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What Future for the Orphan Drugs Market?

Position paper

Strategic insights for pharma companies

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1, rue Houdart de Lamotte – 75015 Paris – France
Tel. +33 6 11 96 33 78
Email: jmpeny@smart-pharma.com – Website: www.smart-pharma.com

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Smart Pharma Consulting has carried out an analysis to evaluate the future of the orphan drugs market and to draw strategic insights for pharma companies

Introduction

Context

- In 2021, orphan drugs sales reached USD 156 B, representing ~11% of the worldwide pharma market
- This market segment offers prospects of strong growth and attractive profit margins
- With orphan drugs currently available for only ~5% of rare diseases, the future is widely open for investment

Objectives

- The objective of this study was to:
  - Better understand orphan drugs market structure and dynamics
  - Anticipate its evolution by 2024
  - Assess the attractiveness of this market segment for pharma companies
  - Determine the key success factors for market players

Methodology

- Literature search regarding the orphan drugs market and its perspectives by 2024
- Analysis of implications for pharma companies and identification of key strategic challenges

Sources: Smart Pharma Consulting

Rare diseases prevalence is defined as particularly low, and its order of magnitude is quite consistent across different geographical regions

Definitions per geographical region – Rare diseases, orphan drugs, orphan diseases

	 Europe	 United States	 Japan
Rare diseases	▪ Population **< 1 / 2,000**	▪ Population **< 200,000**[1] or ▪ Population **> 200,000** without possibility to **cover the cost of development** and **distribution** by sales on the national territory	▪ Population **< 50,000** or ▪ Population **< 1 / 2,500**
Orphan drugs	▪ Drugs for **prevention**, **diagnosis** or **treatment** of **rare diseases, not developed** by the pharmaceutical industry **under normal market conditions** as the **cost of bringing them** to the market **would not be recovered** by the **expected sales** of drugs without incentives provided, but which **respond to public health need**		
Orphan diseases	▪ Diseases **not adopted** by pharma companies as it provides **little financial incentive** for the private sector: – **Rare diseases**, as defined according to geographical regions – **Common diseases** that have been **ignored** (e.g.; tuberculosis, cholera, typhoid, malaria) as they are more prevalent in developing countries than in the developed world		

Sources: Orphanet – Eurordis – FDA – Japanese Ministry of Health, Labor and Welfare – Smart Pharma Consulting analyses

[1] Representing ~1 / 1,650 people (based on USA population in 2020)

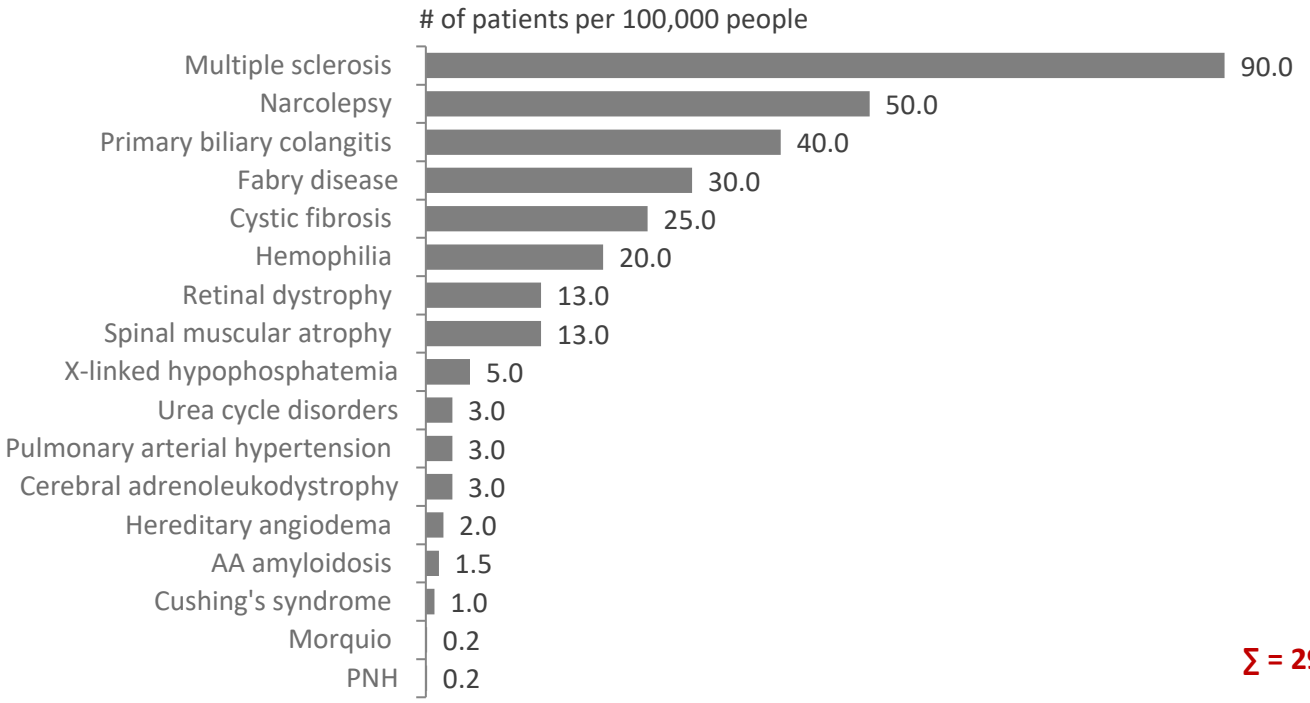
Prevalence rates per condition are low but their collective impact on population and healthcare systems is significant and too often underestimated

Key figures and prevalence of selected rare diseases worldwide

Key figures (2021)

- ~7,000 existing rare diseases, of which ~85% are very serious or life-threatening diseases
- ~5% of rare diseases treated with approved drugs
- More than half of rare diseases starting in childhood
- ~25-30 million patients
- ~25-30 million patients
- ~400 million patients worldwide

Prevalence rate of selected rare diseases worldwide (2017) [1]



∑ = 299.8*

*The collective prevalence of those leading rare diseases is ~300 per 100,000 inhabitants

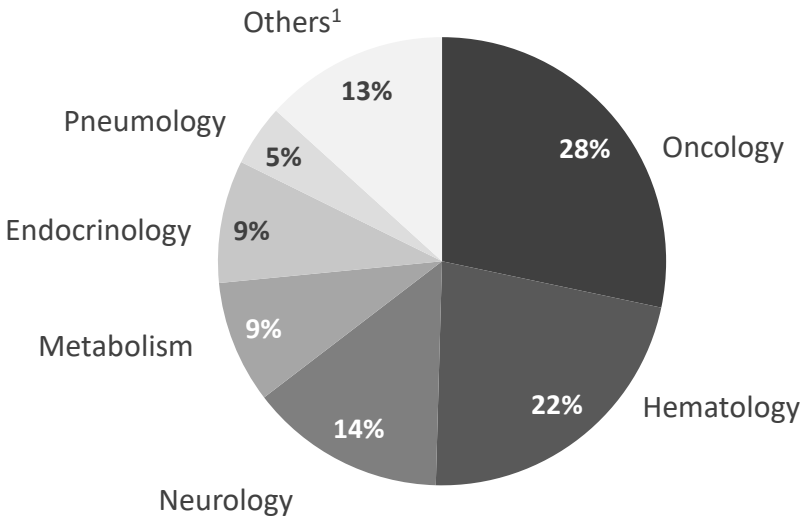
Sources: Orphanet – Genetic and rare disease information center – European Commission – Torreya Partners (2017) – Smart Pharma Consulting analyses

[1] Selection based on leading diseases treated by the top 20 most valuable rare disease companies

Oncology, hematology and neurology are the three major therapeutic areas of rare diseases, accounting for ~64% of EMA orphan drugs approval between 2015 and 2021

Main therapeutics areas covered by orphan drugs (2015-2021)

Distribution of 2015-2021 EMA orphan drugs approvals by therapeutic area



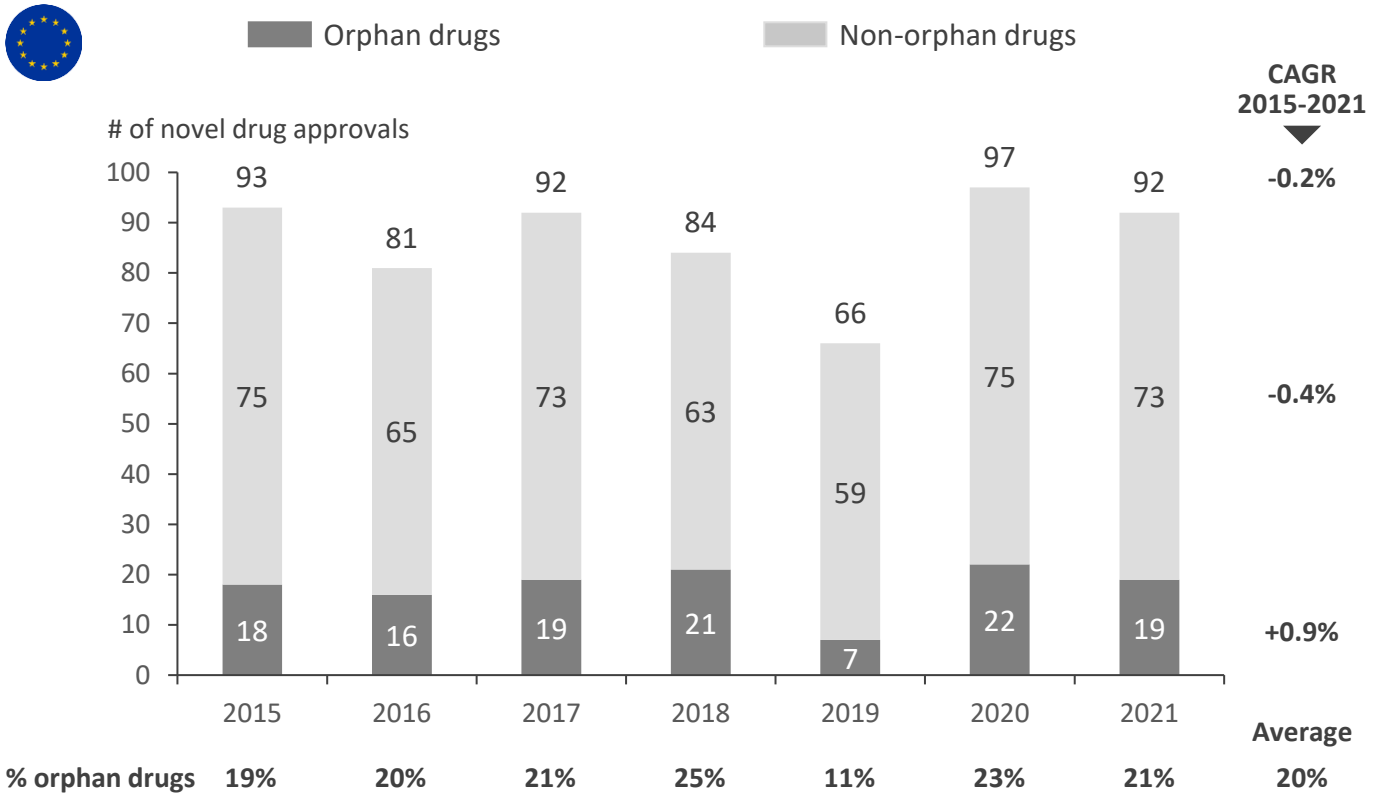
- **Oncology:** most of orphan drugs approvals concern treatments for leukemia (e.g.; ALL[2], AML[3], CLL[4]), multiple myeloma and gastroenteropancreatic neuroendocrine tumors (GEP-NETS)
- **Hematology:** orphan drugs approvals concern diverse pathologies such as sickle cell disease or BPDCN[5]
- **Neurology:** mostly concern treatments for spinal muscular atrophy, for seizures and for neuro-ophthalmology disorders
- **Metabolism:** treatments for diverse pathologies such as neonatal diabetes, Wilson's disease or genetic diseases (e.g.; familial chylomicronemia syndrome)
- **Endocrinology:** treatments for various diseases such as X-linked hypophosphatasemia, acute hepatic porphyria, Cushing's syndrome, mucopolysaccharidosis type VII
- **Pneumology:** mostly concern treatments for cystic fibrosis, hereditary angioedema and pulmonary infections with non-tuberculous mycobacteria

Sources: "Human medicines highlights", EMA (2015-2021) – Smart Pharma Consulting analyses

[1] Incl. infections, hepatology, ophthalmology, uro-nephrology, gastroenterology, immunology, transplantation – [2] Acute lymphoblastic leukemia – [3] Acute myeloid leukemia – [4] Chronic lymphocytic leukemia – [5] Blastic plasmacytoid dendritic cell neoplasm

Over the 2015-2021 period, the weight of orphan drugs approved by the EMA has been quite stable and accounted for 20% on average of all approved drugs

Weight of orphan drugs in EMA novel drugs approvals (2015-2021)

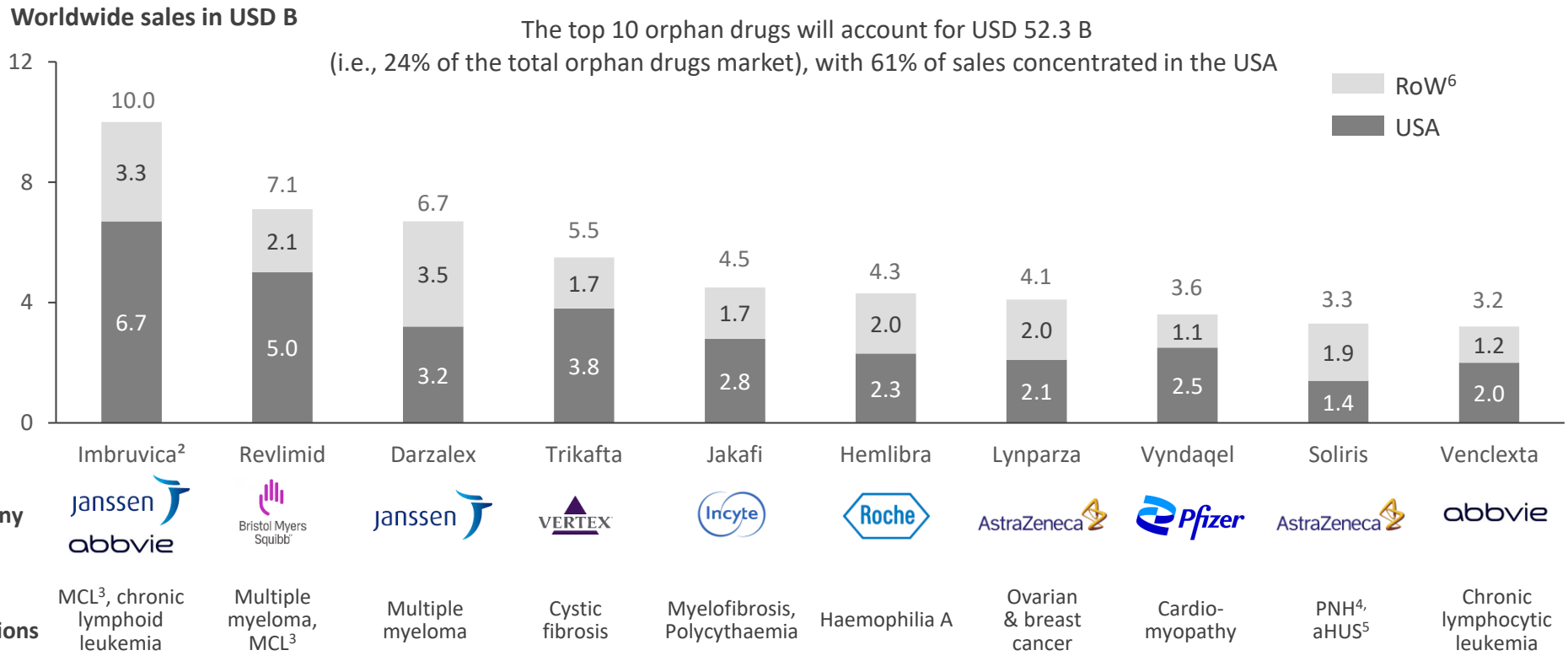


- In **2021**, **orphan drugs** accounted for **~21%** of all EMA drugs approvals
- The **total number of novel drugs** approved by the **EMA** from 2015 to 2021 has been quite stable, with a CAGR of **-0.2%**
- **Orphan drugs** approvals increased slightly, with a **CAGR** of **+0.9%** between 2015 and 2021, accounting, on average, for **~20%** of all EMA approved drugs, over the period
- However, the year **2019** was marked by a **low number of new orphan drugs** approved by the EMA compared with the other years of the 2015-2021 period

Sources: "Human medicines highlights", EMA (2015-2021) – Smart Pharma Consulting analyses

The top 10 drugs addressing cancers, rare genetic diseases, blood disorders and CNS[1] diseases should account for ~24% of the orphan drugs market in 2024 and achieve ~61% of their sales in the USA

Top 10 orphan drugs (2024)

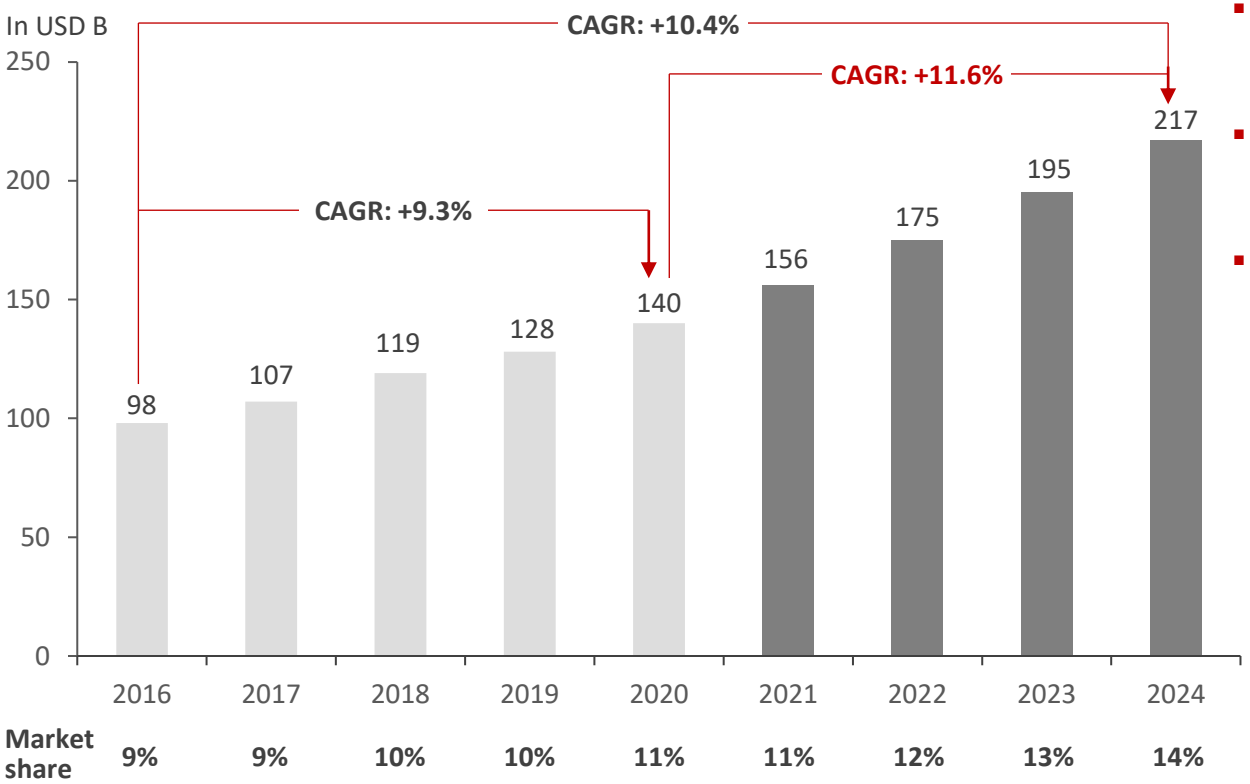


Sources: EvaluatePharma (2020) – FDA – SmPCs – Smart Pharma Consulting analyses

[1] Central Nervous System – [2] Product co-licensed to Janssen and AbbVie in the United States and licensed to Janssen outside the United States – [3] Mantle Cell Lymphoma –[4] Paroxysmal Nocturnal Hemoglobinuria – [5] Atypical Hemolytic Uremic Syndrome – [6] Rest of the world

The weight of the orphan drugs market in the pharmaceutical industry is more and more important and should reach up to ~14% of the worldwide pharmaceutical market by 2024 (+ 5 pts vs. 2016)

Worldwide orphan drug sales (2016-2024)



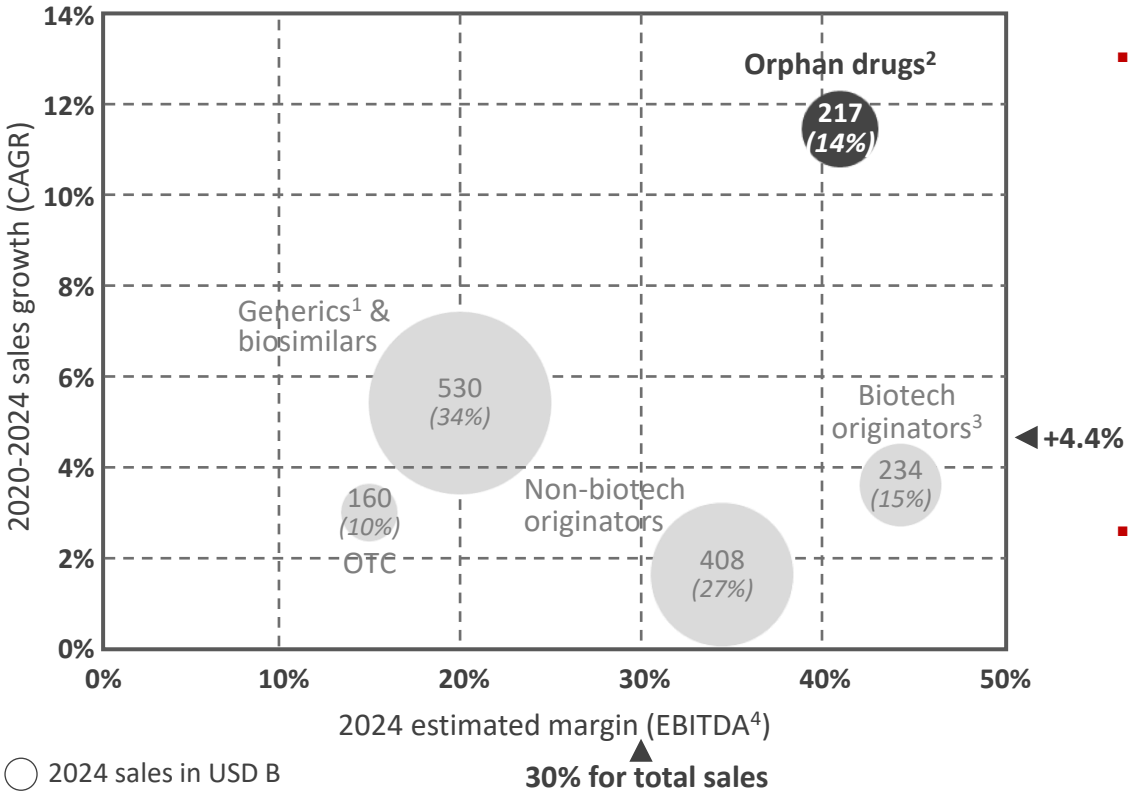
- Orphan drugs have become a **cornerstone** of the pharma market, with **~11%** of the **worldwide market** in **2020** and ~**14%** expected in **2024**
- With a forecasted CAGR of **+11.6%** between **2020** and **2024**, the orphan drugs segment should **grow 2.6 times** faster than the **worldwide pharma market**
- This dynamic growth is driven by:
  - A strong demand from HCPs and patients due to high clinical unmet needs
  - The development of new technologies (e.g., genomics, gene sequencing, gene therapy) enabling to treat rare genetic diseases
  - The "orphanization" of certain TAs (e.g., oncology, diabetes) which consists in identifying rare disease subtypes and developing new drugs or repurposing an existing ones
  - Financial and regulatory incentives (e.g., tax credits, marketing exclusivity, etc.) granted by health authorities to fulfill that demand
  - Generic and biosimilar products[1] improving the access to a larger number of patients

Sources: EvaluatePharma (2020) – Smart Pharma Consulting analyses

[1] Generic (e.g., Imatinib) and biosimilar (e.g., bevacizumab, adalimumab) versions of older original orphan drugs or drugs with orphan indications that have lost their patent

By 2024, orphan drugs should be the main driver of pharma market growth and be one of the most profitable segments due to premium prices and lower costs across the drug value chain

Profitability of orphan drugs companies (2020-2024)



- **High profitability** (~41% EBITDA rate) of orphan drugs due to:
  - **Lower R&D costs** (4 times less): ~ USD 0.5 B for orphan drugs vs. USD 2 B for non-orphan drugs
  - **Premium prices** vs. non-orphan drugs
  - **Incentives** granted by regulatory agencies (e.g.; clinical trials subsidies, reduced regulatory fees, tax credits, etc.)
  - **Fewer commercial** and **promotional investment** due to:
    - Lower number of expert centers and HCPs to target
    - Lower competition intensity
- **Market growth** (+11.6% CAGR over 2020-2024) due to:
  - Favorable means to **speed up registration**
  - Increasing number of **medicines** addressing **unmet needs**
  - Progressive entry of expensive **one-shot therapies** (e.g.; **CAR T-cell therapies**)

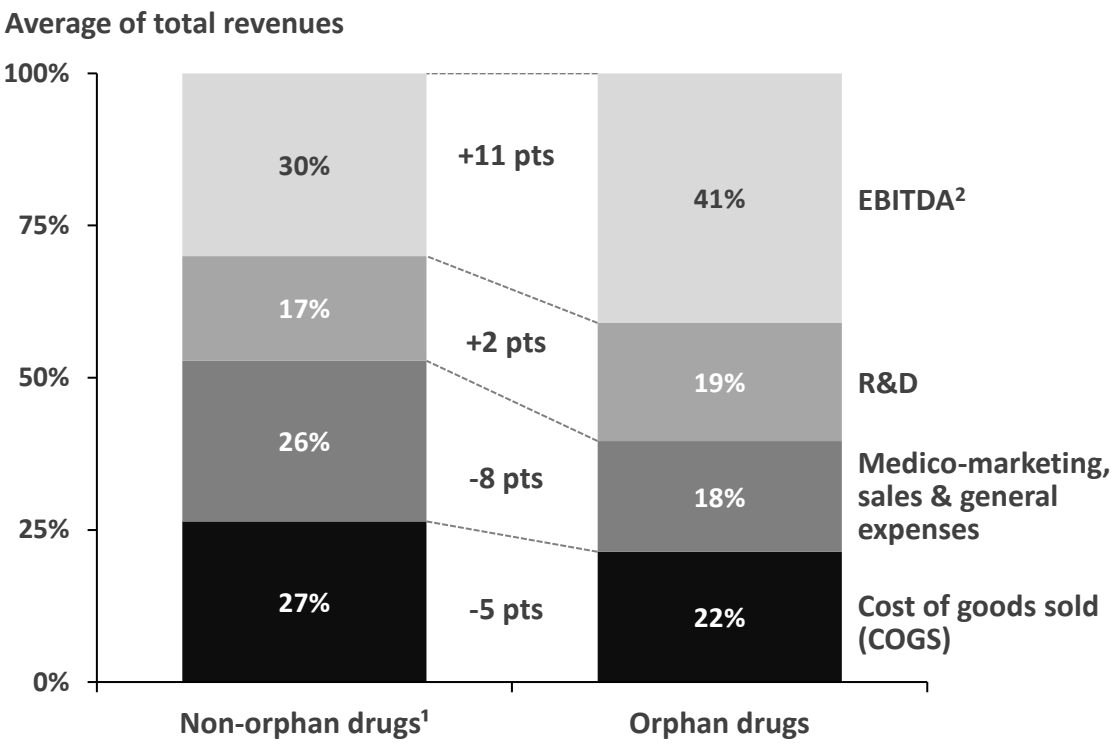
Sources: EvaluatePharma (2020) – Smart Pharma Consulting estimates, based on the 3 latest annual reports of a panel of 5 pure players of the orphan drugs market (Alexion prior to its acquisition by AstraZeneca, Biogen, Shire prior to its acquisition by Takeda, SOBI and Vertex)

[1] Incl. branded and unbranded generics – [2] Incl. chemical and biotech drugs, for 65% and 35% of orphan drugs sales, respectively – [3] Excl. biosimilars – [4] Earnings before interest, taxes, amortization and depreciation

The average EBITDA rate made by orphan drugs is 11 pts higher (41% vs. 30%) than the one drawn by non-orphan Rx-bound drugs (either biological or chemical)

Typical cost structure of non-orphan vs. orphan drugs

Cost structure as a percentage of total revenues



- With an average **EBITDA rate** reaching **~41%** of total revenues, orphan drugs **profitability** is **higher** vs. non-orphan drugs (**+11 pts**)
- This **positive gap** can be explained by:
  - **Fewer medico-marketing**, **sales** and **general expenses** (**-8 pts**) due to:
    - Lower number of expert centers and HCPs to target
    - Lower competition intensity
  - **Fewer COGS as a percentage of revenues** (**-5 pts**) due to **premium prices**…
  - **… partially offset** by higher weight of **R&D investment** in total revenues (**+2 pts**)

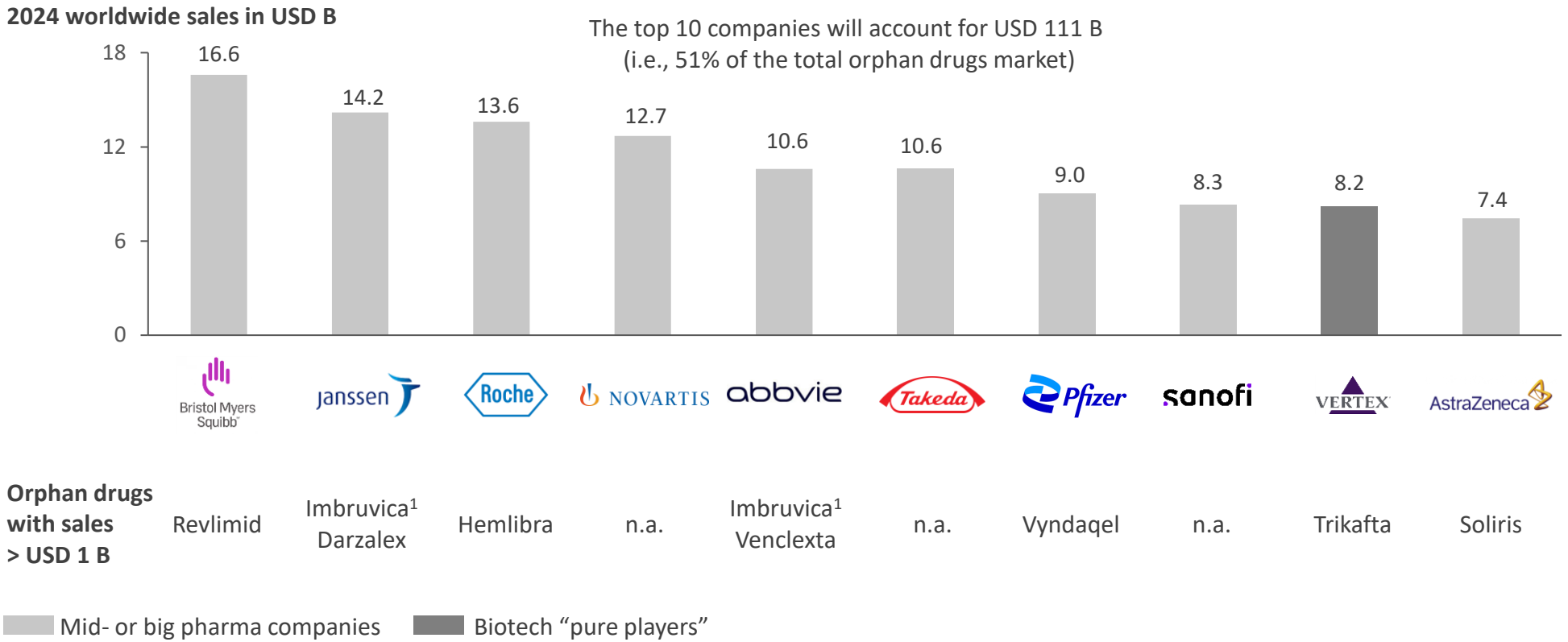
***Note**: reconciliation items between EBIT[3] and EBITDA (incl. amortization, depreciation and one-off items such as restructuring) have been equally distributed between each type of costs. They accounted for ~12% of orphan drugs revenues and ~8% of non-orphan drugs revenues*

Sources: Smart Pharma Consulting estimates, based on the 3 latest annual reports of a panel of the 20 biggest pharma companies (excl. Biogen) and 5 pure players of the orphan drugs market (Alexion prior to its acquisition by AstraZeneca, Biogen, Shire prior to its acquisition by Takeda, SOBI and Vertex)

[1] Rx-bound drugs only – [2] Earnings before interest, taxes, amortization and depreciation – [3] Earnings before interest and taxes

In 2024, the top 10 companies operating on the orphan drugs market should account for 51% of the total market segment, with Bristol-Myers Squibb, Johnson & Johnson and Roche as leaders

Top 10 companies operating on the orphan drugs market (2024)



Sources: EvaluatePharma (2020) – Smart Pharma Consulting analyses

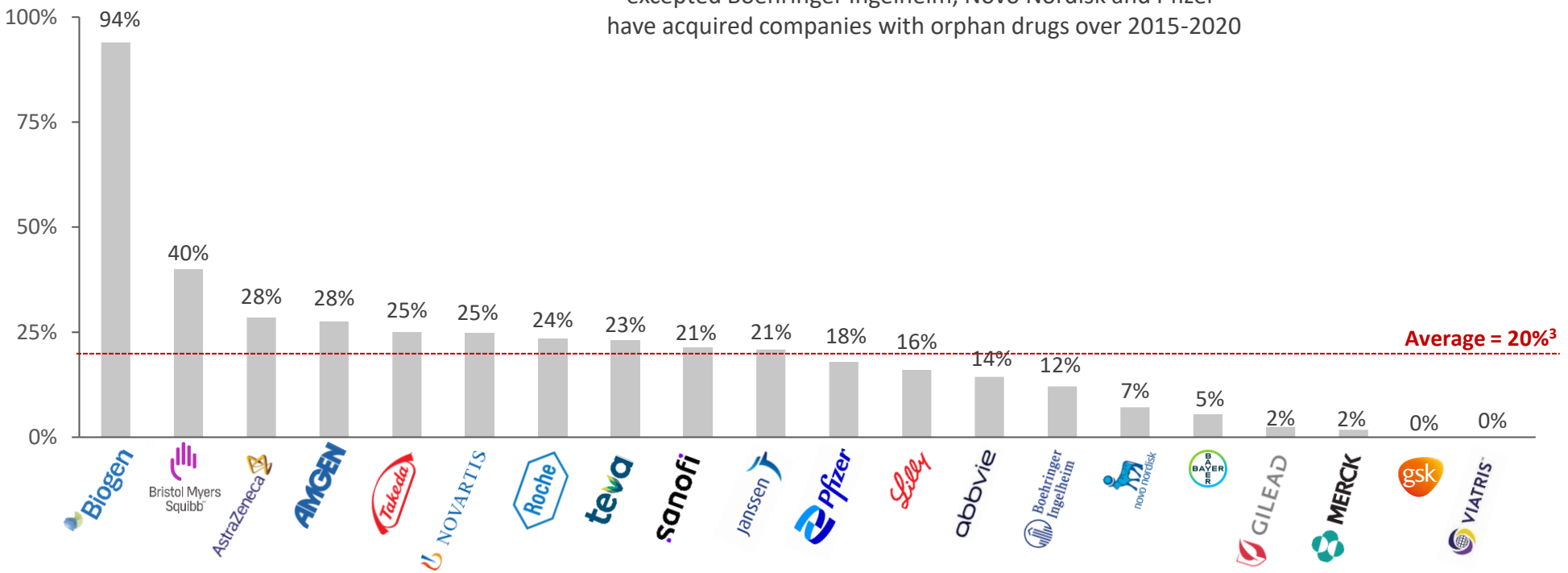
[1] Product originally co-developed by Janssen and Pharmacyclics, an oncology-focused biotech acquired by AbbVie in 2015, co-licensed to Janssen and AbbVie in the United States and licensed to Janssen outside the United States

Among the top 20 pharma companies worldwide, Biogen, Bristol-Myers Squibb, AstraZeneca and Amgen have the most important share of orphan drugs in their portfolio

Strategic importance of orphan drugs in top 20 pharma companies[1] portfolio (2020)

Estimated share of orphan drugs sales in total drugs & vaccines worldwide sales

The top 20 pharma companies with orphan drugs sales – excepted Boehringer Ingelheim, Novo Nordisk and Pfizer[2] – have acquired companies with orphan drugs over 2015-2020



Sources: EvaluatePharma (2019) – Companies annual reports (2020) – Smart Pharma Consulting analyses

[1] Based on drugs & vaccines sales of companies – [2] Boehringer Ingelheim did not make any acquisition over the period but signed a partnership in 2019 with the UK-based drug technology firm Healx to identify approaches to treat rare neurological disorders. Pfizer acquired Arena and Novo Nordisk Dicerna, but in 2021 – [3] If one excludes Biogen, the average weight of orphan drugs drops at 16% of big pharma companies revenues

The acquisition of Celgene by BMS, Shire by Takeda and Alexion by AstraZeneca are the top 3 M&A operations carried out in rare diseases since 2015, by the top 20 pharma companies

Major orphan drugs M&A operations[1] (2015-2021) (1/2)

Item	Acquirer	Acquired	Price (USD B)	Year	Key brands / projects
#1	BMS	Celgene	74,0	2019	Ozanimod, CAR-T therapies
#2	Takeda	Shire	62,0	2018	Advate, Elaprase, Replagal, Vpriv
#3	AstraZeneca	Alexion	39,0	2020	Soliris, Ultomiris
#4	Janssen (J&J)	Actelion	30,0	2017	Opsumit, Uptravi, Tracleer
#5	AbbVie	Pharmacyclics	21,0	2015	Imbruvica
#6	BMS	MyoKardia	13,1	2020	Mavacamten
#7	Gilead	Kite Pharma	11,9	2017	CAR-T therapies
#8	Sanofi	Bioverativ	11,6	2018	Eloctate, Alprolix
#9	MSD	Acceleron	11,5	2021	Reblozyln
#10	Novartis	AveXis	8,7	2018	Zolgensma
#11	Lilly	Loxo Oncology	8,0	2019	Loxo-305
#12	Pfizer	Arena	6,7	2021	Etrasimod
#13	Janssen (J&J)	Momenta	6,5	2020	Nipocalimab

Sources: Smart Pharma Consulting analyses

[1] M&A operations carried out over 2015-2021 by the top 20 pharma companies for prices of USD 2 B or more

During the 2015 – 2021 period, all the top 20 pharma companies with orphan drugs sales have acquired companies with orphan drugs, excepted Boehringer Ingelheim[1]

Major orphan drugs M&A operations[1] (2015-2021) (2/2)

Item	Acquirer	Acquired	Price (USD B)	Year	Key brands / projects
#14	AbbVie	Stemcentrx	5,8	2016	Rova-T
#15	Takeda	NPS	5,2	2015	Naptara
#16	Takeda	Ariad	5,2	2017	Iclusig
#17	Gilead	Forty Seven	4,9	2020	Magrolimab
#18	Roche	Spark Therapeutics	4,3	2019	Voretigene neparvovec-rzyl
#19	AstraZeneca	Acerta Pharma	4,0	2015	Acalabrutinib
#20	Bayer	Asklepios	4,0	2020	Gene therapies
#21	Sanofi	Ablynx	3,9	2018	Caplacizumab
#22	Sanofi	Principia	3,7	2020	Rilzabrutinib
#23	Novo Nordisk	Dicerna	3,3	2021	Nedosiran, Belcesiran
#24	Teva	Auspex	3,2	2015	SD-809
#25	MSD	VelosBio	2,8	2020	VLS-101
#26	Novartis	Endocyte	2,1	2018	CAR-T therapies

Sources: Smart Pharma Consulting analyses

[1] M&A operations carried out over 2015-2021 by the top 20 pharma companies for prices of USD 2 B or more

In the United States as in Europe, regulatory agencies boost orphan drug development by offering incentives including financial, regulatory and marketing benefits

Main incentives to support orphan drugs (2021)

Benefits	Europe	United States
Financial	▪ R&D: scientific advice on study protocols, various fee reductions ▪ Reduced fees for regulatory activities (e.g., protocol assistance, marketing-authorization applications) ▪ Available fundings from Horizon 2020 (the EU Framework Program for Research and Innovation), and E-Rare (a transnational project for research programs on rare diseases) ▪ Specific incentives for SMEs[1] (incl. administrative and procedural support, specific fee reductions, etc.)	▪ Tax incentives "The Orphan Drug Tax Credit": 25% tax credits for expenses engaged during clinical trials[3] ▪ "Waiver of Prescription Drug User Fees": orphan drug products exempt from the usual new drug application fees charged by the FDA ▪ "Orphan Products Grants Program": funding for development of promising orphan products ▪ "Rare Pediatric Disease Priority Review Vouchers": voucher to receive a priority review for a different drug[4]
Access	▪ Centralized authorization procedure: a single application to the EMA (opinion & decision valid in all EU Member States) ▪ Designated orphan medicines eligible for conditional marketing authorization: allowed to be administered to patients under compassionate use[2] ▪ Global benefits: EMA & FDA developed common procedures for applying for orphan designation in the EU/USA	▪ Eligibility of the drug approval process to fast-track procedure for evaluation by the FDA ▪ FDA assistance and guidance in the design of an overall drug development plan ▪ Possible availability of orphan drug to patients before gaining market approval under specific conditions[5]
Marketing	▪ 10 years of marketing exclusivity from EMA approval ▪ Pediatric medicines eligible for 2 additional years of marketing exclusivity	▪ 7 years of marketing exclusivity from FDA approval ▪ 6 additional months of exclusivity if pediatric indication

Sources: EMA – FDA – Smart Pharma Consulting analyses

[1] Small & medium enterprises – [2] Allows the use of an unauthorized medicine outside a clinical study – [3] After the obtention of an orphan drug designation – [4] After receiving the approval for a rare pediatric disease drug – [5] Drug is intended for the treatment of a serious life-threatening disease, no alternative drug is available, and product is in the process of clinical trials and an active phase of marketing approval

The most important challenges faced in the orphan drugs development are the small size of patient populations and the lack of knowledge and awareness of related rare diseases

R&D challenges

Diseases knowledge and awareness

- **Complex diseases**, with a **lack of** widespread **knowledge,** incl. among medical experts
- **Lack of background data** (e.g., treatment pathway, patient subgroups, epidemiology)
- **Delays to diagnosis**, preventing early clinical trial enrolment, and potentially leading to missed therapeutic windows
- **Difficulties to define unmet needs**, due to diagnosis challenges and patient heterogeneity
- Low proportion of patients in each market, potentially making these diseases a **lower priority for regulators and payers**

Clinical evidence

- **Difficult trial design** (comparators, endpoints, outcomes, etc.) and **enrolment**, far from double-blinded randomized clinical trial standards, especially due to:
  - **Small** and **geographically dispersed populations**
  - High **disease burden** and **significant medical challenges**
- **High level of pediatric populations**, leading to several issues (e.g., dose, endpoints and outcomes selection, informed consent, logistics and scheduling)
- Difficult **demonstration of statistically significant impacts** on a mortality outcome, due to the rarity of these diseases, and their long-term evolution

Implications for pharma companies

- **Closely collaborate** with academics, clinicians, PAGs and health authorities to **overcome** the many **hurdles** to **develop orphan drugs**
- Focus on **epidemiological research**[1] to identify possible **new paths of drug developments**
- Ensure an **early collaboration** with **agencies** to get regulatory guidance, protocol design assistance
- Whenever RCTs[2] cannot be applied, due to the small number of patients, **adaptative trials designs**[3] and **new measures for efficacy** should be considered
- **Communicate** about **rare diseases** to patients, PAGs[4], general public and physicians, and **collaborate** with centers of excellence to **recruit patients**
- **Develop patient registries** and generate **RWE data** to **complete** data generated through clinical studies
- Precisely **define patients** with **biomarkers**, **genetic** markers, **specific digital tools** and **artificial Intelligence**
- Overcome **barriers to diagnosis** with appropriate **diagnostic tools**

Sources: Office of Health Economics (2018) – "The balancing act of orphan drug pricing", The Lancet (2017) –Evidera-PPD The Evidence Forum (2020 & 2021) – Mtech Access (2021) – "Six ways to help drugs for rare diseases take off", BCG (2019) – "Orphan drug clinical development ", Therapies 2020 by O. Blin et al – Smart Pharma Consulting analyses

[1] That is: occurrence of the disease, underlying pathophysiology, burden of the disease for patients and care givers, impact on the health system, etc. – [2] Randomized controlled trials – [3] Such as: single-patient (n-of-1) trials, adaptative randomization methods (e.g., play the winner, drop the loser designs) – [4] Patient advocacy groups

Difficulties to demonstrate clinical benefits and cost-effectiveness of orphan drugs are the main challenges faced in terms of registration and pricing

Registration and Pricing challenges

Registration

- Same assessment process as a regular drug, causing a **difficult demonstration of clinical benefit** due to the:
  - **Lack of patients** to conduct clinical trials
  - **Lack of** established **active comparators** and **well-defined clinical end-points**, compounded by the usually short follow-up duration of studies
- **Lack of knowledge** about rare diseases among medical experts and regulatory agencies

Pricing

- **Difficult demonstration of cost-effectiveness**[1] due to:
  - Lack of patients, knowledge, comparators, and defined clinical end-points
  - Geographical **differences between HTA**[2] **bodies** in their evidence requirements
  - Unfavorable ICER[3], above typical willingness-to-pay thresholds
- Debate about **orphan drug premium prices**:
  - **Major burden on the healthcare systems**, yet under financial pressure
  - **Expensive products**, unaffordable by many patients
  - **Several costs** are **lower** than for **non-orphan drug** due to smaller patient number
  - **Budget capping** imposed **for orphan drugs** by certain governments (e.g., France)
- **Increasing price pressure** due to post **Covid-19** healthcare **budget deficits**

Implications for pharma companies

- **Collaborate closely** with **registration** and **HTA agencies** to ensure **alignment** re. **clinical development** and **medico-economic evaluation**, respectively
- Identify **surrogate end-points** w/ **proven clinical utility**
- Design and implement post-launch **real world evidence data collection**
- **Leverage** emerging **data** sets and **AI** to **substantiate** the **long-term value** of therapies
- Develop disease-specific **PROMs**[4] **and PREMs**[5]**,** and **health-related quality of life tools**
- **Involve market access** department in **decision process**, at an early stage of the drug development
- Strengthen **medico-economics** and **cost-effectiveness models**
- **Propose**, with the support of PAGs, physicians, KOLs, centers of excellence, etc., **risk sharing models** (clinical outcome-based, financial outcome-based, indication-based) or **any other win-win approach**

Sources: Berdud et al, "Establishing a reasonable price for an orphan drug" (2020) – Office of Health Economics (2018) – Pharmaceutical Technology (2020) – "The balancing act of orphan drug pricing", The Lancet (2017) – Evidera-PPD The Evidence Forum (2020 & 2021) – Mtech Access (2021) – "Six ways to help drugs for rare diseases take off", BCG (2019) – Smart Pharma Consulting analyses

[1] Especially for one-shot therapies like CAR-T cells – [2] Health Technology Assessment – [3] Incremental cost-effectiveness ratio – [4] Patient-Reported Outcomes Measures – [5] Patient Reported Experience Measures

The success in the orphan drugs market depends on the capacity of pharma companies to develop creative and hands-on approaches focused on HCPs, patients and caregivers needs

Medico-marketing challenges

Each rare disease is specific	Rare diseases are under-diagnosed	Patients are strongly engaged

Implications for pharma companies

- Get to **know the market**:
  - What is the **prevalence** and/or the **incidence**?
  - Are there international or national **PAGs**[1]?
  - Is there a **patient's network**?
  - Are there any decent **sources of information** available to these patients?
  - What is the **patient journey** from first symptoms to diagnosis?
  - How many and which **types of physicians** might patients see in search for a treatment?
  - How many **treatment centers** are there? And where?
  - What are the **barriers** patients might face in accessing treatment?
- Adopt a **holistic approach** by developing close relationships **with** all the involved **stakeholders**[2]

- **Beyond** building **relationships** with **patients** and **PAGs**, pharma companies should use every piece of information that might help them **identify** patients who experience many of the typical **symptoms** of the disease but that **have not been diagnosed**
- Marketers should **map** the **diagnostic patient journey** to identify points in care management to educate **physicians** on their **patient profile**
- If the **diagnostic rate** is **low**, pharma companies could distribute **free diagnostic tests**
- Other **disease awareness initiatives** could also be considered:
  - **Medical congresses**
  - **Forums** and **websites** to share data
  - Quality **interactions** with **medical community**
  - **Early access** programs

- A **tailor-made approach** – around & beyond the drug – must be proposed as unmet needs of **stakeholder**' involved in **rare diseases** are high
- Thus, they should **co-create services** such as:
  - **Information** about patients' **condition** and current **treatment options**
  - **Connection** with **KOLs** / **specialists**
  - Building of the **medical community**
  - Development of **early access programs**
- Information provided by pharma companies must be **comprehensive** and **address** the following **topics**:
  - Therapy access
  - Patients-assistance programs
  - Clinical nursing support
  - Disease education
  - Lifestyle management
- These supports may be **provided** directly or indirectly, depending on **regulatory constraints**

Sources: "How to successfully launch a rare disease drug", McKinsey (2018) – "A nuanced message: marketing to the rare diseases community", Pharma Voice (2017) – Smart Pharma Consulting analyses

[1] Patient advocacy groups – [2] Payers, policy markers, HCPs, PAGs, patients, care givers, etc.

To succeed in the orphan drugs market, pharma companies should work cross-functionally, have close relationships with various stakeholders[1], generate and disseminate real-world evidence

Organizational recommendations

Recommendations	Description	Rationale
1 Embed a culture of **cross-functional collaboration**	▪ Ensure a very strong and constant interactivity between medical, marketing and sales departments	▪ Join the dots between the pieces of information accrued by medical and commercial field representatives and thus generate patients' insights required to craft brand strategy ▪ Avoid inconsistency of messages
2 **Size** field teams accurately and **deploy** them **early**	▪ Give priority to small teams of high-level professionals strongly involved and who will be able to show flexibility and vitality	▪ As a rule, field teams for rare diseases are smaller than those for conventional treatments and very engaged in the disease they are concerned by ▪ Sizing depends on 5 key factors: disease, regulation, patient journey, market access situation and competitive level
3 Excel at generating and disseminating **real-world evidence**	▪ Work on case reports at national and international levels	▪ Impossibility of conducting large cohort studies because of low prevalence of rare diseases ▪ Importance of having a permanent international exhibition in order to favor consensus conferences and consolidate position before new market players' entry

Sources: Smart Pharma Consulting analyses

[1] *Payers, policy markers, HCPs, PAGs, patients, care givers, etc.*

The orphan drugs market will remain highly attractive despite the risks due to increasing healthcare budget deficits and sky-rocketing costs per patient of orphan drugs, especially for gene therapies[1]

Orphan drugs market features

- Size: USD ~156 B in 2021
  (11% of the total pharma market)
- Growth: 2020-2024 GAGR: ~11.6%
  (2.6 times > than the total pharma market)
- Profitability: 2020-2024 EBITDA: ~41%
  (vs. ~30% for the non-orphan RX-bound drugs)

- Orphan drugs weight on average 20% of top 20 pharma companies sales in 2020
- The top 10 players should account for 51% of the orphan drugs market in 2024
- Rare diseases require a strong engagement of medico-marketing and sales teams
- Clinical benefits and cost-effectiveness are difficult to demonstrate due to lack of adapted methodologies
- US and European regulatory agencies have boosted the market development through various incentives

Sources: Smart Pharma Consulting analyses

[1] Zolgensma (onasemnogene abeparvovec) is a one-time treatment for spinal muscular atrophy sold at the price of USD 2.1 million

Pharma companies operating on the orphan drugs market should favor M&As, adopt a "start-up spirit" and offer their stakeholders[1] second to none services, around and beyond their drugs

Key success factors on the orphan drugs market

Strategy

- Pharma companies strategically engaged on the orphan drugs market should **intent to generate 30%** or more of **their sales** (i.e., 37% of their profits), within **5 to 6 years**, from this market segment
- To grow on the orphan drugs market, pharma companies should **favor M&A deals**, rather than organic development, to **save time** and **better control R&D hazards**
- Pharma companies should **prioritize their efforts** on the **US** market which represents **~40% of the total orphan market sales**, and **~85%** of its corresponding **profits**

Tactics

- **Close interactions** with academics, clinicians, PAGs and health authorities **are imperative** to **successfully develop orphan drugs**, due to the poor disease understanding and the lack of patients
- Pharma companies must **collaborate** with **registration** and **HTA agencies** at a very **early stage** of their drug development to agree on clinical protocols and medico-economic evaluation, respectively
- Medico-marketing and sales teams should **focus** on **generating** and **disseminating data**, while **adopting** a **holistic approach** by offering specific **around / beyond** the **drug services** for HCPs and patients

Organization

- **Rare diseases** requiring from pharma companies a **strong engagement** with various key stakeholders …
- … it is essential to **preserve** the rare disease **skills** and **culture** of the **acquired company** by giving it a **certain degree of autonomy**[2], for a period of **one to several years**[3], as AstraZeneca did with Alexion
- Organization should **rely on highly professionals**, very much **customer-focused**, having a **real dedication** for **rare diseases**
- The **structure** should remain **lean** and the **processes simple**
- **Cross-functional** operating mode and **excellence** in **execution** should be a **cultural priority** to **ensure operational efficiency**

Sources: Smart Pharma Consulting analyses

[1] Payers, policy markers, HCPs, PAGs, patients, care givers, etc. – [2] Ideally for the R&D, medico-marketing and sales activities. Other functions such as regulatory and governmental affairs, market access, finance, human resources, legal affairs, etc. should be shared – [3] The ideal duration will depend on the existing portfolio and on the previous experience of the acquirer in the orphan drugs market

Smart Pharma
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- The Market Insights Series has in common to:
  - Be well-documented with recent facts and figures
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  - Determine implications for key stakeholders
- Each issue is designed to be read in 15 to 20 minutes and not to exceed 25 pages

What future for orphan drugs?

Strategic challenges for pharma companies

This paper gives an overview of the worldwide orphan drugs market and is structured as follows:

- Definition of rare diseases and orphan drugs concepts
- Key figures on market structure, dynamics
- Analysis of pure market players profitability
- Identification of key challenges for pharma companies
- Key learnings and recommendations

Smart Pharma Consulting Editions

- Besides our consulting activities which take 85% of our time, we are strongly engaged in sharing our knowledge and thoughts through:
  - Our teaching activities in advanced masters (ESSEC B-school, Paris Faculty of Pharmacy)
  - Training activities for pharma executives
  - The publication of articles, booklets, books and expert reports
- Our publications can be downloaded from our website:
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    3. Market Access
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- Our research activities in pharma business management and our consulting activities have shown to be highly synergistic
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Best regards

Jean-Michel Peny

1, rue Houdart de Lamotte – 75015 Paris – France • Tel.: +33 6 11 96 33 78 • E-mail: jmpeny@smart-pharma.com • Website: www.smart-pharma.com