US Versus Global Pharmaceutical Launches: What are the potential reasons that can result in a pharmaceutical not being commercialized outside the US?

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Introduction

- In this study, we aimed to understand the frequency and potential rationale behind decisions to not launch a specialty medicine product outside the US following their US FDA approval
- Payer expectations have been evolving and are becoming increasingly stringent thereby posing challenges for pharmaceutical manufacturers. Hence, we explored the dynamics of recent pharmaceutical launches to understand the challenges faced in introducing these innovative therapies in the ex-US markets
- Additionally, we identified the markets where no-launches were frequent and explored the potential rationale via case studies

Objectives

This study had two main objectives

1. It explored the frequency of specialty medicine products not launched in key ex-US markets following their US FDA approval and identified markets where this occurred frequently
2. Following this, the rationale behind no-launches in the ex-US markets was hypothesized, such as no submissions, anticipated challenges in pricing negotiations, issues with submitted evidence packages, failed payer negotiations, etc.

Methods

- In-scope markets for the study included Australia, Canada, France, Germany, Great Britain, Italy, and Spain. These markets were chosen considering different geographical regions (EU, APAC, and North Americas), payer dynamics (clinical, cost-effectiveness, and budget impact), and launch perspectives
- Case studies were developed focusing on a few products (refer to Table 1) with no launches in ex-US markets, to understand the rationale behind the same
- Detailed methodology is shown in the flow-chart below

List of products that have been US FDA-approved in the last 5 years
- Only NMEs/NCEs in Oncology and Specialty (e.g., rare diseases)
- *Launch indications only (no expansions)*
- *Only monotherapy (no combinations/fixed combinations)*
- *Products with all types of trial data (SAT, RCT)*

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List of products that received regulatory approval by EMA (EU), MHRA (UK), TGA (AU), and Health Canada (CA)

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List of products that skipped reimbursement or applied for reimbursement, underwent assessment and later, did not launch/withdraw from the in-scope markets

We analyzed the rationale for such decisions (e.g., company strategy, failed negotiations, issues with evidence package, etc.)

[1] We did not include products that did not file with EMA (EU) and products that have been in the ongoing trials/ abandoned/approved prior to the US FDA

Results

Figure 1 | Overall trend of no launches in the ex-US markets

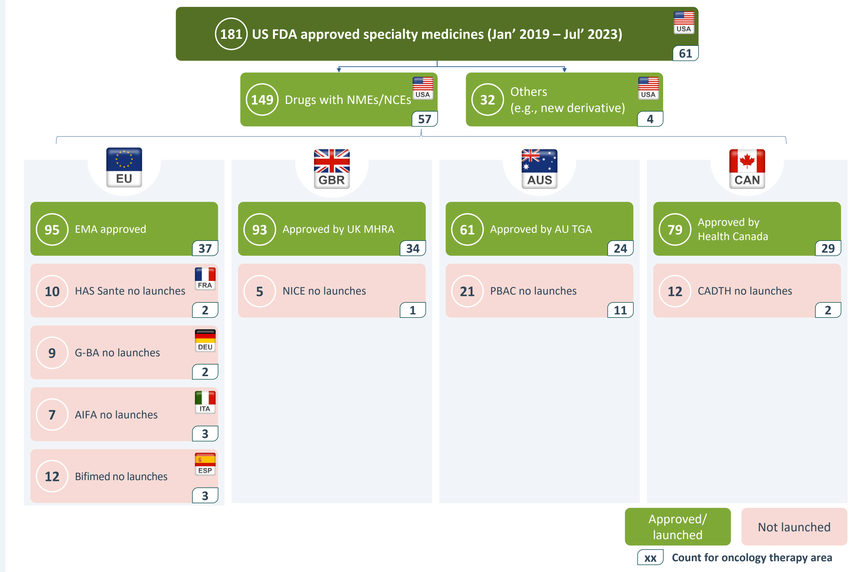

Figure 2 | Trend for no launches with a focus in the oncology therapeutic area

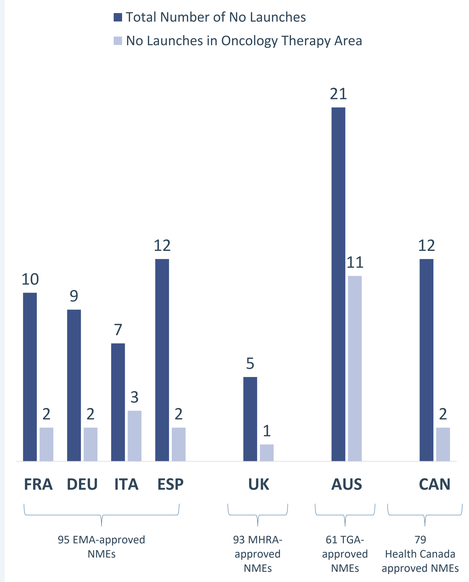

Table 1 | Selected examples with no-launches in the ex-US markets (non-exhaustive)

Drug	Indication	Markets with no launch/withdrawal	Potential Rationale behind no launch/withdrawal
Crizanlizumab	Vaso-occlusive crises in sickle cell diseases	EU (EMA revoked MA)	Challenges arose with the evidence package for crizanlizumab. Initially conditionally approved, subsequent trial results revealed that its risks outweighed the benefits
Betibeglogene autotemcel; elivaldogene autotemcel	Severe beta thalassemia; Cerebral adrenoleukodystrophy	EU / DEU	Bluebird bio cited inability to sustain operations owing to prolonged and failed pricing negotiations with EU payers specifically Germany
Amivantamab-vmjw; spesolimab	NSCLC with EGFR Exon 20 insertion mutation; Generalized pustular psoriasis	DEU	Janssen and Boehringer Ingelheim withdrew their drugs from DEU before pricing negotiations due to anticipated HTA framework challenges. Poor HTA outcomes (no added benefit) likely meant lower reimbursement prices, potentially impacting prices in other countries via IRP
Lenacapavir	Treatment for HIV	DEU	Gilead decided not the launch lenacapavir in DEU due to anticipated challenges with the HTA framework

Given that multiple withdrawals are seen in DEU, the potential rationale behind these trends can be classified into three overarching themes.

Table 2 | Selected examples with no-launches in DEU (non-exhaustive)

Overarching theme for no launch	Example	Potential hypothesis	Outcome	Manufacturer's/Stakeholder's perspective
Issues with the submitted evidence package	Amivantamab	The G-BA deemed the comparative data from ITCs insufficient for assessing Amivantamab's benefits and drawbacks due to a lack of specific endpoint magnitudes. OS versus chemotherapy data in the ITC did not address inherent bias, and there was insufficient data for other patient-relevant endpoints like QoL and side effects. Additionally, chosen German registries lacked patient severity data for comparison. As a result, the G-BA assigned Amivantamab a no added benefit rating	**Janssen** withdrew amivantamab before pricing negotiations due to the anticipated low reimbursement price, potentially affecting prices in other markets through the IRP mechanism	The outcome "highlights high methodological requirements for the acceptance of comparisons based on RWE data in Germany, even with high medical need" – Janssen representative
Challenges with the AMNOG negotiation framework ↕ Interdependent	Capmatinib	G-BA found no proven additional benefit for Capmatinib, citing lack of suitable data for the benefit assessment in all three patient sub-populations that were assessed	**Novartis** opted out of the rebate negotiation process due to the anticipated low reimbursement price, potentially affecting prices in other markets through the IRP mechanism	Basic solidarity consensus in pricing appears to be eroding - to the detriment of patients" – The German Society of Hematology and Medical Oncology Association (DGHO)
Prolonged and failed pricing negotiations with German payers	Betibeglogene Autotemcel	The G-BA provided non-quantifiable benefit (default rating owing to orphan drug designation) however, cited concerns such as the small number and limited selection of patients along with uncertainties due to the lack of long-term safety data, in the submitted studies	**Bluebird Bio** opted to withdraw the product because they felt the proposed price did not reflect the value of the one-time gene therapy, which offers lifelong benefits for those with TDT	Germany's proposed price for the gene therapy failed to recognize the innovativeness and benefit Zynteglo provides to patients living with this disease, which is severely burdensome " – Bluebird representative

Discussion & Conclusion

Key learning from the analogues

The frequency of no-launches is overall rare and consistent across countries

While no launches are overall rare, there have been a few recent high-profile withdrawals EU-wide and specifically in DEU as a reaction to overall pricing pressure and policy changes

Issues with the evidence package submitted by manufacturers and anticipated challenges with HTA frameworks and pricing negotiations are the key drivers for no-launches in the ex-US markets

DEU FRA – likely driven by an inability to justify strong clinical outcomes based on evidence package

GBR CAN AUS – likely due to inability to reach CE thresholds

ITA ESP – lower frequency of no-launches as there is more openness to negotiate and seek alternative strategies to achieve access (e.g., subgroups)

Key learnings

Improved communication between payer/regulator industry
Early alignment and collaboration between manufacturers and payers is critical to ensure evidence generation meets their needs. Payers, industry, clinicians and patients should agree on appropriate ways to measure a product's value and adapt HTA frameworks with evolving science (e.g., surrogate markets, utilization of value attributes beyond clinical outcomes)

Innovation in Evidence Generation
Manufacturers and payers should embrace exploring novel value drivers (e.g., equity, productivity, time burden of treatment) and evidence-collection methods to better reflect the value of innovative therapies (e.g., utilizing digital tools, leveraging RWE to address evidence gaps, etc.)

Health Economic Analysis
Fully align value of a product to clinical/humanistic/societal benefit vs. limited components

Changes in the policy landscape that are likely to have NME launch implications

DEU: Confidential reimbursement prices for new drugs would empower manufacturers in negotiations without impacting IRP, potentially reducing market withdrawals to avoid global price erosion

DEU: Introduction of a 20% rebate in the AMNOG negotiation for brand-brand combinations

FRA: Temporary reimbursement scheme - ASMR IV or better-rated drugs will receive 100% reimbursement after TC evaluation

GBR: Severity-based modifier (replaces end-of-life criteria) gives extra weight to QALY gains for severe diseases

Limitations

- This study covers specialty medicines only. The analysis also excluded following therapy areas: Infectious Diseases and Vaccines, Dermatological Conditions, Endocrine and Metabolic Disorders, Pain Management and Anesthesia, Gastrointestinal and Urinary Tract Disorders, Respiratory and Allergic Conditions, etc.
- Analysis is indicative and non-exhaustive and covers drugs approved by the US FDA between January 2019 - July 2023
- Internal considerations on the MNF's end or any other external, non-market factors which could potentially be driving no-launches have not been considered

References

1. Evaluate Pharma database as accessed on 07th January 2024
2. Regulatory labels: EMA for EU approvals; MHRA for the UK; Health Canada for CAN, TGA for AUS
3. Reimbursement sources: G-BA for DEU, HAS for FRA, Official Gazette for ITA, Bifimed for ESP, NICE for the UK, PBAC for AUS, CADTH for CAN
4. The regulatory and reimbursement data is as of 29th January 2024; any updates post this date have not been covered

Appendix

Abbreviations: FDA: Food and Drug Administration; EU: Europe; APAC: Asia–Pacific; NME: New Molecular Entity; NCE: New Chemical Entity; SAT: Single Arm Trial; RCT: Randomized Control Trial; EMA: European Medicines Agency; MHRA: Medicines and Healthcare products Regulatory Agency; UK: United Kingdom; TGA: Therapeutic Goods Administration; AU: Australia; CA: Canada; HAS: French National Authority for Health; G-BA: Federal Joint Committee; AIFA: Italian Medicines Agency; NICE: The National Institute for Health and Care Excellence; PBAC: Pharmaceutical Benefits Advisory Committee; CADTH: Canadian Agency for Drugs and Technologies in Health; DEU: Germany; MA: Marketing Authorization; NSCLC: Non Small Cell Lung Cancer; EGFR: Epidermal Growth Factor Receptor; HTA: Health Technology Assessment; IRP: International Reference Pricing; HIV: Human immunodeficiency viruses; TDT: Transfusion-Dependent β-Thalassemia; ITC: Indirect Treatment Comparison; OS: Overall Survival; QoL: Quality of Life; RWE: Real World Evidence; CE: Cost Effective; AMNOG: German Medicines Market Reorganization Act; ASMR: Improvement of Medical Service Rendered; TC: Transparency Committee; QALY: Quality Adjusted Life Years; MNF: Manufacturer

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