Expert Opinion on Orphan Drugs

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EXPERT OPINION

Recent orphan drugs that are first-in-class

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Although the pipeline for new drugs seemed to be drying up, the number of new 'first-in-class' drugs appeared to be increasing. First-in-class drugs are those which use a new and unique mechanism for treating a disease or medical condition. They are a subset of new molecular entities (NMEs). The FDA reports that in 2012, 39 NMEs were approved. Twenty of these NMEs (~ 50%) were identified by the FDA as first-in-class drugs. Of the 39 NMEs, 13 were designated orphan drugs and 9 of those orphan drugs were first-in-class. In 2013, there were 27 NMEs of which 9 were first-in-class. In 2013, numbers of NMEs are lower than the 2011 or 2012 but are based on fewer applications than in those years. There were 33% of NMEs that were first-in-class and 33% of the NMEs were orphan drugs. The FDA data indicate that creative new products are being developed for rare diseases.

Keywords: best-in-class, FDA, first-in-class, mechanism, me-too, new molecular entity, orphan drug

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At a time when the pipeline for new drugs seemed to dry up because of expiry of the pool of patents for major drugs, there comes an increase of 'first-in-class' drugs. First-in-class is defined by the FDA as '[t]he first drug approved within its respective drug class, pharmacologically innovative representing a new pathway for treating a disease' [1]. Some examples in 2012 were Kalydeco, the first drug to target the genetic mechanism of cystic fibrosis, and Gattex, a polypeptide that improves mucosal cell growth and improves digestion in patients with short bowel syndrome. In 2013, Kynamro was the first antisense oligonucleotide approved since 1998 and targets the gene for homozygous familial hypercholesterolemia.

'First-in-class' indicates that the drug is innovative and has revealed a new path to follow for developing drugs for specific diseases [2]. There will be followers – the 'me-too' drugs – based on using the same idea with enough variation on the theme to be different. The owner of a first-in-class drug usually gets an advantage. The brand name becomes associated with a new class of drugs and when there is no better drug for a disease, it may rule in the absence of competitive alternatives. The me-too drugs are less profitable but not always. If the me-too drug is superior in effectiveness, safety and has fewer side effects, then the me-too drug will be deemed superior or 'best-in-class' and take over. This happened years ago when Bristol-Myers Squibb introduced Captopril, the first-in-class ACE inhibitor (ACEI) for hypertension. Within a few years, Merck introduced Enalapril, a superior ACEI and established it as the 'best-in-class.'

A report from the Center for Drug Evaluation and Research (CDER) at the FDA on 'Impact. Innovation. Predictability. Access.' in January 2013 reported that there was a 63% increase in approved new molecular entities (NMEs) in 2012 over the average of the past 9 years [1,3]. Thirty-nine NMEs were approved by the FDA in 2012. Over half (51%) of these NMEs were identified by the FDA as 'first-in-class' drugs. These data point to the emphasis on developing very innovative new drugs. In 2012, 13 of the 39 NMEs were orphan drugs – drugs approved to treat patients

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Table 1. Orphan drugs from 2012 that are first-in-class.

Drug name (active component)	Indication(s)	Mechanism	FDA designation
Bosulif (bosutinib)	A TKI, which blocks Src and Brc-Abl kinases in CML [5]	It is indicated for adult patients with chronic, accelerated or blast-phase Philadelphia chromosome-positive CML (Ph + CML) with resistance or intolerance to traditional therapies [6]	4 September 2012
Cometriq (cabozantinib)	For metastasized thyroid cancer [7]	A kinase inhibitor which targets multiple receptor tyrosine kinases implicated in tumor growth and angiogenesis, pathologic bone remodeling and metastatic progression of cancer [8]	29 November 2012
Elelyso (taliglucerase alfa)	An enzyme replacement therapy for type 1 Gaucher's disease that must be administered every other week [9]	It effectively clears Gaucher cells from marrow (indicated by increase in marrow:fat ratio); however, Elelyso's effect on bone pain is yet to be determined [10]	1 May 2012
Gattex (teduglutide)	For treatment of short bowel syndrome in adults [11]	A glucagon-like peptide 2 analog which promotes mucosal growth [11]	21 December 2012
Iclusig (ponatinib)	For CML [12]	A protein inhibitor that targets TKI-resistant CML that have the *T315I* mutation, which makes these cells resistant to currently approved TKIs. It has been designated for the treatment of chronic, accelerated and blast phases of CML as well as Philadelphia chromosome-positive ALL (Ph + ALL) [12]	14 December 2012
Juxtapid (lomitapide)	For homozygous familial hypercholesterolemia [13]	Designed to lower low-density lipoprotein. An inhibitor that blocks the function of 'microsomal triglyceride-transfer protein' that is present in the liver and gut. This protein functions in the assembly of cholesterol and triglyceride into larger lipoproteins [13,14]	21 December 2012
Kalydeco (ivacaftor)	For cystic fibrosis [15]	This increases the activity of defective protein channels in cystic fibrosis patients with the *G551D* mutation thereby alleviating symptoms [16]. It is a targeted therapy designed to treat patients with a specific genetic makeup (personalized medicine) [15]	31 January 2012
Kyprolis (carfilzomib)	For multiple myelomas [17]	A proteasome inhibitor which blocks cellular breakdown of proteins that are no longer needed. It is expected to reduce the number of multiple myeloma cells [17,18]	20 July 2012
Raxibacumab	For treatment of inhalation of anthrax [19]	A mAb that neutralizes toxins produced by Bacillus anthracis. It has been designated for the treatment of inhalational anthrax or as a preventative measure where no satisfactory alternative therapy exists [19]	14 December 2012
Signifor (pasireotide diaspartate)	For Cushing's disease [20]	This drug functions as a somatostatin analog. It binds receptors for somatostatin which inhibits the release of ACTH [20,21]	14 December 2012
Synribo (omacetaxine mepesuccinate)	For adults with chronic myelogenous leukemia [22]	Derived from harringtonine, a substance from a Chinese evergreen, omacetaxine, the active substance of Synribo, functions as an inhibitor of protein synthesis of the Brc-Abl tyrosine kinase enzyme [23]. Because it does not rely on binding the tyrosine kinase receptor, it is not affected by the *T315I* mutation [23]	26 October 2012
Voraxaze (glucarpidase)	For treatment of patients with toxic levels of methotrexate due to kidney failure [24]	As a copy of the naturally occurring enzyme carboxypeptidase G2, Voraxaze (glucarpidase) degrades methotrexate into nontoxic molecules for excretion by the body [25]	17 January 2012

ACTH: Adrenocorticotropic hormone; ALL: Acute lymphoblastic leukemia; CML: Chronic myelogenous leukemia; TKI: Tyrosine-kinase inhibitor.

Table 2. Orphan drugs from 2013 that are first-in-class.

Drug name (active component)	Indication(s)	Mechanism	FDA designation
Adempas (riociguat)	To treat pulmonary arterial hypertension or persistent/recurrent chronic thromboembolic pulmonary hypertension [3]	It is a stimulator of sGC, an enzyme in the cardiopulmonary system that responds to nitric oxide and catalyzes the synthesis of cGMP [26]. The sensitized sGC improves patients' exercise capacity and cardiopulmonary hemodynamics [26]	8 October 2013
Gazyva (obinutuzumab)	To treat chronic lymphocytic leukemia [3]	It is a mAb against CD20 that induces apoptosis in B lymphocytes [27]	1 November 2013
Gilotrif (afatinib)	To treat late-stage (metastatic) non-small-cell lung cancer [3]	Gilotrif is a TKI that blocks proteins that promote the development of cancerous cells and is intended for use in patients whose tumors express the EGFR exon 19 deletions or exon 21 L858R substitutions [28,29]	12 July 2013
Imbruvica (ibrutinib)	To treat mantle cell lymphoma [3]	It works by blocking the function of Bruton's tyrosine kinase, an enzyme important for the growth and survival of B cells, as well as their migration to the organs where these cells normally divide [30]	13 November 2013
Kynamro (mipomersen sodium)	To treat homozygous familial hypercholesterolemia [3]	Kynamro is an antisense oligonucleotide designed to block production of apolipoprotein B, the main component of low-density lipoprotein, intermediate density lipoprotein and very low-density lipoprotein cholesterol [31]	13 January 2013
Mekinist (trametinib)	To treat melanoma [3]	A MEK inhibitor specific to melanoma cells expressing *BRAF V600E* or *V600K* mutations that inhibits growth factor-mediated cell signaling and cellular proliferation [32,33]	29 May 2013

sGC: Soluble guanylate cyclase; TKI: Tyrosine-kinase inhibitor.

who have a disease that has a prevalence of < 200,000 in the USA. Of the 13 orphan drugs, 9 were first-in-class. The drugs had received orphan drug designation prior to receiving approval for sale to patients (**Table 1**).

Recently the FDA CDER published its list of 2013 approved drugs [3]. There were 27 approved NMEs in the report (**Table 2**). A total projected number of 36 NME approvals for the calendar year 2013 are expected when all applications currently filed are included. However, the 27 NMEs is a drop in number from the 39 NMEs approved in 2012. The hope that after a record year in 2012 of approvals of NMEs over the previous 9 years would be continued in 2013 was not sustained.

In 2012, 13 of the 39 approved drugs were orphan drugs (Bosulif, Cometriq, Elelyso, Gattex, Iclusig, Juxtapid, Kalydeco, Kyprolis, raxibacumab, Signifor, Sirturo, Synribo, Voraxaze) and 9 of these are first-in-class drugs (Cometriq, Gattex, Juxtapid, Kalydeco, raxibacumab, Signifor, Sirturo, Synribo, Voraxaze) [1,3]. In the data for 2013, of the 27 approved drugs, 9 are orphan drugs (Adempas, Gazyva, Gilotrif, Imbruvica, Kynamro, Mekinist, Opsumit, Pomalyst, Tafinlar) and 4 of these are first-in-class drugs (Adempas, Imbruvica, Kynamro, Mekinist) [1,3].

Taken together these NMEs cover a variety of mechanisms to treat human disease ranging from the pioneering therapies of 2013's Kynamro, an antisense oligonucleotide, and Gattex, a polypeptide therapy, to tyrosine-kinase inhibitors (Bosulif, Cometriq, Iclusig, Gilotrif, Imbruvica). Included within the list are new therapies for those patients where therapy options are limited (Adempas, Elelyso, Gazyva, Juxtapid, Imbruvica, Opsumit, Pomalyst, raxibacumab, Signifor, Voraxaze) or where standard therapies have ceased working due to the disease acquiring resistance (Bosulif, Cometriq, Iclusig, Kyprolis, Synribo). These drugs achieve their effect through enzyme replacement, inhibition of alternative steps in pathogenesis, functioning as analog or stimulating compensatory pathways. Orphan drugs such as Gilotrif, Kalydeco, Mekinist and Tafinlar are aimed at personalized or mutation-specific therapies.

The FDA has shown flexibility in advancing these novel drugs [4]. About 41% of the 39 NME drugs, in 2012, were approved with 'Priority Reviews', that is, 16 drugs were deemed so promising for medical therapy that they were reviewed in 6 months compared to the standard 10 months. In 2013, 10 of the 27 were given priority reviews and 4 of them were orphan drugs (Adempas, Gazyva, Gilotrif, Imbruvica). In 2012, 36% (14) of the NMEs were given 'fast track reviews' in which the FDA works closely with the developers of the drugs to review parts of the application before submission of the full application. Of the 39 NMEs, 4 (10%) received 'accelerated approval', a new program for making a drug available for life-threatening cases based on a surrogate end point or marker that predicts clinical benefit. In 2013, there were 10 fast track reviews, of which 5 were orphan drugs, and 10 priority reviews, of which 4 were orphan drugs.

These new regulatory measures indicated that first-in-class drugs meet a high level of promise for unmet needs. Although the title helps expedite development and approval, safety and effectiveness of the drugs are not compromised. To ensure that the benefits of Gattex outweigh the potential risks, the drug is being approved with a 'risk evaluation and mitigation strategy', consisting of a communication plan and training for prescribers requiring a post-market study of short bowel syndrome patients treated with the drug in a routine clinical setting.

We conclude that there is movement toward first-in-class drugs, indicating more innovation in drug discovery. A majority of first-in-class drugs are orphan drugs. In 2013, nine such drugs were approved by the FDA and four of them were orphan drugs (Adempas, Imbruvica, Kynamro, Mekinist). The challenges of the rare disease market may require more innovation to treat complex rare diseases for which no drug is available. Ultimately, such innovation could benefit non-orphan diseases too by producing new ideas for developing drugs.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents, received or pending, or royalties.

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