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An Overview and Analysis Regarding the Use of Adjudication Methods in EU and US Drug Approvals

Stephanie Krumholz-Bahner, Dr rer medic[1], Mimmo Garibbo[2], Kenneth A. Getz, MBA[3], and Beat E. Widler, PhD, ETH-Z[4]

Abstract

Background: Several regulatory guidelines recommend that assessments of endpoints supporting drug approval should be verifiable by applicants and the regulatory agencies to minimize the potential for bias. This becomes especially critical when assessments are not based on measurable data but are derived from the interpretation of measurements, when they require the application of complex endpoint assessments, or when a study cannot be blinded. To make such interpretation more robust, a verification of (subjective) assessments by an independent panel of experts is frequently utilized. The objective of this paper was to analyze how often adjudicated methods across efficacy and safety assessments were used in drug approvals in the European Union and United States in 2013 and early 2014. *Methods:* A total of 35 new molecular entities (NMEs) approved by the US Food and Drug Administration (FDA) and 88 European Medicines Agency (EMA) approvals in Europe were included in this analysis. *Results:* An adjudication method was used in phase III development programs in 69% of the NMEs approved in the United States and 41% of EMA approvals. Drugs developed for oncology and endocrinology typically used an independent review committee (IRC) in line with recommendations made in relevant regulatory guidance, whereas nervous systems, antivirals, and vaccines drugs typically did not. Central reading was most frequently used for efficacy endpoints or in a combination of efficacy endpoints and safety measures. Overall, approximately 20% to 30% of the primary endpoints analyzed in the US/EMA documentation were classified as subjective endpoints that were based on clinician-dependent (and subject-dependent) assessments. The remaining 70% to 80% were more robust endpoints that were reviewed by a central committee and/or were based on objective (measurable) endpoints, including laboratory tests. *Conclusion:* While no one size fits all, the need to include an IRC depends on the subjectivity of the primary endpoint, the therapeutic area concerned, the clinical trial design, the need to assess reliability of marginal positive events, or if a critical assessment is required for adverse event accuracy.

Keywords

adjudication, drug approval, EMA, FDA

Introduction

Several regulatory guidelines issued by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend that assessments of endpoints supporting drug approval should be verifiable by applicants and regulatory agencies.[1-8] Assessments that are derived from the interpretation of data such as the determination of tumor size or QT prolongation, complex endpoints, or essential trial parameters that cannot be blinded are usually viewed as being subjective.[4,8] An independent panel of experts, blinded to patients' data, is frequently utilized to make subjective interpretation more robust.[9] Confidence in the data quality is enhanced if the assessments of the independent review committee (IRC) and the investigators' assessments concur.[7] These review panels are known as IRCs, independent radiology review committees (IRaCs), blinded independent IRCs (BICRs), endpoint assessment/adjudication

[1] NDA Regulatory Service Switzerland GmbH, Zurich, Switzerland
[2] Ethical GmbH, Basel, Switzerland
[3] Tufts University, Boston, MA, USA
[4] Widler & Schiemann Ltd, Zug, Switzerland

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Corresponding Author:
Stephanie Krumholz-Bahner, Dr rer medic, NDA Regulatory Service Switzerland GmbH, 8703 Erlenbach, Switzerland.
Email: s.krumholz-bahner@ndareg.com

committees, or clinical events committees.[1,4,5,7,10] For the purpose of this paper, the term *IRC* is used. An IRC assessment can occur in phase II trials and is especially recommended in confirmatory studies.[2,5] Different types of endpoints, such as efficacy endpoints, safety endpoints, laboratory data, pathology assessments, imaging data, autopsy reports, or physical descriptions, can be the subject of an IRC.[4,5]

Due to the vast amount of endpoints utilized as a basis for drug approvals across several therapeutic areas, there is no unique endpoint classification that provides a consistent and fully endorsed overview of subjective to objective endpoints for the purpose of this paper. Therefore, the following definitions were reviewed and used as a basis to establish an endpoint categorization for the analysis described in this paper: surrogate markers of disease (typically laboratory derived, quantitative, and easily standardized), imaging or histological endpoints (measurements of accuracy requiring standardization), and clinician-dependent (and subject-dependent) assessments (based on validated scales and considered subjective).[11]

Rationale for This Analysis

Review of literature showed that an assessment of the use of adjudication methods across therapeutic areas supporting regulatory approvals by the EMA and FDA has not been conducted. As a centralized adjudication process would represent an additional logistic and financial burden, it is of interest to sponsors, academic researchers, and regulators to determine the importance and eventually impact of an independent adjudication process.

Purpose

The objective of this paper was to analyze the use of IRCs across efficacy and safety assessments in European Union (EU) and US drug approvals across different therapeutic areas. A timeframe of approximately 1.5 years was chosen (2013 to early 2014). Endpoints were categorized, as described in the Methods section below. The robustness of endpoints is not discussed in this paper.

Methods

A total of 35 new molecular entities (NMEs) approved by the FDA and 88 EMA approvals (new drugs, orphan drugs, biosimilars, withdrawn submissions, negative opinions) from January 2013 to approximately April 2014 were included in this descriptive analysis. This short timeframe is chosen to gain an initial understanding of the extent and importance of IRCs in the EU and US approval process.

The primary endpoints of the pivotal studies summarized in the European Public Assessment Report (EPAR) and the US Summary Basis of Approval (SBOA) were the sources of this analysis. The approval documents were searched for the following terms: *adjudication/adjudicate*, *central*, *independent*, and *IRC*. The CenterWatch classification in the United States and the EMA classification from the monthly approval reports were used to categorize the approvals into the therapeutic areas.[12,13] An alignment between the US and EU therapeutic areas was made; in that effort, some EU categories with few approvals were combined in the category "others," while an additional therapeutic area for "vaccines" was created.

The primary endpoints were classified according to the following main categories:

- "Hard" and measurable endpoints ("objective"): overall survival; laboratory measures such as hemoglobin A1c, sustained viral response at week 12 (SVR12), forced expiratory volume in 1 second (FEV1), or human immunodeficiency virus (HIV) RNA; and numerical assessments measured by a machine
- Central Reading Committee–reviewed endpoints: adjudicated endpoints such as adjudicated progression-free survival (PFS), major cardiovascular events (MACE), or safety measures
- Endpoints based on observation, interpretation, and scales ("subjective"): endpoints that are based on clinician-dependent (and subject-dependent) assessments or incorporate scales in the assessment, such as depression scales or seizure frequency, any endpoint based on an observation, or requiring interpretation by a physician (eg, magnetic resonance imaging [MRI] scan)
- A combination of the above categories: each product can have employed a combination of the above 3 categories

Study coauthors independently assessed classified endpoint measures (see the Appendix), which were then reviewed and confirmed as final. Products were then divided by therapeutic area, and the classifications was reviewed for consistency.

To understand the type of central review, the IRC-reviewed endpoints were further divided into the following categories:

1. Efficacy endpoint(s)
2. Safety assessments
3. Population assessments (such as inclusion or exclusion criteria)
4. A combination of categories 1 through 3

Results

In total, 35 NMEs in the United States and 88 EMA approvals were analyzed. Most approvals occurred in oncology (23%, United States; 18%, EU), followed by approvals in the metabolic/endocrinology, cardiovascular, and central nervous system (CNS) therapeutic areas (Figures 1 and 2).

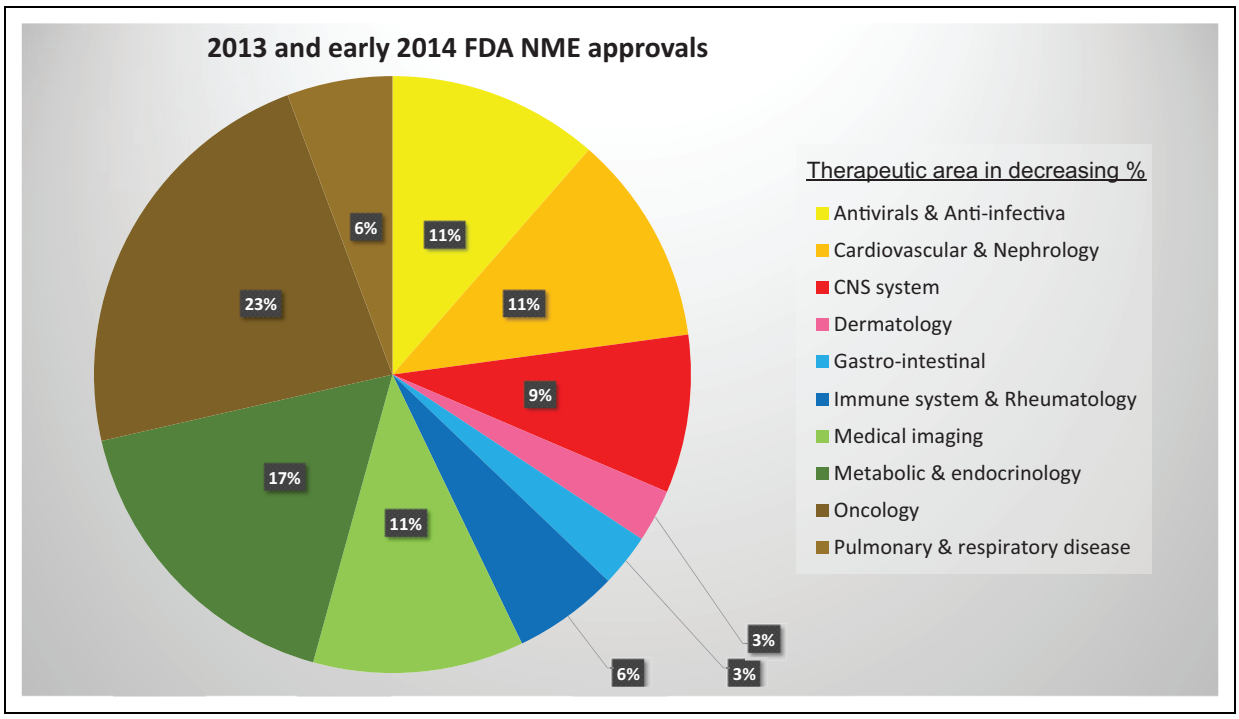

Figure 1. US approvals by therapeutic areas.

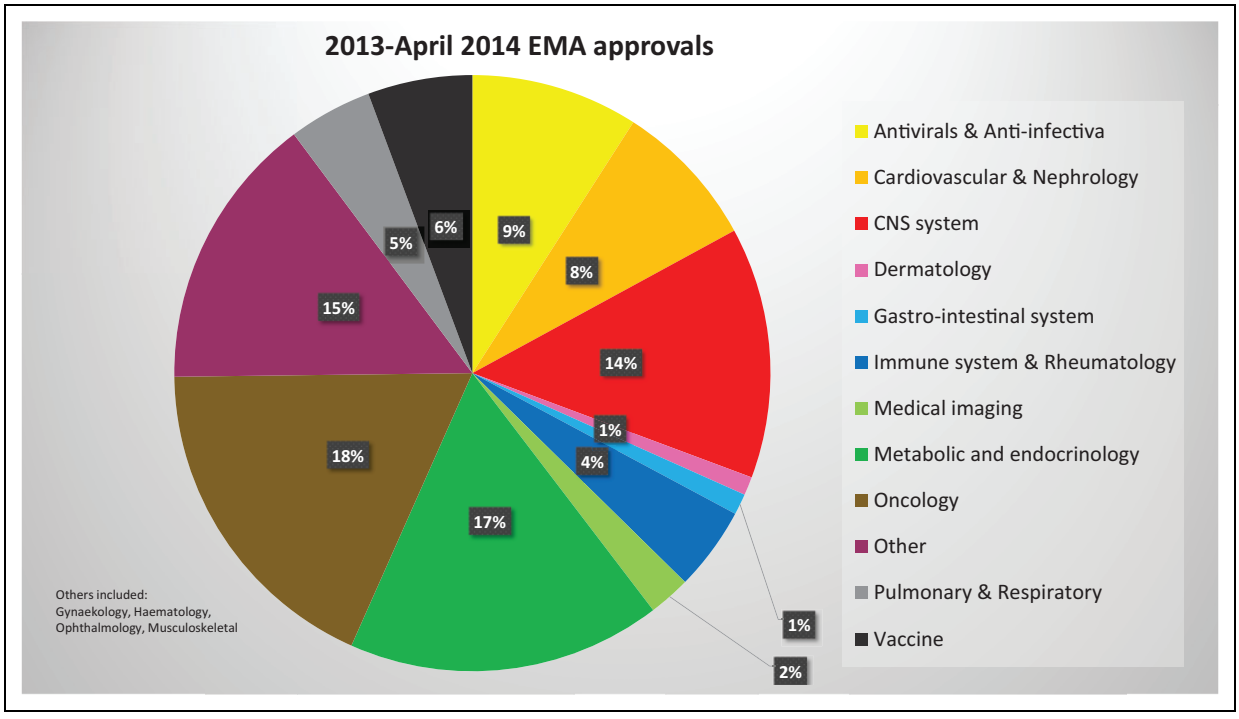

Figure 2. European Union approvals by therapeutic areas.

In both regions, the majority of primary endpoint(s) supporting EU and US approvals were objective measures, IRC-reviewed endpoints, or a combination thereof. Objective and/or IRC-reviewed primary endpoints were typically found in drugs of the oncology, metabolic, vaccine, and antiviral therapeutic area (TA) (Figures 3 and 4). Subjective endpoints were the primary efficacy endpoint (s) in 20% to 30% of drug approvals (United States, 7/35; EU, 26/88).

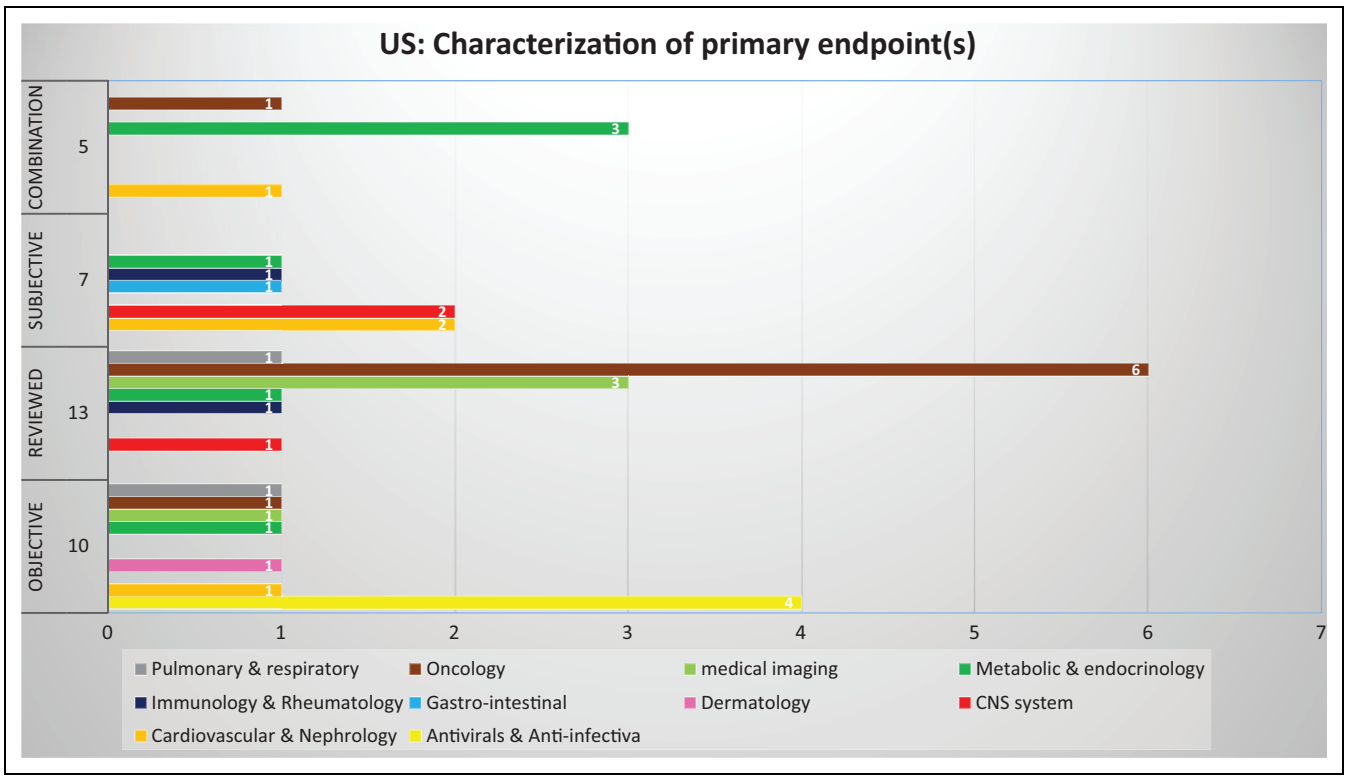

Figure 3. Type of endpoints used in US submissions.

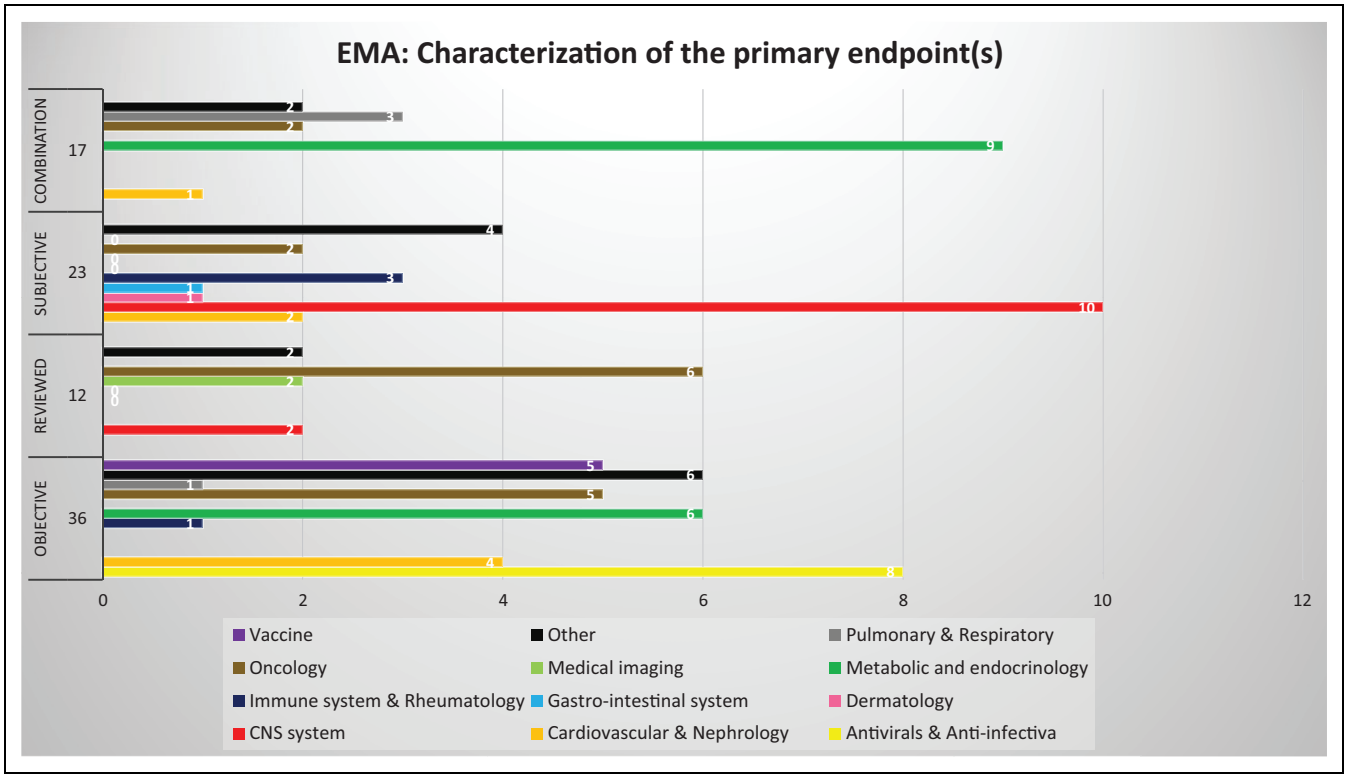

Figure 4. Type of endpoints used in European Union submissions.

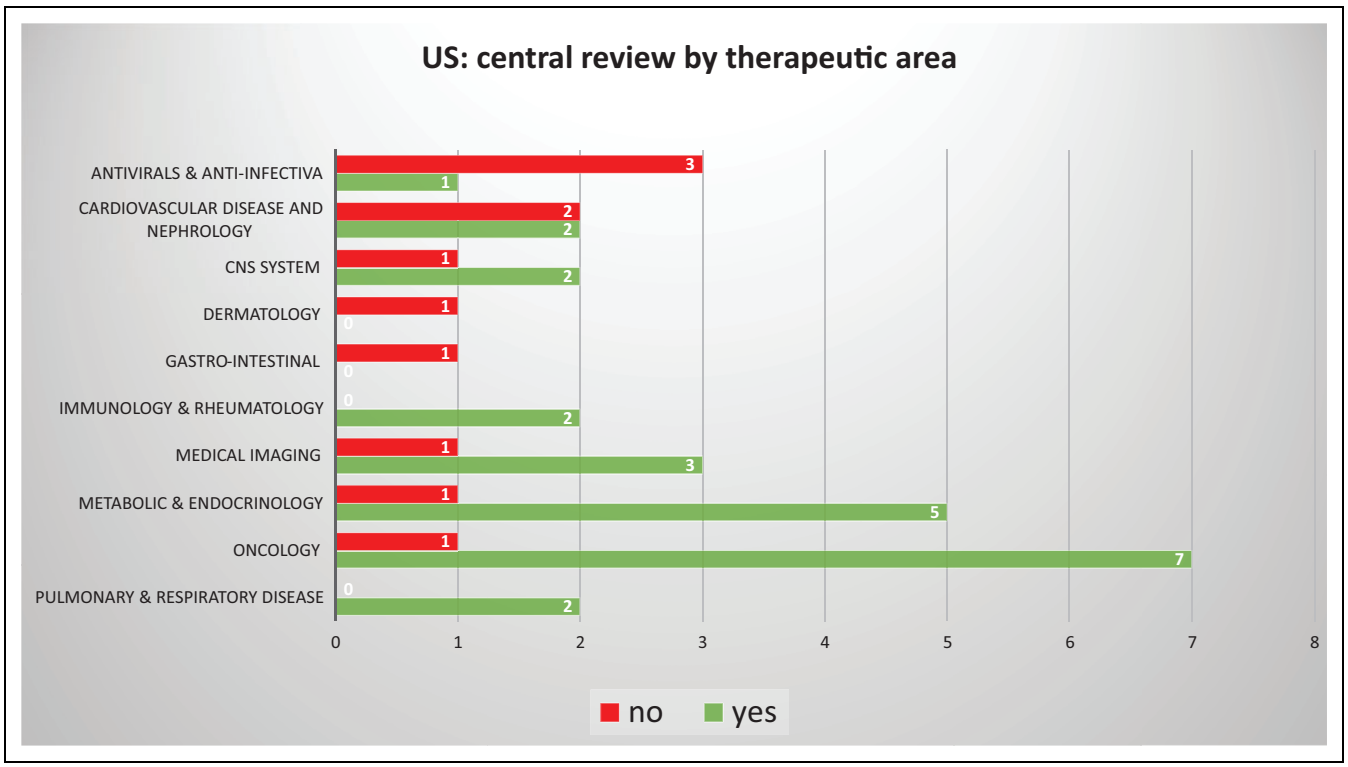

Figure 5. United States: independent review committee use by therapeutic area.

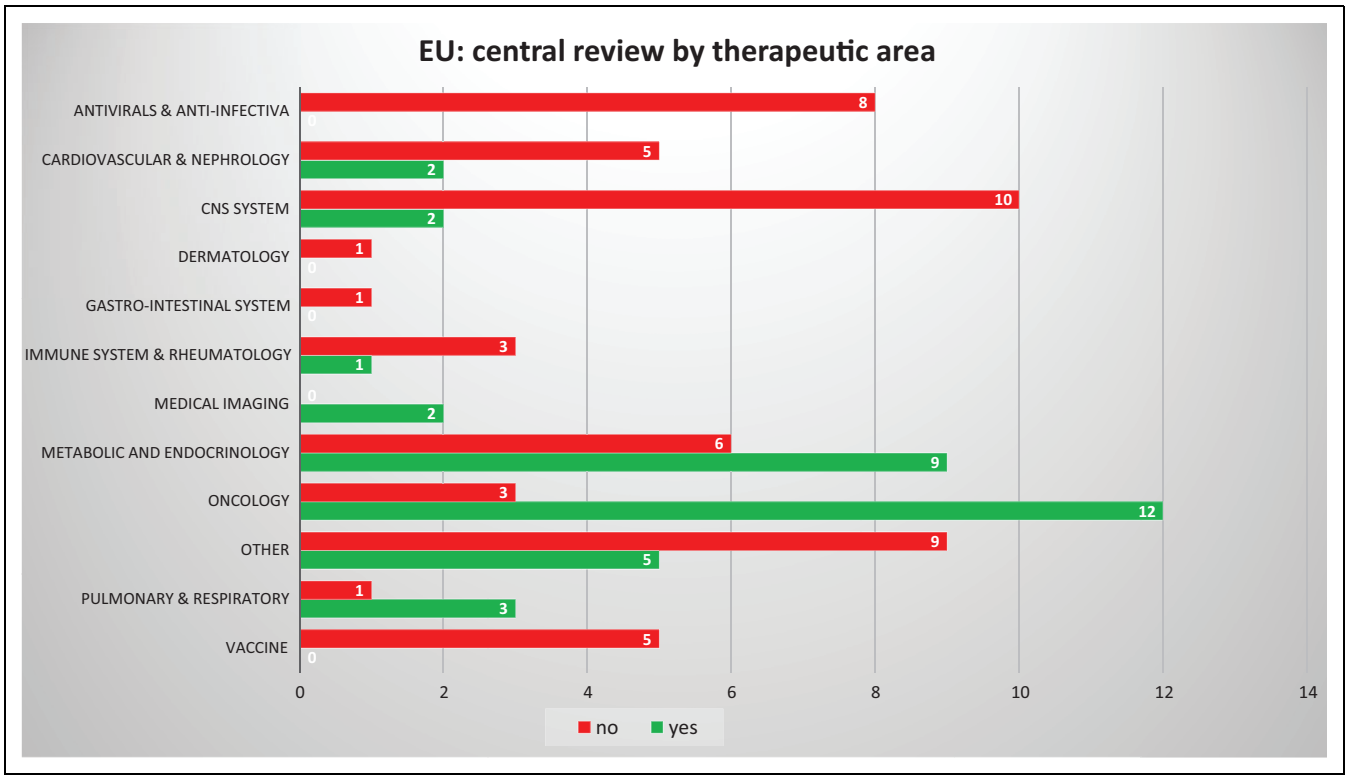

Figure 6. European Union: independent review committee use by therapeutic area.

Table 1. Independent Review Committee Distribution in the United States (US) and European Union (EU).

	Efficacy		Safety		Population		Combination	
	US	EU	US	EU	US	EU	US	EU
Immune system and rheumatology	1		1	1				
Antivirals and anti-infectiva			1					
Oncology	4	7		2		1	3	2
Metabolic and endocrinology	1			1			4	8
Medical imaging	2	2						
Cardiovascular and nephrology	2	1			1	1		
Pulmonary and respiratory disease		2	1				1	1
Central nervous system	1	2					1	
Musculoskeletal system		1						
Other[a]		3		1				

[a]Men's health, hepatic veno-occlusive disease, ophthalmology, and hematology.

A central reading method was used in 69% of the NMEs (24/35) in the US approval packages, compared to 41% in Europe (36/88). While it was common for oncology, metabolic, and endocrinology drugs to include at least one central review, drugs in the antiviral, CNS, and vaccine TAs rarely used an IRC to support the respective drug approval packages (Figures 5 and 6).

In a subsequent analysis, the IRC-identified endpoints were categorized in efficacy, safety, or population assessments or a combination thereof. Across all therapeutic areas, central reading was most frequently used, either for efficacy endpoints only or for a combination of efficacy endpoints and safety assessments. Oncology drugs typically use an IRC for their primary efficacy endpoint, whereas drugs in the endocrinology and metabolic TAs use a combination of efficacy endpoint(s) and safety parameters that are centrally assessed (Table 1).

In conclusion, approximately 20% to 30% of the primary endpoints forming the basis of the US and EMA approval documentation were classified as subjective endpoints. The remaining 70% to 80% were endpoints that were objective, measurable, IRC reviewed, or a combination thereof.

Discussion and Conclusion

The results of the review of the SBOA and EPAR found that 70% to 80% of the primary endpoints were objective, measurable, or reviewed by an IRC. Of these, 70% to 80%, approximately 15% to 34% (EU and United States, respectively) used an adjudication process. Overall, 20% to 30% of the endpoints were classified as subjective endpoints. The 2004 study by Willke et al[14] reviewed the use of patient-reported outcomes (PROs) versus clinician-reported outcomes (CROs) and laboratory test/devices. While the endpoint grouping differs between our analysis and that of Willke et al,[14] those authors found a consistent number in that of the 214 product labels reviewed, 30% were PRO-related endpoints, 50% laboratory/device endpoints, and 62% clinician-reported endpoints.

An adjudication method was used in phase III development programs in 69% of the NMEs approved in the United States, whereas in Europe, 41% of the approvals included an IRC. The difference in the percentage in the EU vs US dossiers may be due to the fact that only NMEs were included for the United States, whereas for Europe, the review also included categories for which use of central adjudication is less likely (eg, biosimilars).

Drugs developed for the oncology and endocrinology TAs typically used an IRC for their endpoint(s), in line with recommendations made in relevant regulatory guidance,[1-3] whereas CNS drugs, antivirals/anti-infective drugs, and vaccines typically did not.[15-20]

Central reading was most frequently used for efficacy endpoints and in combination for efficacy endpoints and safety measures. This is in line with applicable guidance and regulations.[4] Adjudication of the (primary) endpoint occurred (eg, in oncology studies for PFS, objective response rate, first morbidity or mortality events in pulmonary arterial hypertension, or in a multiple sclerosis submission) by confirming patients who experienced a relapse. In a chronic obstructive pulmonary disease (COPD) submission, moderate to severe COPD exacerbations were adjudicated to ensure that these were true exacerbation events.

Adjudication was often utilized for the primary endpoint and certain safety parameters. For type 2 diabetes, MACE-plus was typically adjudicated as a primary endpoint, whereas certain safety parameter such as pancreatitis, fractures, and hepatic and renal events were also independently reviewed. Other adjudications focused on safety parameters only (eg, cause of death such as cardiovascular death vs noncardiovascular death, electrocardiograms, serious/opportunistic infections,

gastrointestinal perforations, interstitial lung disease, adverse events related to malignancies). One company used safety adjudication (fatal deaths, all severe adverse events) in all of their 3 NME filings (TAs: respiratory and oncology).

PFS endpoints for which IRCs are traditionally required in registration studies to eliminate the perceived bias associated with investigator assessment has been the controversy of more recent discussion between industry and agencies.[1,10] A potential for bias seems to remain even if an IRC is in place.[21] A meta-analysis conducted by the Pharmaceutical Research and Manufacturers of America (PhRMA) and FDA showed that some degree of disagreement between investigators and central readers may not affect the conclusions about the efficacy of a study. In an Advisory Committee discussion (July 2012, Oncologic Drugs Advisory Committee [ODAC]), focusing on a general discussion of oncologic products seeking marketing approval in the United States for the treatment of nonhematologic malignancies, several ODAC members felt that the available data support a sample-based IRC.[22] However, no definite conclusions were drawn. Concerns were raised that in small-sized trials, studies with a moderate PFS improvement, and certain difficult-to-assess tumor types, this sample approach would not be adequate.[22] Dodd et al[21] and Amit et al[23] suggest using BICR as an auditing tool to assess the reliability of marginally positive results or to use a sample-based BICR in not adequately blinded studies. In their view, a full BICR would only be required for smaller trials or in situations in which confidence in the local evaluation results needs to be increased.

Real-time adjudication may prevent statistical issues associated with informative censoring. Although barriers in the past have challenged the use of a real-time adjudication process, technology has evolved and systems are now available to support this approach. Additionally, competitive pricing and training of reviewers are enhanced.[24]

Using a cloud portal for an IRC can potentially improve the efficiency and the quality of the assessments while potentially reducing times and costs for completion of a study.

In conclusion, overall, approximately 20% to 30% of the primary endpoints analyzed in the US/EMA documentation were classified as subjective endpoints that are based on clinician-dependent (and subject-dependent) assessments. The remaining 70% to 80% were more robust endpoints that were reviewed by a central committee and/or based on objective (measurable) endpoints, including laboratory tests. While doubts were raised on the need for an adjudication process for PFS-related assessments,[21,25] other therapeutic areas such as assessments on cardiovascular outcomes benefit from an adjudication process of the primary endpoint.[2,26] Therefore, the need to include an IRC is based on several factors: the subjectivity of the primary endpoint, the therapeutic area concerned, the clinical trial design, the need to assess reliability of marginal positive events, or if a critical assessment is required for adverse event accuracy.[21,27,28]

Appendix. Categories of Endpoints

Endpoints Based on Observation, Interpretation, and Scales	Central Reading Committee–Reviewed Endpoints	Hard and Measurable Endpoints
6 MWT[29]	Seizure frequency + review	Laboratory values (eg, FEV1, LDL, serum phosphor, urinary bile value)
HAM-D24 or MADRS[30]	PFS + review[1]	Overall survival[1,7]
ACR 20 without review[31]	MACE + review[2]	Complete cure (antifungal)
MRI scan without independent review[5]	Images + review[5]	Number of oocytes retrieved
Major cytogenetic response (no review)[32]	Nonsurgical resolution of focal VMA + review	Height velocity
Complete loss of heartburn by diary card[33]	Relapsing MS + review	SVR12, HIV1-RNA
Mean pain score[17]	COPD exacerbation + review	Time to sputum culture conversion
Positive and negative syndrome scale[18]		Incidence rate of FV8 inhibitor, hemostasis
SIB, ADCS-ADL[34]		Immunogenicity (vaccine)
OHQ rating scale		Intraocular pressure
		Validated acute serious bacterial infection rate
		"Concordance" with blue dye at the node level

ACR, American College of Rheumatology; ADCS-ADL, Alzheimer Disease Cooperative Study ADL scale; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; HAM-D24, Hamilton Depression Scale; HIV1, human immunodeficiency virus type 1; LDL, low-density lipoprotein; MACE, major cardiovascular events; MADRS, Montgomery-Åsberg Depression Rating Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; OHQ, Orthostatic Hypotension Questionnaire; PFS, progression-free survival; SIB, Severe Impairment Battery; 6 MWT, 6-minute walk test; SVR12, sustained viral response at week 12; VMA, vitreomacular adhesion.

Declaration of Conflicting Interests

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