Outcome Assessments of Primary Endpoints of New Drugs Approved by the FDA (2011-2015)

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BACKGROUND

- Outcome assessments are used to define efficacy endpoints when developing a therapy for a disease or condition.
- Primary outcomes in clinical trials may be assessed by endpoints relating to survival, biomarkers, and clinical outcome assessments (COAs).
- COAs consist of clinician-reported outcomes (ClinROs), observer-reported outcomes (ObsROs), patient-reported outcomes (PROs), and performance outcomes (PerfOs), as defined by the Food and Drug Administration (FDA).
- The extent of use of each type of outcome as primary endpoints in clinical trials has not been well described in the literature.

ClinROs

- A ClinRO is based on a report that comes from a trained health care professional after observation of a patient's health condition. A ClinRO measure involves a clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient (e.g., pain intensity).

ObsROs

- An ObsRO is a measurement based on an observation by someone other than the patient or a health care professional. This may be a parent, spouse, or other nonclinical caregiver who is in a position to regularly observe and report on a specific aspect of the patient's health. An ObsRO measure does not include medical judgment or interpretation. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life. For patients who cannot respond for themselves (e.g., infants or cognitively impaired patients), we encourage observer reports that include only those events or behaviors that can be observed. As an example, observers cannot validly report an infant's pain intensity (a symptom) but can report infant behavior thought to be caused by pain (e.g., crying). For example, in the assessment of a child's functioning in the classroom, the teacher is the most appropriate observer. Examples of ObsROs include a parent report of a child's vomiting episodes or a report of wincing thought to be the result of pain in patients who are unable to report for themselves.

PROs

- A PRO is a measurement based on a report that comes from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. PRO measures can also assess the patient perspective on functioning or activities that may also be observable by others.

PerfOs

- A PerfO is a measurement based on a task(s) performed by a patient according to instructions that is administered by a health care professional. Performance outcomes require patient cooperation and motivation. These include measures of gait speed (e.g., timed 25-foot walk test), memory recall, or other cognitive testing (e.g., digit symbol substitution test).

OBJECTIVE

- To assess the extent of use of endpoints based on survival, biomarkers, ClinROs, ObsROs, PROs, and PerfOs as primary endpoints in confirmatory studies of new drugs approved from 2011 through 2015.

METHODS

- New drugs approved between January 2011 and December 2015 were identified using the Drugs@FDA database.
- Labeling and medical review sections from FDA drug approval packages were reviewed to identify indication and the primary endpoint of confirmatory studies.
- ICD-10 codes were used to classify disease, and the primary endpoints were classified based on the type of outcome assessment.
- Descriptive data were recorded in Microsoft Excel; frequency of measured characteristics was analyzed.

RESULTS

Table 1. Approvals of NMEs (FDA, 2011-2015)

Disease Type	All Products
Cancer	50 (27.5%)
Infectious and parasitic diseases	29 (15.9%)
Endocrine, nutritional, and metabolic diseases	28 (15.4%)
Other disease types	75 (41.2%)
All disease types	**182 (100%)**

NME = new molecular entity.

Table 3. PROs as Primary Endpoints in Approved NMEs (FDA, 2011-2015)

Disease Type	NMEs Approved	PROs as Primary Endpoint
Genitourinary system	5	4 (80.0%)
Musculoskeletal system	3	2 (66.7%)
Digestive system	6	3 (50.0%)
Nervous system	12	6 (50.0%)
Others	156	9 (5.8%)
Total	**182**	**24 (100.0%)**

Table 2. Types of Primary Endpoints of Approved NMEs (FDA, 2011-2015)

	Primary Endpoint, n (%)										
Disease Type	**Survival**	**BM**	**ClinRO**	**PRO**	**PerfO**	**Survival and ClinRO**	**BM and ClinRO**	**BM and PRO**	**ClinRO and PRO**	**ClinRO, PRO, and BM**	**All Products**
Cancer	5 (10.0)	7 (14.0)	25 (50.0)	0 (0.0)	0 (0.0)	13 (26.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	50 (100.0)
Infectious and parasitic diseases	1 (3.4)	14 (48.3)	9 (31.0)	3 (10.3)	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	29 (100.0)
Endocrine, nutritional, and metabolic diseases	1 (3.6)	24 (85.7)	0 (0.0)	0 (0.0)	1 (3.6)	1 (3.6)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	28 (100.0)
Other disease types	0 (0.0)	22 (29.3)	26 (34.7)	15 (20.0)	1 (1.3)	5 (6.7)	1 (1.1)	1 (1.3)	1 (1.3)	3 (4.0)	75 (100.0)
All disease types	**7 (3.8)**	**67 (36.8)**	**60 (33.0)**	**18 (9.9)**	**2 (1.1)**	**19 (10.4)**	**3 (1.6)**	**1 (0.5)**	**2 (1.1)**	**3 (1.6)**	**182 (100)**

BM = biomarker.

- A total of 182 new NMEs were approved by the FDA from 2011 through 2015.
- Table 1 shows that approvals related to cancer; infectious and parasitic diseases; and endocrine, nutritional, and metabolic diseases accounted for 58.8% of the NMEs approved.
- Table 2 shows that the majority of the primary endpoints of NMEs constituted ClinROs and/or biomarkers.
  - ClinROs were the sole primary endpoint for 33.0% of the approvals; and in combination with other types of endpoints for 14.8% of the approvals.
  - Biomarkers were the sole primary endpoints for 36.8% of the approvals; and in combination with other types of endpoints for 3.8% of the approvals.
- PROs were the sole primary endpoint for 9.9% (n = 18) of the approvals; and in combination with other types of endpoints for 3.3% (n = 6) of the approvals.
- Survival was the sole primary endpoint for 3.8% (n = 7) of the approvals; and in combination with other types of endpoints for 10.4% (n = 19) of the approvals.
- PerfO was the primary endpoint for 1.1% (n = 2) of the approvals.
- Primary endpoints related to biomarkers and survival were prominent in endocrine, nutritional, and metabolic diseases (85.7%) and cancers (36.0%).
- Primary endpoints related to PROs (Table 3) were common in diseases related to genitourinary (80.0%), musculoskeletal (66.7%), digestive (50.0%), and nervous (50.0%) systems.
- PROs were primary endpoints in 13.2% (n = 24) of NMEs approved from 2011 through 2015.

DISCUSSION

- To the best of our knowledge, this is the first analysis to quantify the types of endpoints utilized as primary endpoints in pivotal clinical trials.
- This analysis shows the prominence of various types of endpoints as primary endpoints. However, these findings should not be interpreted as a reflection of the importance of individual endpoint types for decision making.
  - For example, although primary endpoints based on ClinROs are key to determine disease progression in cancer, PRO-based endpoints in addition to ClinROs may provide vital information when assessing the risk-benefit profile of new anticancer agents.

CONCLUSIONS

- This analysis shows that majority of the 182 approvals of NMEs during the past 5 years were related to cancer; infectious and parasitic diseases; and endocrine, nutritional, and metabolic diseases.
- The primary endpoints for the vast majority of studies were largely based on ClinROs and biomarkers. This is evidence that demonstration of treatment benefit in the majority of pivotal studies is based on clinician opinion and laboratory findings.
- Survival as a primary endpoint was most prominent in pivotal studies related to cancer. Primary endpoints related to PROs were common in diseases related to genitourinary, musculoskeletal, digestive, and nervous systems.
- The number of approvals based on PROs as primary endpoints was small.
- Selection of clinical trial endpoints is largely influenced by regulatory guidelines. Inclusion of COAs, in particular PROs, in emerging guidance documents may demonstrate a shift in regulatory acceptance.

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