TIMING OF EU5 & US ORPHAN DRUG APPROVALS AND PRMA BETWEEN 2009 AND 2013

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OBJECTIVE

- To examine pricing, reimbursement and market access of orphan drugs approved by EMA and FDA between January 2009 and December 2013

METHODS

- Analyzed the orphan drugs approved by both FDA and EMA between Jan 2009 and Dec 2013, by country (US & EU5) regarding:
  - Time to market
  - US/EU5 and intra EU5 pricing differences
  - Reimbursement and HTA
- Data collection cut off was January 2015

Sources: US (AnalySource, Fingertip Formulary), UK (UKMI, MIMS, NICE, SMC), Germany (Pharmazie, Rote Liste, GBA), France (Theriaque, HAS), Italy (AIFA), Spain (Botplus Portalfarma)

METHODS (CONT'D)

Definitions

- Orphan diseases are defined by the US and EU legislation
- In the US, these are diseases with a prevalence of fewer than 200,000 affected persons
- In the EU, prevalence must be fewer than 5 per 10,000 of the population, i.e. 251,500 affected persons (EU population - 503 million)
- Although no official definition of 'ultra-orphan disorders' has been adopted globally, this informal subcategory introduced by NICE is applied to drugs with indications for conditions with a prevalence of fewer than 1 per 50,000 persons

RESULTS

Orphan Drug Approvals: US vs. EU

- MME reviewed drugs that had an orphan designation in the US and were approved by the FDA between January 2009 and December 2013
- 102 drugs with orphan designation received FDA approval during this period
- MME assessed the availability and orphan status of these 102 drugs in the EU and found that:
  - 31 were not available in the EU including specific actions of 4 having marketing authorization refused and 2 with the application withdrawn by manufacturer
    - Several of these drugs that were not available in the EU, were older drugs/reformulations with potentially lower pricing and reimbursement prospects in the EU
  - 71 were launched in the EU but:
    - 49 were not designated as orphan drugs in the EU including 12 approved via mutual recognition/decentralized procedure
    - 9 were orphan designated but received EMA approval either before 2009 or after 2013
  - Only the 13 remaining drugs (12.7%) were orphan designated in both the US and EU and approved in the 5 year window examined

US and EU Orphan Drug Approvals in Common (January 2009 - December 2013)

- Of the 13 orphan drugs approved by both EMA and FDA between January 2009 to Dec 2013, 6 were oncology orphans, 4 were ultra orphans and 3 met neither of these criteria

Orphan Approvals, Time to Filing and Time to Market

- Of the 13 drugs approved by both the regulatory agencies (FDA and the EMA), time from filing to approval was:
  - 45 weeks with the FDA (11 to 26 weeks for the 4 drugs granted priority review)
  - 66 weeks with the EMA
- Average US time to launch from approval was 9 weeks (only 2 weeks if one outlier is removed)
- In the EU, all 13 drugs were available and reimbursed only on the German market in an average of 16 weeks while for instance only 5 had completed P&R in Spain in an average of 97 weeks
- In the UK, although in theory launch time is short, it took on average 71 weeks for positive reimbursement decision from the SMC for the 3 drugs eventually recommended on NHS Scotland

Figure 1: Orphan drug approvals - Oncology/non oncology and ultra-orphan

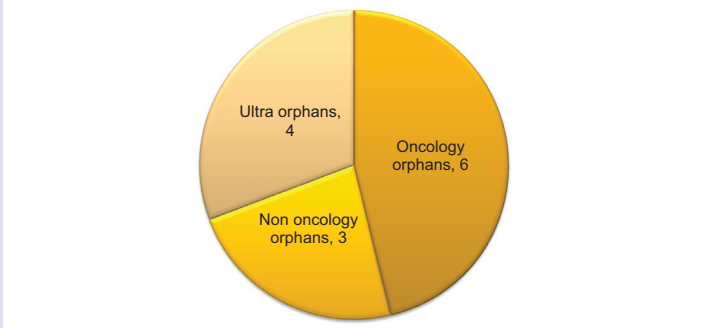
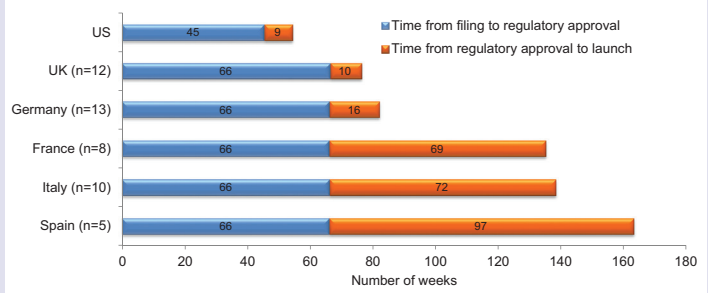


Figure 2: Time to filing and time to market (US and EU5)



Comparison of EU5 Average vs. US Launch and US Current WAC/Ex-Factory Price

- Relative EU5 prices determined first using US WAC/ex-factory price at launch as the base (100) and repeating the exercise using US current WAC/ex-factory prices as the base (100)
- Imnovid and Vpriv are the only two drugs where EU5 average is above the current US price
- Price differential between EU5 and US widens due to price inflation in the US as clearly demonstrated by Cayston and Jakavi

Intra EU5 Ex-Factory Price Variance

- Intra EU price differences reported using EU5 average ex-factory price as the base (100)
- Germany is consistently above EU5 average whereas UK and Spain are commonly below EU5 average
- Cayston and Imnovid have high prices in Italy but are not reimbursed (Class C) therefore should not be seen as pricing success stories

Table 1: Comparison of EU5 average vs. US launch/ current WAC price and intra EU ex-factory price variance

Drugs	EU5 average vs. US launch	EU5 average vs. US current	France vs. EU5 average	Germany vs. EU5 average	Italy vs. EU5 average	Spain vs. EU5 average	UK vs. EU5 average
Adcetris (brentuximab)	-3%	-20%	-5%	+20%	+1%	0%	-16%
Arzerra (ofatumumab)	-33%	-33%	n/a	+15%	+3%	-8%	-10%
Bosulif (bosutinib)	-28%	-37%	n/a	+19%	-10%	n/a	-9%
Iclusig (ponatinib)	-23%	-28%	n/a	+6%	-5%	n/a	-1%
Imnovid (pomalidomide)	+30%	+23%	-14%	+2%	+27%	-10%	-5%
Jakafi/Jakavi (ruxolitinib)	-21%	-40%	-8%	+17%	-4%	n/a	-5%
Cayston (aztreonam)	-27%	-46%	-22%	+19%	+21%	-16%	-3%
Opsumit (macitentan)	-47%	-47%	n/a	+13%	-6%	n/a	-7%
Signifor (pasireotide)	-66%	-66%	-7%	+10%	-1%	n/a	-3%
Kalydeco (ivacaftor)	+4%	-1%	0%	+15%	n/a	0%	-14%
Procysbi (cysteamine bitartrate)	-51%	-54%	n/a	0%	n/a	n/a	n/a
Vpriv (velaglucerase alfa)	+47%	+44%	-11%	+26%	-12%	-6%	+3%
Revestive/Gattex (teduglutide)	+14%	-3%	n/a	+18%	n/a	n/a	-18%

n/a= Product not available in the country or price not publicly available

Reimbursement & HTA

- France:
  - 8 orphan drugs reimbursed; no agreement reached with the manufacturer on Bosulif
  - Of the 9 drugs assessed by HAS, only 1 ultra-orphan (Kalydeco) assigned ASMR II
- Germany:
  - All 13 drugs available and reimbursed in Germany
  - GBA assessments for only 9 of the 13
  - 3 drugs launched pre-AMNOG and one exempt from AMNOG assessment (Procysbi)
  - Of the 9 evaluations, only 2 oncology orphans (Imnovid, Jakavi) and 1 ultra orphan (Kalydeco) assigned significant additional benefit
- Italy:
  - 8 orphan drugs reimbursed; 6 of which classified as hospital only (Class H)
  - 2 orphan drugs, (Cayston, Imnovid) although available in Italy are not reimbursed (Class C)
- Spain:
  - Only 5 of the 13 orphan drugs completed P&R negotiations
  - All 5 drugs fully reimbursed for hospital use only with hospital only restriction
- UK:
  - In theory 12 of the 13 orphan drugs available in the UK
  - However, only 3 recommended for reimbursement by the SMC, 2 of which were recommended on the basis of a patient access scheme (PAS)
  - Only 4 oncology orphans reviewed by NICE- none of which are recommended

CONCLUSIONS

- Significant differences exist between the number of orphan drug approvals in the US and EU (only 12.7% are common in the study period)
  - The differences can be explained in part by the different definitions of orphan drugs as per US and EU legislations
  - Furthermore, innovative uses of existing molecules are not always rewarded in the EU as reflected by fewer launches in the EU compared to the US
- Time to regulatory approval longer in the EU vs. the US (66 weeks compared to 45 weeks)
- Time to access is significantly longer in the EU than in the US possibly related to country processes and varying financial constraints
- Orphan drugs are perceived as offering significant incremental value only in selected cases by HTA agencies
- Variation across EU countries in HTA assessment process frequently means the same molecule with the same clinical package is likely to receive different benefit evaluations
- For pricing, the US is not always the highest price country although the gap widens due to post-launch price increases in the US
- Within the EU5, Germany tends to have higher prices than the EU5 average