Rare Disease Landscape: Will the Blockbuster Model Be Replaced?

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The impact of rare diseases

Whither the pharmaceutical blockbuster? The pharma industry entered the 21st century buoyed by a series of mega hits that had carried it through the nineties on a wave of promise. But soon, the perceived wisdom became that the age of the mega-selling, mass-marketed drug was over; no more Prozacs, Lipitors or Viagras. With the ‘blockbuster bubble’ seemingly burst and patent protection giving way to huge rises in generic competition, the pharma industry would now seek to sustain itself by focusing on niche markets; high value drugs for rare diseases of low prevalence, but for which a rich return on investment could be reaped. But is this picture correct? If so, what are the rare diseases currently commanding the most attention, and which pharma companies are occupying these spaces? In this analysis we take a look at the landscape for rare diseases and report on the density of development by phase, developing company and by disease using current Citeline data.

In the EU a rare disease is defined as one with a prevalence of 1 in 2,000 people, and in the US, as affecting fewer than 200,000 people (equivalent to 1 in 1,600 people as of 2013 population figures). In this report, we will focus on rare diseases defined as per above. By these definitions, there are between 6,000 and 8,000 recognised rare diseases, most of them arising from genetic origin and being chronic or life-threatening. Despite the term, rare diseases still cumulatively affect vast numbers of people, with current data indicating 30 million sufferers in the EU alone, with a further 30 million affected in the US.

The landscape for rare diseases

As of November 2013, Citeline data reports that there are 2,907 drugs in active development for at least one rare disease. In terms of disease status (the highest status reached for a particular disease), the landscape shows relatively high activity at preclinical and early-to-mid clinical trials, with less active development taking place at Phase III (Figure 1). This very much mimics the pattern seen across all diseases. Pharmaprojects covers over 30 years of drug development, and to date there have been just 657 launches for drugs used to treat rare diseases, representing 23% of the total active drugs in development for rare disorders.

So at first glance it would appear that the pharmaceutical industry is taking up the mantle and that a drive towards drug development for rare diseases is certainly well underway. As of November 2013, Citeline’s Pharmaprojects noted active drug development in 364 rare diseases. Among these diseases, a total of 223 had nine or fewer drugs in development. Fifty-five diseases, or 15% of all rare disorders — with 20 or more drugs in active development — draw the most research and development focus.
Therapeutic focus for rare disease development

A look across all the drugs in development for rare diseases as a function of therapeutic areas (Figure 2) reveals that the top five areas are Infectious Diseases, Neurological Disorders, Alimentary/Metabolic Diseases, Cancers, and Blood and Clotting disorders.

Figure 1. Rare Disease Drug Development Phases*

*Since drugs may be in development for >1 rare disease, a drug may be represented at multiple phases with the data.
Source: Citeline’s Pharmaprojects®, data accessed November 2013

Figure 2. Rare Disease Drugs in Development by Therapeutic Area

Source: Citeline’s Pharmaprojects®, data accessed November 2013
Within Infectious Diseases, the top five rare diseases are tuberculosis, malaria, tetanus, pertussis and Haemophilus influenza. Interestingly, all five are only rare by our Western definition; they are unfortunately all too common still in the developing world. The top five rare diseases in the Neurological area are amyotrophic lateral sclerosis, Huntington’s disease, Duchenne’s muscular dystrophy, and uveitis. For Alimentary/Metabolic, Gaucher’s disease, acromegaly, Pompe’s disease, Cushing’s disease and primary biliary cirrhosis are the conditions with the most active drug development. For the cancer area, pancreatic, ovarian, liver, myeloma and renal have the largest numbers of drugs in active development. Haemophilia A, Haemophilia B, idiopathic thrombocytopenic purpura, sickle cell anemia and Waldenstron’s hypergamma-globulinaemia, are the Blood and clotting conditions with the largest numbers of active drugs.

Looking at the number of active drugs in development by therapeutic area, cancer leads the way, with nearly two times as many drugs compared to the second-place infectious diseases, and nearly seven times as many as there are for blood and clotting disorders.

**Infectious diseases**

By far the greatest number of rare diseases being pursued is within the infectious diseases arena, with tuberculosis, malaria and tetanus having the most drugs in development, respectively. Tuberculosis is top of the list, with 88 drugs in active development. (While many of the diseases are rare in Europe and North America, they are quite prevalent in other regions). There are already number of launched drugs including carbocysteine, an adenosine antagonist that is also launched for other infectious diseases including otitis media, bronchitis, bronchiectasis and respiratory tract infections. However, widespread drug resistant TB means that there is still an urgent need for new antimycobacterial agents, and new TB vaccines. In the latter category, Cadila’s Immuvac is a mycobacterium vaccine which has completed several Phase III trials in tuberculosis patients as an adjunct to first-line therapy. Also of note is Sequella’s SQ-109, an orally-active ethambutol analogue targeting the MmpL3 membrane transporter of trehalose monomycolate. It is currently in a pivotal Phase II/III trial in Russia to assess efficacy in patients with multi-drug resistant TB.

Among upcoming therapies for malaria (78 drugs in development) is artesunate, an artemisinin derivative originally developed by the Walter Reed Army Institute of Research and the US Army Medical Materiel Development Activity, and now licensed to Sigma Tau for development and manufacturing. Following Phase II trials conducted by Sigma Tau, it is awaiting approval in the US for severe and complicated Plasmodium falciparum malaria.

There are 77 drugs in development for tetanus prophylaxis including Shantha Biotechnics’ Shan5, a pentavalent vaccine containing both tetanus and diphtheria toxoids, and under development for several other infectious diseases including diphtheria, Haemophilus influenzae, hepatitis B and pertussis. It is in a Phase III non-inferiority trial in India in 1100 children and infants. Also showing promise for tetanus prophylaxis is GC-1107, a triple toxoid vaccine under development by Green Cross. Having completed Phase II trials for prophylaxis of tetanus and diphtheria, the vaccine is currently in a randomized, double-blind Phase II/III trial in 171 healthy children, to assess immunogenicity and safety.
Figure 3. Rare Diseases with 5 or More Drugs in Development

Infection, tuberculosis
Infection, malaria
Infection, tetanus prophylaxis
Infection, pertussis prophylaxis
Infection, Haemophilus influenzae prophylaxis
Infection, malaria prophylaxis
Infection, polio prophylaxis
Infection, meningococcal prophylaxis
Otitis media
Infection, leishmaniasis
Infection, Clostridium difficile
Infection, tuberculosis prophylaxis
Infection, anthrax prophylaxis
Infection, anthrax
Infection, dengue virus prophylaxis
Infection, rabies prophylaxis
Infection, onychomycosis
Infection, dengue virus
Infection, Haemophilus influenzae
Infection, trypanosomiasis, American
Infection, typhoid prophylaxis
Infection, Clostridium difficile prophylaxis
Infection, Kawasaki disease
Infection, rubella prophylaxis
Infection, Japanese encephalitis virus prophylaxis
Infection, smallpox virus prophylaxis
Infection, Aspergillus
Infection, trypanosomiasis, African
Infection, helminth, unspecified
Infection, onchocerciasis
Infection, Ebola virus
Infection, mumps prophylaxis
Infection, Mycobacterium avium complex
Infection, schistosomiasis
Infection, smallpox virus
Infection, Ebola virus prophylaxis
Infection, Marburg virus prophylaxis
Infection, rabies
Infection, Burkholderia pseudomallei
Infection, filariasis
Infection, Chikungunya virus prophylaxis
Infection, Marburg virus

Source: Citeline’s Pharmaprojects®, data accessed November 2013
The oncology landscape for rare diseases

Among the drugs in development for rare cancers, the most active development is in pancreatic and ovarian cancer, with 290 and 279 drugs in active development, respectively. Perhaps no surprise here is the presence of Roche’s bevacizumab. The blockbuster anti-VEGF MAb, long on the market for non-rare cancers such as colorectal and non-small cell lung cancer, has also been launched in the EU countries as Avastin since 2011 for ovarian cancer, with a US filing expected to follow in 2013. Bevacizumab is in a European Phase III trial (AURELIA) in 361 patients with ovarian, fallopian tube or peritoneal cancer to assess its efficacy and safety in combination with chemotherapy. A further Phase III trial in patients with epithelial ovarian cancer is also ongoing. Avastin was also in development for pancreatic cancer; however, Phase III trials investigating its efficacy in combination with standard chemotherapy agents did not meet the primary endpoints in terms of overall- and progression-free survival.

Amgen’s trebananib is also showing promise in rare cancers. The drug targets TIE-2 tyrosine kinase, and is being developed in partnership with Takeda and Dyax. Trebananib is currently in a Phase III trial (TRINOVA-2) in 380 women with ovarian, peritoneal or fallopian tube cancer to assess efficacy in combination with liposomal doxorubicin. Completion is expected in 2014. The drug is also in Phase I trials for pancreatic cancer, as well as for gastrointestinal stromal tumours (GIST). Trebananib represents a good example of a targeted therapy that has shown potential across several rare diseases.

Another kinase inhibitor in the pipeline for rare cancers is Bayer’s regorafenib. Acting on a broad spectrum of kinase targets, the drug is already launched for GIST in Canada, Japan and the US, and is one of only three drugs to gain approval thus far for this rare cancer. It is currently in a Phase III trial (RESORCE) in patients with hepatocellular carcinoma, with completion expected in 2015. Regorafenib is also in a Phase II trial for advanced renal cell cancer, where preliminary results have demonstrated a disease control rate of 81%. With activity against several rare cancers as well as already having achieved approval, regorafenib is another good prospect in the landscape for rare cancer indications.

Among drugs for some of the lesser pursued rare cancers, Takeda is developing alisertib, an orally-available aurora kinase inhibitor. The drug is being investigated in a Phase II trial in neuroblastoma, a rare childhood cancer with an incidence of just 1 in 200,000 in the US. To date, there are only 2 drugs available for the treatment of neuroblastoma, these being Novartis’ teniposide and Baxter’s trofosfamide.

Also being investigated for neuroblastoma is erismodegib, under development by Novartis. The drug targets the hedgehog pathway. It is currently in a Phase II trial for several cancer indications, including neuroblastoma and other rare childhood cancers including rhabdomyosarcoma and osteosarcoma. It was also in development for Gorlin syndrome, but development was terminated during Phase III trials. If development continues as planned, erismodegib is shaping up to be a major player in the treatment of rare cancers, particularly those in children.
Figure 4. Rare Cancer Diseases with 10 or More Active Drugs

Source: Citeline's Pharmaprojects®, data accessed November 2013
Major players in rare cancers

In ovarian cancer, Roche is leading the way in terms of numbers of drugs, with 11 drugs in active development. This includes one launched drug, bevacizumab (see above), and pertuzumab which is currently in Phase II for this disease. A large proportion of Roche’s rare disease pipeline for ovarian cancer is currently in Phase I trials including PI3K/mTOR kinase inhibitor apitolisib, anti-IG1 antibody vesencumab, and the immunotoxin DMUC-5754A. Abbott is close behind with 6 drugs in active development for ovarian cancer. Of these, volociximab and veliparib are the most advanced candidates. Volociximab, a chimeric monoclonal antibody targeting alpha5-ß1 integrin has completed a Phase II trial in combination with liposomal doxorubicin, in patients with advanced epithelial ovarian or peritoneal cancer. Results showed partial responses and a median progression-free survival time of 193-221 days. Veliparib is an orally-available PARP inhibitor under development by AbbVie, following its separation from Abbott. It has completed a Phase II trial in patients with ovarian, fallopian tube and peritoneal cancers.

Figure 5. Top 15 Originator Companies Developing Drugs for Ovarian Cancer

Source: Citeline’s Pharmaprojects®, data accessed November 2013
In the landscape for pancreatic cancer Pfizer leads with a total of 10 active drugs; 6 of which are in Phase I and three in Phase II. Roche is in second-place, with 8 drugs currently in active development (Figure 6). Its most advanced candidate is the oral hedgehog pathway inhibitor, vismodegib. The drug is in a Phase II trial in patients with metastatic pancreatic cancer in combination with gemcitabine, with completion expected in 2013. Roche currently has 5 candidates in Phase I trials for pancreatic cancer. These include vesencumab, an anti-IG1 antibody that has completed a Phase I in advanced or metastatic solid tumours including ovarian cancer. Also in the Phase I pipeline is DMOT-4039A, for which the mechanism of action is as yet undisclosed. The drug is in a Phase I trial in both pancreatic and ovarian cancer, with completion expected in 2015.

Figure 6. Top 15 Originator Companies Developing Drugs for Pancreatic Cancer

Source: Citeline’s Pharmaprojects®, data accessed November 2013
Recurring candidates

Amongst the drug landscape for rare diseases, there are some drugs that stand out in that they are under investigation for multiple rare diseases. Not surprisingly, the greatest activity involves oncology drugs, with many companies focusing on a number of rare cancer indications. The top drugs being tested for efficacy in rare diseases include: tivantinib, rigosertib, carboazantinib, everolimus and bevacizumab. ArQule’s MET tyrosine kinase inhibitor tivantinib is in development for 13 rare cancers; biliary, esophageal, non-small cell lung cancer, Merkel cell carcinoma, mesothelioma, ovarian, liposarcoma, pancreatic, renal, soft tissue sarcoma, testicular, liver and oral cancer. The drug is currently in a pivotal Phase III trial in patients with inoperable hepatocellular carcinoma. Filings in several territories are expected in 2015. The drug also has EU orphan drug status for soft tissue sarcoma.

Another drug showing promise in rare diseases is Oncanova’s rigosertib. This small molecule polo-like kinase inhibitor is in development for 11 forms of rare cancer, the most advanced indications being chronic myelomonocytic leukaemia, pancreatic cancer and myelodysplastic syndrome, all of which are in Phase III trials. The drug also boasts early stage development for leiomyosarcoma.

Staying within kinase inhibitors, Exelixis’ cabozantinib is also in development for a number of rare cancers. Having recently been launched in the US for thyroid cancer, this spectrum-specific kinase inhibitor is in active development for 10 rare cancers. The most advanced of these are liver, bone and renal cancers, for which Phase III trials are ongoing. Earlier stage trials for other rare cancers including GIST and leiomyosarcoma are also underway, giving the drug a potentially diverse use across a wide range of rare cancers.

With infectious disease being a far second to oncology for development of drugs for rare diseases, several drugs again stand out as being major players. Sanofi, in collaboration with the Drugs for Neglected Diseases initiative (DNDi) has a project to develop therapies for several rare infectious diseases, including both American and African trypanosomiasis, filariasis and onchocerciasis. In total, seven rare infectious diseases are under investigation, with the project currently in early preclinical development.

Microbion’s MBS-105 also features here, focused on the prophylaxis and treatment of tuberculosis and anthrax. The broad spectrum antimicrobial is intended for use against Gram-negative pathogens in the bio-defence space, and is also under investigation for Brucella and Yersinia pestis infections. Development is currently at the lead series stage, and Microbion is seeking partners for commercialization.
This ‘promiscuity’ of certain drugs is particularly apparent in oncology, where multiple drugs are in development across a range of rare cancer indications. This can be explained if we consider mechanisms of the drugs in question. It stands to reason that drugs developed to attack a particular disease pathway will later be found to be active against other diseases with similar aetiology. Accordingly, the most promiscuous drugs for rare cancer indications include specific disease pathway-targeting drugs such as MEK and PLK inhibitors, as well as specifically-targeted monoclonals. Conversely, more traditional cancer drugs such as classical cytotoxics do not feature heavily. Therefore, it would seem that the drive towards developing drugs for rare diseases could be happening in tandem with a move within the pharma industry towards developing mechanistically-targeted drugs with activity in multiple diseases within a particular therapeutic space.
What’s happening elsewhere?

Beyond infectious diseases and oncology, 38 rare diseases can count 10 or more drugs in active development (Figure 8).

Figure 8. Non-cancer, Non-ID Diseases with 10+ Active Drugs

Source: CiteLine's Pharmaprojects®, data accessed November 2013
In terms of drugs in development, amyotrophic lateral sclerosis (ALS), boasts 71 drugs in active development. Despite this, there is currently only one drug on the market to treat ALS, this being Sanofi’s riluzole. The glutamate antagonist was launched for ALS in 1996, for which it gained US orphan drug status. It is now widely launched for the disease worldwide. In Phase III for ALS is free radical scavenger edaravone, under development by Mitsubishi Tanabe Pharma. Already launched in Japan for cerebral infraction, edaravone is currently in a Japanese Phase III trial in ALS patients. Completion is expected in March 2015.

Another non-cancer rare disease with substantial drug development activity is cystic fibrosis (CF). The multi-system genetic disorder currently has 66 drugs in active development, including 4 drugs on the market. These include Genentech’s aerosolized DNase therapy, which was first launched in 1994 and is now in widespread use, as well as Dompe’s Flutifort, a carbocysteine lysine salt that has been available since 1995. More recently launched drugs for CF include ivacaftor, developed by vertex Pharmaceuticals. The drug targets the source of CF directly by potentiating the gating activity of CFTR, the defective chloride channel behind the disease. Currently launched in several markets, ivacaftor represents an innovative therapy for the treatment of CF. Vertex Pharmaceuticals is also developing a combination product, combining ivacaftor with another CFTR-targeting drug, lumacaftor. A Phase III program is currently underway, with several further Phase III trials in CF patients planned. The active development of ivacaftor and lumacaftor now makes Vertex Pharmaceuticals a major player in the future of CF treatment.

Drug development outside oncology and Infectious Diseases spans a wide range of rare diseases. Other diseases under investigation to a lesser extent include Sjogren’s syndrome. To date, just one drug is available for this autoimmune disease. Cevimeline is a muscarinic agonist and has been launched since 2000. In clinical development for the disease now is belumumab. Originally developed by Human Genome Sciences (now GlaxoSmithKline), the anti-BLyS antibody completed a Phase II proof-of-concept trial in patients with Sjogren’s syndrome.
Why go after rare diseases?

Since the blockbuster days of the 1990s, drug development and the pharma industry has undergone a big change. As Novartis’ CEO Joseph Jimenez recently put it, “the definition of a blockbuster is changing”. The proposed solution is to produce drugs for smaller disease segments rather than chasing big markets. Examining the market picture for rare diseases, it seems that adoption of this strategy is already well underway. Progress in genomics and biomedical science over the past 20 years now means that the molecular basis of diseases is far better known, giving companies a better ‘roadmap’ to develop molecular targeted drugs, which means rare diseases can be targeted much more effectively. Today, the genetic aetiology of 4,500 diseases is known, compared to 50 such diseases 20 years ago.

There are other reasons behind companies’ wishes to develop drugs for diseases of low prevalence. In the US, the Orphan Drug Act of 1983 sought to bolster development for orphan drugs by offering incentives including a 7-year period of market exclusivity following launch (regardless of patent life), a waiver on Food and Drug Administration (FDA) fees, and a 50% tax credit on clinical studies. Similarly in the EU, Regulation 141/2000 offers 10-year market exclusivity, with tax credits offered by individual EU markets. These incentives have had the desired effect, with the number of treatments for rare diseases rising from 10 to over 400 in the period since the legislation was passed. Add to this the 2012 FDA Safety Innovation Act that has made it easier for drugs for rare diseases to progress through clinical trials, and the legislative framework with its ‘developmental drivers’ is now much more conducive towards development of drugs for rare diseases than in decades past. This has translated into the market, with global sales of orphan drugs increasing nearly 10% a year between 2005 and 2011, resulting in over 400 approvals for orphan drugs in the US and the EU.

The flip side of this increased development drive and the raised profile of rare diseases is the continuing trend of pharma companies seeking to command very high prices for such drugs, propagated by the often life-threatening nature of these diseases and the few alternatives available in terms of drug therapy. Development of orphan drugs may be on the rise, but the final decision on whether these new drugs are funded lies with individual healthcare systems and providers, and government programs. Several new orphan drugs approved in 2013 were priced at least $150,000 per patient per year, with 3 of these coming in at an annual cost of $300,000. At a time when there is global pressure to reduce the economic cost of healthcare, governments and healthcare bodies are now starting to question reimbursement of expensive orphan drugs, the overall cost of which must be spread over a relatively small patient population. This reluctance to reimburse these drugs may in the end slow the continued advance of the ‘bull’ rare diseases market.

Progress in systems biology has shown that “pathways” are not siloed, but rather their component enzymes, metabolites, or signalling messengers participate/converge in multiple functionalities. As genomics, systems biology and translational medicine continue apace, repurposing of rare disease therapies may be possible, and will perhaps help drug developers recover their research costs across wider patient populations. But until this happens, the economics of pricing for rare diseases is at risk.