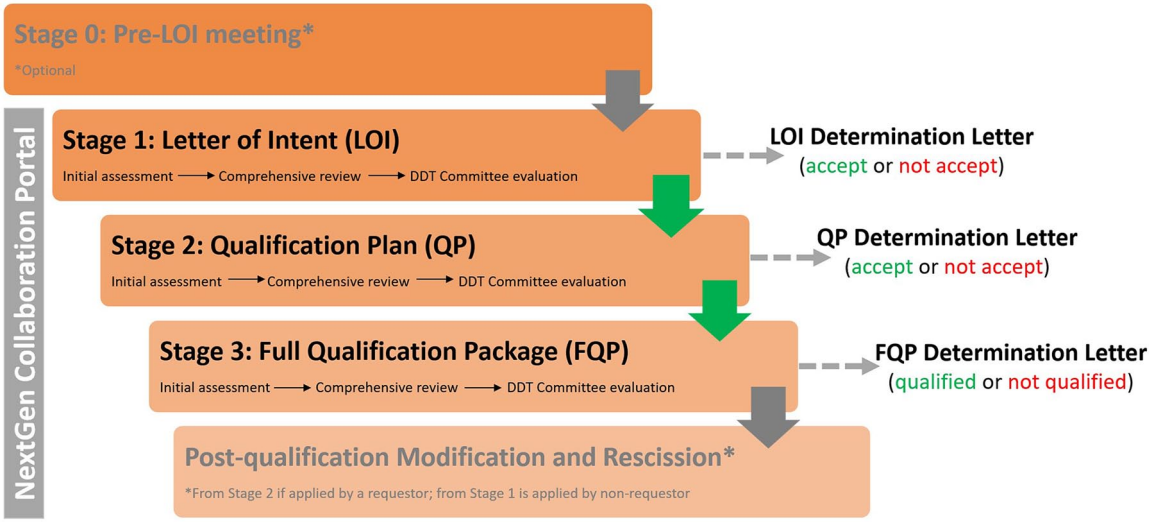

Figure 4. FDA Biomarker Qualification Program procedure. DDT, Drug Development Tools; LOI, Letter of Intent, Figure created based on the information provided in FDA draft guidance for industry and FDA staff 'Qualification process for drug development tools'.[38]

Table 2. Description of each step of the FDA Biomarker Qualification Program procedure.

STAGE	DESCRIPTION	TIMELINE (AFTER INITIAL ASSESSMENT IS COMPLETED)
Stage 1: Letter of Intent (LOI)	Concise document Describes biomarker, drug development need and a proposed COU Scientific rationale is expected	3 months
Stage 2: Qualification Plan (QP)	Describes available relevant data, knowledge gaps, data collection, analysis plan and study protocols Addresses recommendations from the previous stage Timeframe for data collection, analysis and reporting should be estimated	6 months
Stage 3: Full Qualification Package (FQP)	Describes detailed description of all studies, analysis, and results Addresses recommendations from the previous stage Evidence should include full study protocols and reports, statistical analysis plans and program files, as well as subject-level data	10 months

Table created based on the information provided in FDA draft guidance for industry and FDA staff 'qualification process for drug development tools'.[38]

Qualified biomarkers. In addition to EMA and FDA efforts to promote biomarker qualification, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals (ICH) issued the draft harmonised Guideline E16 in August 2010 summarising recommendations on the structure for biomarkers qualification applications, format of submissions and formulation of context of use.[41] This guideline is mainly focused on genomic biomarkers, but principles are applicable to other types of biomarkers. ICH E16 has already been implemented in the EU, US, Canada, South Korea, Japan and Switzerland.[42] This was a crucial step to the increasing acceptance of biomarkers in drug development globally.[43]

The biomarkers already qualified by EMA and FDA are shown in Tables 3 and 4, respectively. 21 novel methodologies have been qualified by EMA SAWP/CHMP, 8 of which are biomarkers.[44] Moreover, further 10 biomarkers have received a Letter of support from CHMP and may be qualified in the future. Eight biomarkers have already been qualified using FDA CDER BQP, as shown in Table 4, 4 of which are related to kidney disease or injury.[45] Qualified biomarkers belong to safety, diagnostic, prognostic and monitoring categories according to the BEST Resource glossary. In addition, 41 biomarkers have been submitted to FDA, but were not qualified yet, including legacy projects in transition to 507 process.[46]

Qualification of urinary renal safety biomarkers, including kidney injury molecule-1 (KIM-1), clusterin (CLU), albumin, total protein, β2-microglobulin, cystatin C and trefoil factor 3 (TFF3) is the first formal qualification of biomarkers for both EMA and FDA.[32] The request was made by Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group. This qualification required extensive communication between FDA/EMA and PSTC in order to address data gaps, reach scientific consensus and initiate establishment of new biomarker qualification processes in both agencies.[32,47] It was demonstrated that following the qualification of KIM-1 biomarker for the detection of acute drug-induced nephrotoxicity

Table 3. EMA SAWP/CHMP biomarker qualifications to date (as of 30th of March 2020).

NAME OF BIOMARKER	REQUESTOR	DESCRIPTION	QUALIFICATION DATE
Kim-1, albumin, total protein, β2-microglobulin, cystatin C, clusterin and trefoil factor 3	Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	The urinary kidney biomarkers are considered acceptable in the context of nonclinical drug development for the detection of acute drug induced nephrotoxicity, either tubular or glomerular with associated tubular involvement	22 January 2009
Clusterin, renal papillary antigen (RPA-1)	International Life Sciences Institute (ILSI)/Health and Environmental Sciences Institute (HESI)	The urinary kidney biomarkers are considered acceptable in the context of nonclinical drug development for the detection of acute drug induced nephrotoxicity in good laboratory practice (GLP) toxicology studies which are used to support renal safety in clinical trials	21 October 2010
Two cerebral spinal fluid (CSF) related biomarkers: Aβ1-42 and total tau	Bristol-Myers Squibb	The CSF biomarker signature based on a low Aβ1-42 and a high total tau qualifies to identify mild cognitive impairment (MCI) patients who most nearly equate to the prodromal stage of Alzheimer's disease (AD) and who are at risk to evolve into AD-dementia. Collection, handling and measurements of all CSF samples should be performed according to GLP and to the specific international standards for these measurements	14 April 2011
Two CSF biomarkers (Aβ1-42 and t-tau) and PET-amyloid imaging (positive/negative)	Bristol-Myers Squibb	CSF biomarker signature based on a low Aβ1-42 and a high T-tau and/or amyloid related positive/negative PET signal qualify to identify patients with clinical diagnosis of mild to moderate AD who are at increased risk to have an underlying AD neuropathology, for the purposes of enriching a clinical trial population CSF biomarker signature based on a low Aβ1-42 and a high T-tau and amyloid related positive/negative PET signal are not qualified as diagnostic tool or outcome or longitudinal measure	16 February 2012
Total kidney volume (TKV)	Critical Path Institute's Polycystic Kidney Disease Outcome Consortium (PKDOC)	CHMP support baseline total kidney volume, in combination with patient age and eGFR as a prognostic biomarker to identify patients likely to experience a progressive decline in renal function, as characterised by a decline in eGFR or progression to end-stage renal disease	22 October 2015
Ingestible sensor (IS) system for medication adherence	Proteus® Digital Health™ Inc.	The CHMP agrees in considering the use of the Proteus technology (IS) as a qualified method for measuring adherence in clinical trials	17 December 2015
Plasma fibrinogen	The COPD Foundation, COPD Biomarker Qualification Consortium (CBQC)	Plasma Fibrinogen can be a useful enrichment biomarker in the context of a trial where all-cause mortality or hospitalised exacerbation is an outcome of interest, but a number of additional factors outlined by CHMP have to be considered	28 April 2018
Dopamine transporter (DAT) density imaging	Critical Path Global Ltd.'s Critical Path for Parkinson's (CPP) supported by Parkinson's UK and industry/CPP Imaging Biomarker team	Dopamine transporter neuroimaging is qualified to be used as an enrichment biomarker in Parkinson's disease clinical trials targeting patients with early Parkinsonian symptoms	29 April 2018

Table created based on the information provided in EMA qualification of novel methodologies for medicine development webpage.[44]

assessment in rats, citation rate for KIM-1 biomarker increased significantly and the biomarker was widely further investigated both in research and drug development.[48]

Information published by requestors following the successful biomarker qualification allows to identify the most common challenges experienced during the biomarker qualification procedure:

1. *Data sharing and collection*. Carefully planned clinical studies with large numbers of subjects are required to generate evidence for biomarker qualification.[49] Obtaining clinical data from the sponsors of the clinical trials can be extremely challenging; participation might be required from other stakeholders, such as diagnostics manufacturers, which makes it even more difficult to

Table 4. Qualified biomarkers by FDA CDER BQP to date (as of 19th of February 2020).

NAME OF BIOMARKER	REQUESTOR	ABBREVIATED DESCRIPTION	ABBREVIATED COU	QUALIFICATION DATE
Albumin, β2-microglobulin, clusterin, cystatin C, KIM-1, total protein and trefoil factor-3	Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary nephrotoxicity biomarkers as assessed by immunoassays	Safety biomarker to be used with traditional indicators to indicate renal injury in rat	14 April 2008
Clusterin, renal papillary antigen (RPA-1)	International Life Sciences Institute (ILSI)/Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group	Urinary nephrotoxicity biomarkers as assessed by immunoassays	Safety biomarker to be used with traditional indicators to indicate renal injury in rat	22 September 2010
Cardiac troponins T (cTnT) and I (cTnI)	PJ O'Brien, WJ Reagan, MJ York and MC Jacobsen	Serum/plasma cardiotoxicity biomarkers as assessed by immunoassay	Safety biomarker to indicate cardiotoxicity in rats, dogs or monkeys when testing known cardiotoxic drugs and may be used to help estimate non-toxic human dose	23 February 2012
Galactomannan	Mycoses Study Group	Serum/broncho-alveolar lavage fluid biomarker as assessed by immunoassay	Diagnostic biomarker used with other clinical and host factors to identify patients with invasive Aspergillosis	14 November 2015
Fibrinogen	Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)	Plasma biomarker as assessed by immunoassay	Prognostic biomarker used with other characteristics to enrich for COPD exacerbations	14 September 2016
Total kidney volume (TKV)	Polycystic Kidney Disease Outcomes Consortium	TKV as assessed by MRI, CT and US	Prognostic biomarker with patient age and baseline glomerular filtration rate for autosomal dominant polycystic kidney disease	15 September 2016
Clusterin (CLU), cystatin-C (CysC), kidney injury molecule-1 (KIM-1), N-acetyl-beta-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL) and osteopontin (OPN)	Critical Path Institute's Predictive Safety Testing Consortium Nephrotoxicity Working Group (CPATH PSTC-NWG) and Foundation for the National Institutes of Health's Biomarker Consortium Kidney Safety Biomarker Project Team (FNIH BC-KSP) DDTBMQ000014	Urinary nephrotoxicity biomarker panel as assessed by immunoassays	Safety biomarker panel to aid in the detection of kidney tubular injury in phase 1 trials in healthy volunteers	25 July 2018
Plasmodium 18S rRNA/rDNA	University of Washington Department of Laboratory Medicine	*Plasmodium falciparum* 18S rRNA/rDNA (copies/ml) measured in blood samples by a nucleic acid amplification test	Monitoring biomarker informs initiation of treatment with anti-malarial drug following controlled human malaria infection (CHMI) with *P. falciparum* sporozoites in healthy subjects in clinical studies for vaccine and/or drug development	12 October 2018

Table is adapted from FDA list of qualified biomarkers webpage.[45]

collect data across multiple organisations.[50,51] Based on experience with EMA qualification of several Alzheimer's Disease biomarkers, such as Aβ1-42 and total tau, all other issues 'represent minor concerns when compared to the data access issue'.[50]

2. Data standardisation. Data standardisation challenges are caused by differences in sample collection, storage, handling, analytical procedures and data analysis methods across clinical studies and regions.[47,50]
3. Time and resources. Despite decades of research and availability of numerous studies for some biomarkers, qualification of biomarkers is often a resource- and time-intensive.[50,51] Greater evidence of positive benefit-risk assessment is normally required for qualification than for

Table 5. Regulatory framework for investigational medical devices in the US.

INVESTIGATIONAL DEVICE CATEGORY	APPLICABLE REGULATION[1]
Significant risk (SR)	CFR Part 812 – full IDE requirements, application to FDA for IDE approval
Non-significant risk (NSR)	CFR Part 812.2 (b) – abbreviated IDE requirements, approval of the investigation by an institutional review board (IRB) and compliance with informed consent requirements
Excepted	CFR Part 812.2(c) – investigations are exempt from most of the requirements of IDE regulation

Source: FDA guidance for industry and FDA staff '*in vitro* diagnostic (IVD) device studies – frequently asked questions'.
[1]CFR Part 812.119 applies to all investigational devices.

assessment as part of an individual drug regulatory approval. This leads to extended data collection and data review periods. Often extensive communication is required between the agency and the applicant in order to reach consensus. This is illustrated by plasma fibrinogen qualification experience. Plasma fibrinogen is qualified by both EMA and FDA as a prognostic biomarker to enrich for COPD exacerbations.[52,53] Even though plasma fibrinogen is a recognised biomarker with established mechanism of predicting risk in COPD,[54,55] its qualification by FDA took nearly 4.5 years from initial LoI submission in 2011 until issuance of the draft guidance by FDA in 2015.[49] Furthermore, it is reported that the qualification process required significant multidisciplinary human resources and approximately $1.4 million investment.[49]

Therefore, in order to overcome these challenges and gain regulatory endorsement of a biomarker, input from numerous organisations and experts is required. This explains why biomarker qualifications are more often requested by academic groups and consortia, rather than by single commercial drug developers. Collaboration allows sharing the cost and risks associated with biomarker qualification and gives access to more extensive and diverse clinical data. Furthermore, commercial drug developers are often reluctant to invest upfront into biomarkers and make biomarkers data available in public domain.

Companion diagnostics

The term companion diagnostic (CDx) is used for the assay that is utilised to test predictive biomarkers to classify patients and identify those with higher chance to respond to therapy, those who are likely to develop certain side effects and/or to monitor response to treatment. Thus, CDx plays an important role in the development of more efficacious and safe medicines and is a crucial part of precision medicine.[56] Certain disease areas, like oncology and neurodegenerative disorders, require more rapid testing to facilitate monitoring of the disease status and to guide more efficient treatment strategies.[57] Development of CDx leads to an increased number of tumour-agnostic (histology-independent) approvals, creating new clinical and regulatory challenges and causing a paradigm shift, especially in oncology.

FDA defines CDx as 'a medical device, often an *in vitro* device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional to determine whether a particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks'.[58] CDx are also very closely defined in the new EU's *in vitro* diagnostics medical device regulation (IVDR[59]) as 'a device which is essential for the safe and effective use of a corresponding medicinal product to:

- identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- identify, before and/or during treatment, patients likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding medicinal product'.

The regulatory path for the development and approval of CDx differs significantly between FDA and EMA. In the US, the development of IVDs is guided by The Investigational Device Exemptions (IDE) regulation, Title 21, Code of Federal Regulations (21 CFR) Part 812, which sets regulatory requirements for studies of investigational devices.[60] Investigational IVDs may belong to one of the following categories depending on the level of risk that the study presents to subjects: significant risk (SR), non-significant risk (NSR) or excepted devices. Applicable regulations for each category are presented in Table 5.

FDA classifies CDx as Class III Medical Devices in the vast majority of cases, because the risk associated with CDx is similar to the risk associated with the drug that will or will not be administered on the basis of a CDx test.[61] Class III Medical Devices require a premarketing approval (PMA) procedure according to section 515 of the FD&C Act,[62] 34 of 38 currently FDA-approved CDx have undergone the PMA procedure.[63] Two CDx tests (MRDx BCR-ABL Test and FerriScan) have been cleared by 510(k) and 2 further devices cleared by a Humanitarian Device Exemption (HDE) (device intended to be used for a disease that affects less than 8000 individuals in the US per year).[64] FDA issued the Guidance for Industry on *In Vitro* CDx in 2014.[65] This guidance underlines the importance of early strategic decisions on whether CDx is needed,

provides recommendations on co-development of drugs and IVDs and emphasises the importance of collaboration between FDA and CDx developers.

In July 2016 FDA released an extensive draft guidance 'Principles for Co-development of an *In-vitro* Companion Diagnostic Device with a Therapeutic Product',[66] which discusses potential issues developers might face when co-developing IVD CDx and a therapeutic product, for example, (a) different schedules and agency interactions for therapeutic agents and CDx development and corresponding managing issues; (b) determination of the 'goals of the therapeutic product development programme that are dependent on the IVD'; (c) deciding on what data are needed for NDA/BLA; (d) IVD in therapeutic product clinical trial design and assessment of the associated risks. Along with CDx, further definition of 'Complementary Diagnostics' is now being developed, meaning 'Tests that identify a biomarker-defined subset of patients that respond particularly well to a drug and aid risk/benefit assessments for individual patients, but that are not pre-requisites for receiving the drug'. For example, PD-L1 IHC 28-8 pharmDx test may be used to determine PD-L1 expression that may be associated with enhanced survival from Opdivo® (nivolumab).[67]

In the EU, the legal framework for IVDs and thus for CDx is currently changing. Between the in vitro diagnostic medical device European Directive 98/79/EC (IVDD), the Directive currently in place, and the IVDR, the new regulation to come, a transition period is currently active. Accordingly, the IVDR will fully become effective on 26 May 2022.[59] The companion diagnostics definition stated in IVDR is similar to the one provided by FDA. CDx are considered class C. Hence strict quality management, analytical testing and clinical trials are now required for CDx.[68] In the EU, any device clinical trial application, including those needed for biomarker and CDx establishment, is regulated by national agencies and the procedure differs in each country according to the individual laws. The development process for investigational IVDs and CDx is thus required to be agreed by the sponsor, the national competent authority and the chosen notified body on a case-by-case basis. For example, according to the German Act on Medical Devices, some IVDs are eligible for a waiver of the authorisation of a clinical trial.[69]

In future, according to the IVDR, the conformity assessment process for CDx requires consultation between a notified body (currently involved in CDx assessment) and a competent authority, that is, EMA or national competent authority, which are not involved in the CDx assessment in the current system.[68] The dialogue between notified bodies and EMA/national competent authorities will allow to assess the evidence that CDx is beneficial in combination with a particular drug and the evidence of CDx impact on patient outcome (clinical utility).[68] The future CDx consultation procedure allows notified bodies to request a scientific opinion from the EMA or national competent authorities 'on the basis of the draft summary of safety and performance and the draft instructions for use'. The timeframe for this assessment is set to 60 days and can be optionally extended to 120 days.[59] To further support CDx development, EMA issued the 'Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle'.[70] This concept paper acknowledges that legislations covering medicinal products and IVDs are not directly linked in the EU and addresses the interface between predictive biomarker-based assays including CDx, and the development and lifecycle of medicinal products. If the labelling states 'that a medicinal product should be used in conjunction with a predictive biomarker, any commercial assay used for this purpose will be considered a CDx' and thus require CE-mark.[70] It is not clear when the draft guideline based on this concept paper will be released.

In general, CDx development involves numerous scientific, operational and commercial decisions, such as choosing the sample type (eg, snap frozen, formalin-fixed, paraffin-embedded (FFPE) or RNA*later*® preserved tissue samples; fresh samples or archived samples) and the analysis method (eg, immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH), silver in situ hybridisation (SISH) or quantitative polymerase chain reaction (qPCR) for molecular diagnosis). Due to the high development cost, it is crucial to formulate a clear development and commercialisation strategy, which is usually based on 4 key developmental steps: identification of user need, definition of the intended use, creation of an integrated development plan and implementation of the quality management system.[57] Setting a strategy for CDx/therapeutic product co-development requires diligent planning, experience and multidisciplinary work. Synchronising of co-development in different regions is challenging and requires constant monitoring of the regulatory framework and potential differences in regional regulations.

Biomarker Acceptance in Drug Development in the EU and the US

To evaluate the acceptance of biomarkers in the EU and the US, the number of approved drugs with at least 1 biomarker used during development was analysed.

Method: EMA approvals

For analysis of the approvals in the EU, the centralised procedure was considered (EMA). For EMA approvals, the 'Download medicine data' tool of the EMA website was used to access a table of all European public assessment reports (EPARs).[71] EPARs are full scientific assessment reports of medicines authorised at the EU level. EPARs provide public information on human and veterinary medicines, including how it was assessed by EMA, and normally consist of several documents, such as summary for the public, product

information, risk-management plan, public assessment report, summary of positive CHMP opinion, changes since initial authorisation of medicine.

The downloaded table of EPARs was then used to filter approvals using the following criteria:

- Medicines for human use were considered.
- Medicines with the date of marketing authorisation between 2015 and 2019 were considered.
- Withdrawn and refused marketing authorisations were not taken into account.
- Generics were excluded.
- Biosimilars, orphan drugs and medicines authorised under exceptional circumstances and accelerated assessments were included.
- Fixed combinations (including drug-device combinations) were included.

The list of all approved drugs that followed these criteria was created and each EPAR was scanned for 'biomarker' and 'marker' keywords. The context in which these keywords appear in the assessment report was carefully evaluated, that is, 'biomarker' and 'marker' keywords were not taken into account if they are used in the wrong context, such as:

- Colour markers used to test the speed of digestion.
- Recommendation/advice/proposal from the agency.
- Suggestion issued by the agency to use biomarkers to preselect eligible patients for the treatment.
- Monitoring of biomarkers after drug is discontinued.
- Marker genes, radiolabel marker.
- Biomarkers used in the diagnostics of the disease of interest, but not related to the drug under consideration.
- Biomarkers used for testing of blood as starting material for markers of infectious diseases before manufacturing.

Cases when biomarkers were used for preselection of patients eligible/not eligible for a treatment, were included in the statistics.

Method: FDA approvals

Both CDER and CBER approvals were considered and several FDA tools were used, that is, list of FDA-approved biosimilars,[72] CDER statistics,[73] CBER statistics,[74] and Drugs@FDA[75] (to access fixed combinations approvals). The selection of drugs was performed using the following criteria:

- Medicines for human use were considered.
- Medicines with the date of marketing authorisation between 2015 and 2019 were considered.
- Approvals of New Drug Applications (NDAs) and Biologics License Applications (BLAs) were taken into account as opposed to Abbreviated New Drug Applications (ANDAs), Supplemental Approvals and tentative ANDA approvals.
- Biosimilars and orphan drugs were included.
- For NDAs only the following classification codes were considered: Type I New molecular entity, Type II New active ingredient, Type IV News combinations as well as Type 1/4 and 3/4.
- Reagents, diagnostic tests and blood components approved by CBER were not considered.
- Withdrawals were not taken into account.

The list of all approved drugs that followed these criteria was created. For CDER-approved drugs, Drugs@FDA tool was used to access drug approval package, which includes approval letter, printed labelling, product quality review, multi-discipline review, clinical review, statistical review, administrative and correspondence documents as well as other reviews. FDA CBER website was used to access the same documents for CBER-approved drugs. Every product approval package was then scanned for 'biomarker' and 'marker' keywords. The context in which these keywords appear in the assessment report was carefully evaluated using the same criteria as for EMA approvals.

Results

Figure 5 illustrates the number of drugs approved by EMA and FDA with at least 1 biomarker used during development (ie, biomarker acceptance) between 2015 and 2019. It can be clearly seen that more than half of the approvals were supported by biomarker data during at least 1 of the development stages. Remarkably, the proportion of approvals with biomarkers is comparable between EMA and FDA with average of 69% and 59%, respectively for the time period under consideration. There has been a slight increase in acceptance of biomarkers in recent years, even though the growth is not continuous. As of 16th of April 2020, more than 33 000 clinical trials involving biomarkers are registered in ClinicalTrials.gov database including around 4000 Phase 3 and 4 trials. Thus, the biomarkers acceptance is expected to grow rapidly in the nearest future.

Interestingly, as compared to the average EMA biomarker acceptance of 69%, EMA biomarker acceptance among orphan drugs is 87% and among drugs approved via EMA accelerated assessment is 88%. This implies that intrinsically more sophisticated development programmes are more open to innovative approaches, such as utilisation of biomarkers to facilitate determination of the benefit-risk profile, regulatory and development decisions. Biomarker acceptance is also relatively high among biosimilars: at least 1 biomarker was used during the development of 77% of biosimilars approved by EMA between 2015 and 2019. Moreover, approval documentation of more than 85% of monoclonal antibodies approved during the same period includes biomarker-related information.

Biomarker acceptance varies significantly with the pharmacotherapeutic group of the drug. As illustrated in Figure 6,

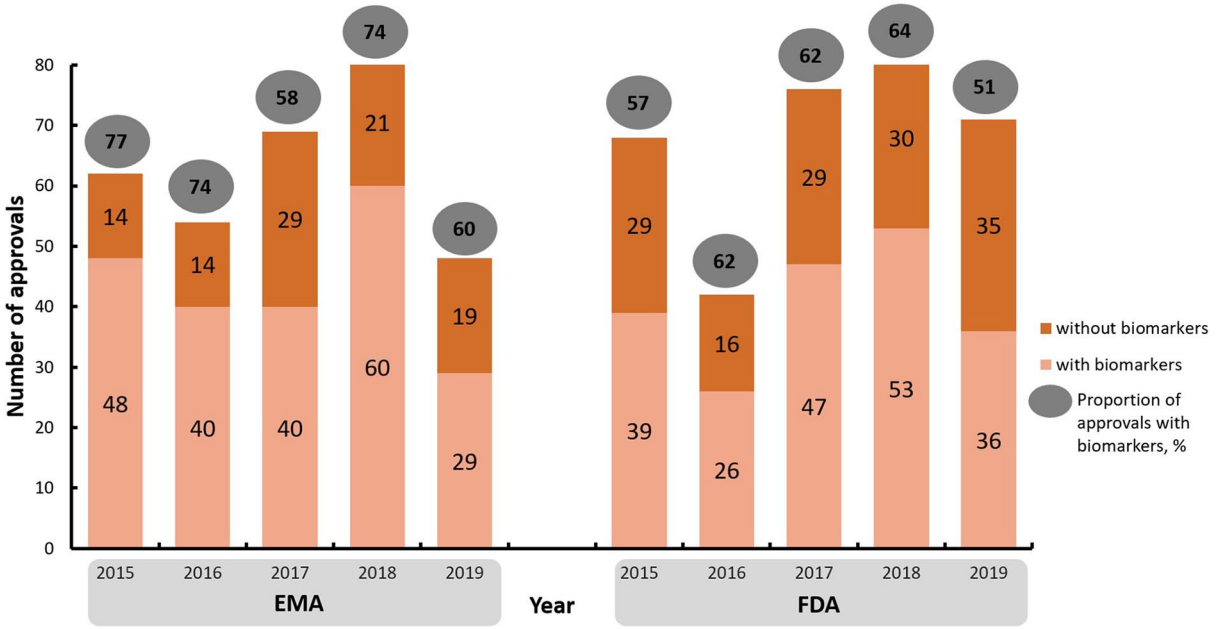

Figure 5. EMA and FDA drug approvals with and without biomarkers between 2015 and 2019.

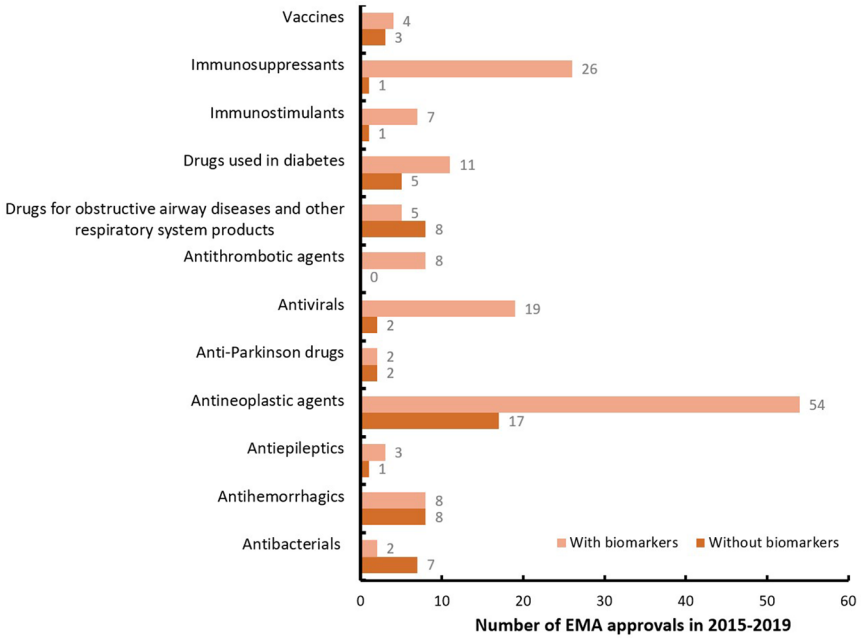

Figure 6. Selected EMA drug approvals with and without biomarkers between 2015 and 2019 by pharmacotherapeutic group.

biomarkers are rarely used during the development of antibacterial and respiratory system therapeutic products. On the other hand, for certain pharmacotherapeutic groups, approvals with biomarkers are more common than without. Examples include immunosuppressants, immunostimulants, drugs used in diabetes, antithrombotic drugs, antineoplastic agents and antivirals. The latter is strongly driven by human immunodeficiency virus (HIV) therapies. Biomarker-guided discovery, development and treatment is common in HIV area, for example, Odefsey (treatment of HIV-1 infection) was approved based on 2 surrogate biomarkers: viral suppression and CD4+ cell counts.[76] Average biomarker acceptance in vaccine development is lower than for therapeutic medicines. Even though utilising of biomarkers in vaccinology may facilitate development of vaccines for diseases with unpredictable epidemiology, such as Zika, Chikungunya, Malaria and Lassa Fever, the utilisation of biomarkers has not yet been used in these developments and regulatory agencies often hesitate to give green light to biomarker-based strategies.[77]

Challenges and Opportunities for Drug Development

Biomarkers are crucial tools for drug discovery, development and approval of new medicines. They can contribute to a

quicker development of safer and more effective medicines and thus add substantial value to a development programme. Over 20% of drugs approved by FDA between 2014 and 2018 and around 42% in 2018 alone belong to 'personalised medicines'.[68,78] In this article, it was shown that in average around 65% of drug approvals by EMA and FDA between 2015 and 2019 have been associated with incorporation of at least 1 biomarker in the development programme and higher percentage of biomarker acceptance is expected in the nearest future. Even though this percentage depends on a number of factors, such as recent scientific development, features of a product class, development of the regulatory landscape, it is clear that biomarkers are now essential part of drug development. This is associated with numerous benefits for patients and opportunities for drug developers, for example:

- Biomarkers are widely used in diagnostics, drug research and development and can be beneficial for each step of this process, ranging from generation of suitable animal model to preselecting suitable patients for clinical trials and differentiation from competitors.
- Biomarkers support selection of the most favourable drug candidates, which significantly reduces discovery costs and probability of failure at later stages.
- Biomarkers can help to understand the mechanism of action better, and thus predict unwanted adverse reactions and Drug-Drug Interactions (DDIs).
- Biomarkers facilitate regulatory and development decisions.
- Biomarkers have the potential to reduce the number of patients in clinical trials as less patients are needed to show clinical benefit and non-inferiority. Patient stratification using suitable biomarkers can reduce the chance of failure related to issues with safety and efficacy.[79]
- Biomarkers may be used as surrogate endpoint for a clinical study. From drugs approved by FDA in March-May 2016, 27% have used at least 1 surrogate marker as a primary endpoint. For example, Odefsey (treatment of HIV-1 infection) was approved based on 2 surrogate markers: viral suppression and CD4+ cell counts.[76]
- Biomarkers facilitate the determination of the benefit-risk profile for a drug under development, thus, allowing a more straightforward decision making by regulatory agencies.
- Biomarkers contribute to the development of medicines by allowing a clearer definition of the target population which has the highest potential of a benefit and the lowest risk to develop unwanted adverse reactions. This has a positive impact on healthcare spending and provides arguments for reimbursement agreements.

Overall, the use of biomarkers in a suitable way has the potential to make development more sustainable, improve quality and safety of a drug, reduce development costs and accelerate approval process significantly. Biomarker development, however, is associated with certain challenges such as:

- Scientific justification behind some biomarkers cannot always be validated, causing future challenges in biomarker validation and qualification. Furthermore, inappropriate interpretation of biomarker measurements and improper connection between a biomarker and a disease have to be avoided.
- Biomarker development may be associated with additional testing requirements or extended clinical trials, hence possible increase in development costs. Furthermore, commercial drug developers are often reluctant to invest upfront into biomarkers and to make biomarkers data available in public domain.
- Biomarkers development and qualification is usually resource- and time-intensive. Greater evidence of positive benefit-risk assessment is normally required for qualification than for assessment as part of an individual drug regulatory approval. This explains why biomarker qualifications by both EMA and FDA are more often requested by academic groups and consortia, rather than by single commercial drug developers.
- Early strategic decisions related to the target population are required for the development of 'personalised medicines' to make sure that smaller subset of eligible patients will still allow to generate sufficient profit.
- As described in this article, regulatory landscape is complex and evolves constantly, requiring constant monitoring.

Continuous development of the biomarker scientific and regulatory landscape is driven by collaborations between industry, private organisations, academic institutions and regulatory agencies. These collaborations have resulted in the increase in biomarkers acceptance in the EU and US in recent years. Biomarkers acceptance is expected to grow further in the nearest future.

Author Contributions

MG: development of the concept of the article, data collection, analysis and interpretation, writing (original draft). AV: critical revision and editing. GD: critical revision of the content, provided crucial feedback and helped to shape the manuscript. DS: substantial contribution to the concept of the work, supervision, critical revision of the content and help in shaping of the manuscript.

ORCID iD

Mariya Gromova https://orcid.org/0000-0002-7602-7598

Supplemental material

Supplemental material for this article is available online.

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