

Looking for and Quantifying VALUE in Rare Diseases

and reducing uncertainty at the same time

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groupH

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Rare diseases present a number of challenges for manufacturers absent in more prevalent conditions



The list can be long, just a few examples ...

- Epidemiology patchy or absent
- Small # of experts
- No off-the-shelf reports
- No awareness among doctors and payers
- No or unreliable audit data
- Efficacy endpoints uncertain
- Patient segmentation uncertain

Which approach can you take?

So, for sake of argument:

Imagine the responsibility of choosing a life partner at some point in your life - what kind of Market Research could you undertake prior to decision making?

Get 10 of your best friends rate your candidate between 1 – 10?

You do a **BIG Conjoint** to understand the trade offs between your candidate and the ideal candidate?

100 experts (all screened, 50% >20 years married) look at your *value proposition* and give it their *estimated chance of success*?



Surely, the answer is all about **Behavioural Science** and system 1 and system 2 decision making and you go down this route?

Conduct research using a **novel methodology** purportedly *perfect* for this situation that simulates how your partner would get on with your family and friends

You compare yourself to **5 other analogue couples**, learn from the problems they had and develop some actionable insights?

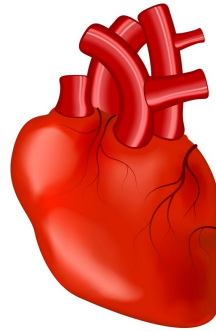
Main issues with these approaches (besides from this being unromantic!)

- There is only that much you can objectively measure – much is due to experience
- Everyone has a different idea of what they value in another person
- No approach on its own is likely to be useful or give you ‘the answer’

The analogy is not perfect of course. How would agencies look at product candidates **you** bring to the table – what would they do?

Value

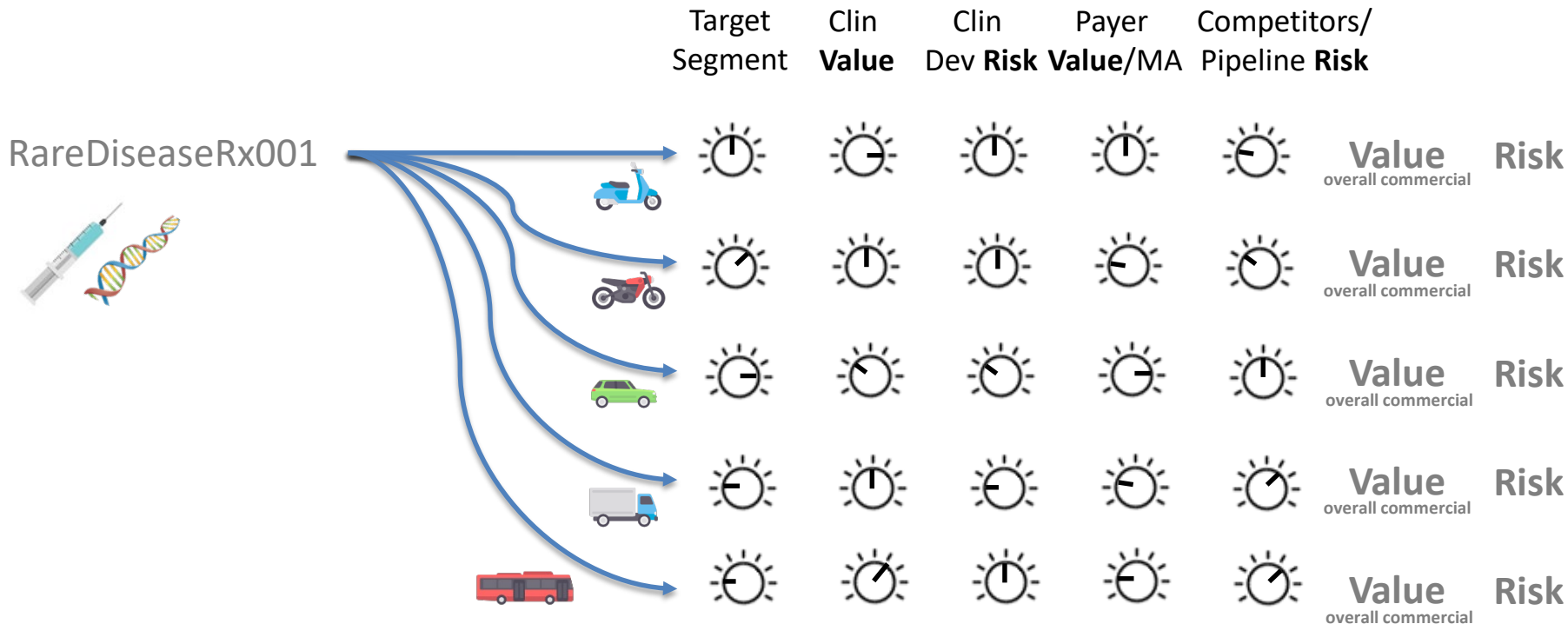
Identify / Quantify / Increase



Risk

Identify / Quantify / Reduce

For a given opportunity RareDiseaseRx001 you end up with a number of different development options: a trade off between value and risk



When we talk about **value** what do we mean?

And exactly **value** for **whom**?



Payers

“Relative efficacy, safety and tolerability compared to existing treatments”

+

“Access restrictions, Budget impact, Payment by Result and Patient Access Programs, direct Healthcare System savings”



Doctor / Regulator

“Absolute Efficacy, Safety and Tolerability” in RCT circumstances

+

Better QoL

BUT doctors have also an important role to play in validating patient segments and clinical trial endpoints



Patient

“Cure, symptom relief, better QoL and impact on activities of daily living for patient and family”

+

Help validate Activities of Daily (ADL) Living for regulators and payers, PRO - Patient Reported Outcome measures



Investor

“ROI, NPV, Peak Sales”



Assessor

“Different HTA methods such as relative efficacy scores and rankings, cost per QALY, EF, HEOR models”

Value and Reimbursement in Rare Diseases from an EU payer point of view

- In your experience, what are the main differences between reimbursement decisions for novel treatments for Rare Diseases different compared to more prevalent indications?
- Is 'Payer Value' the same for Rare Diseases and for more prevalent indications?
- What does this mean for the manufacturer generating data and preparing for reimbursement in your country?
- If you could communicate a message to anyone developing treatments in rare diseases how to positively influence their chances of reimbursement:
 - What should they stop doing?
 - What should they start doing?
 - What should they continue doing?



Bruno Falissard

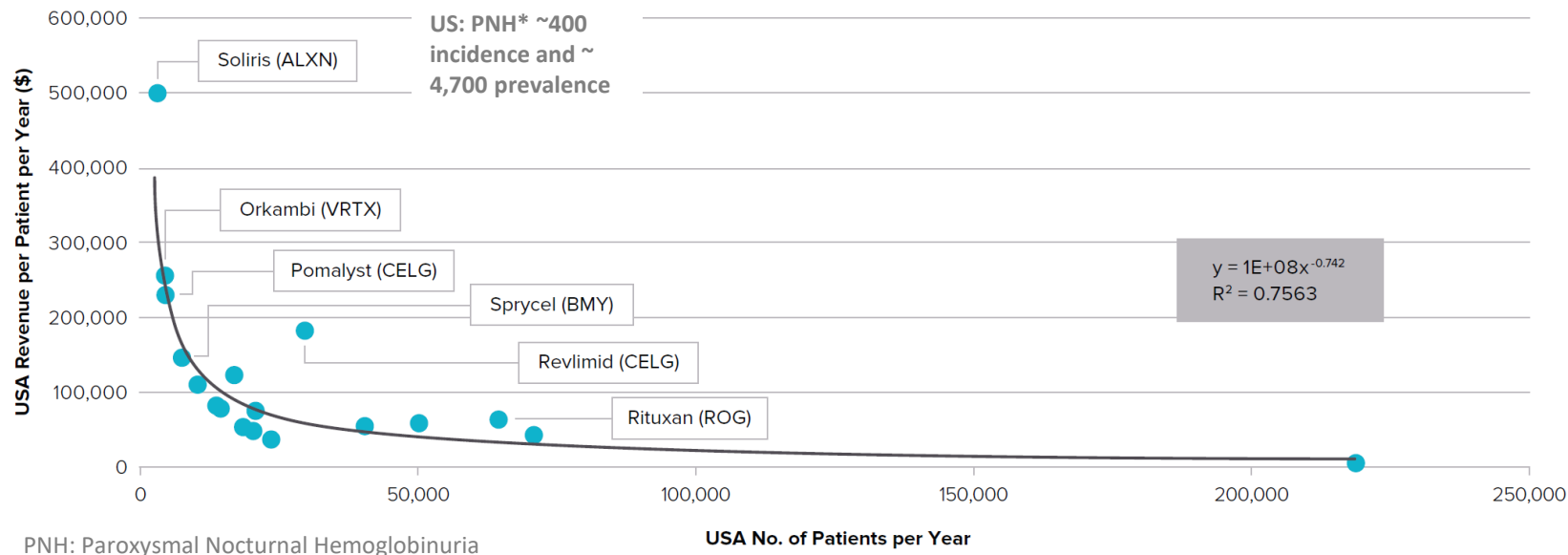


- Former Member of the Transparency Commission at HAS
- Psychiatrist and Biostatistician
- Head of Research Unit Inserm U669 on Eating Disorders in Teenagers

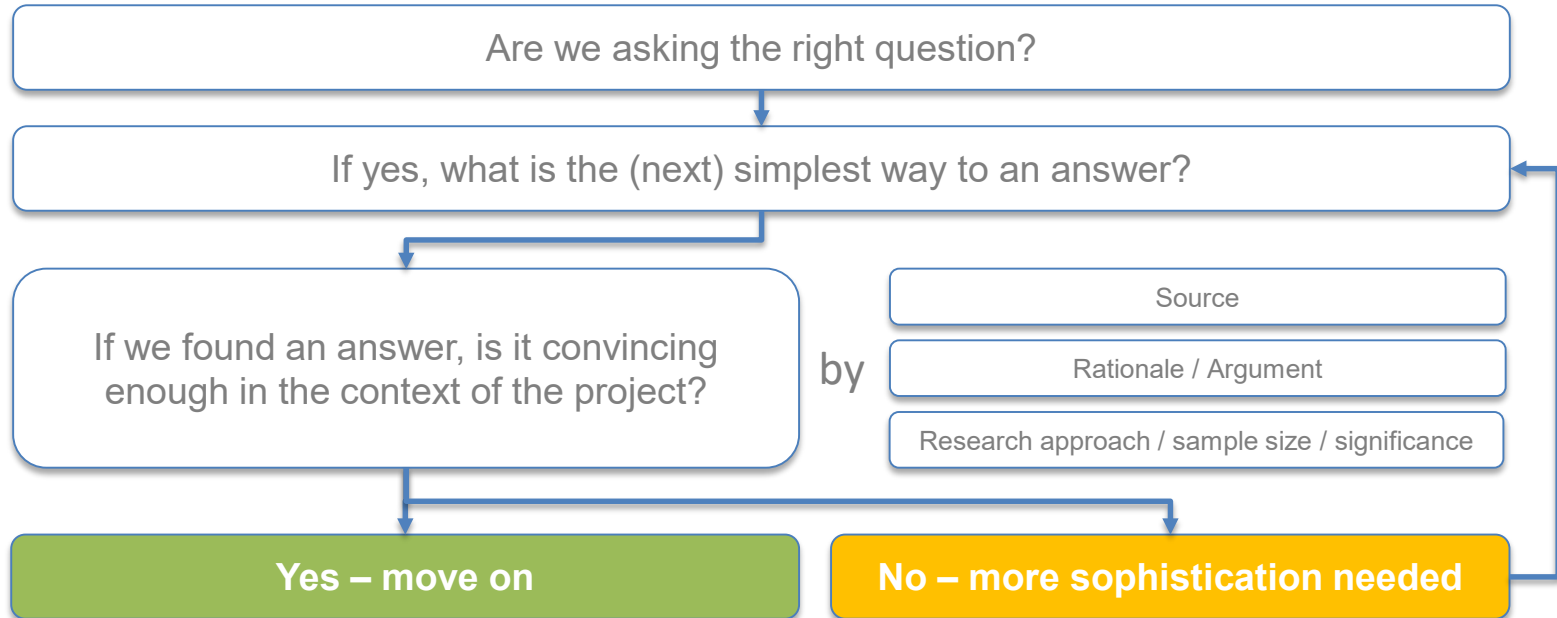
Payers reflect the rarity of a condition in its reimbursement - but rarity on its own does not guarantee favourable reimbursement

Top 20 USA Orphan Drugs in 2017 by Sales; Revenue per Patient Vs. No. of Patients Treated

Source: EvaluatePharma[®] May 2018

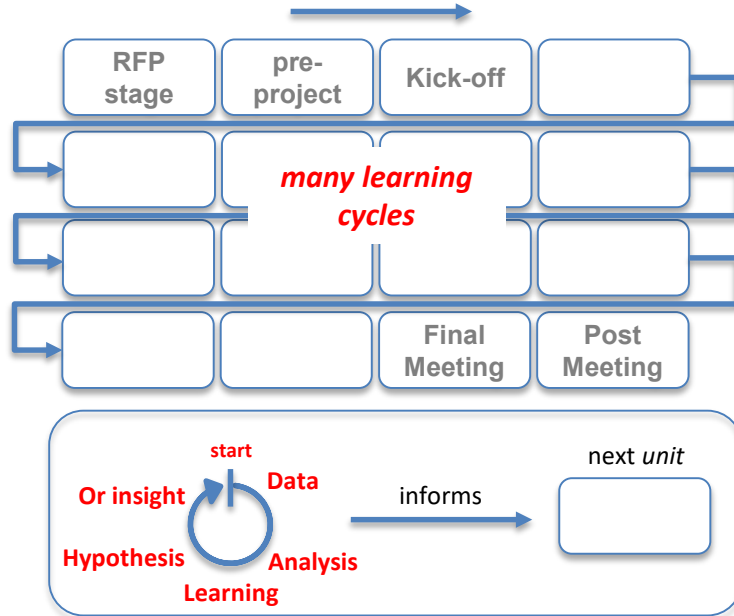


There is another type of value: **value generated by a project team** during any given project with a fixed amount of resources and time

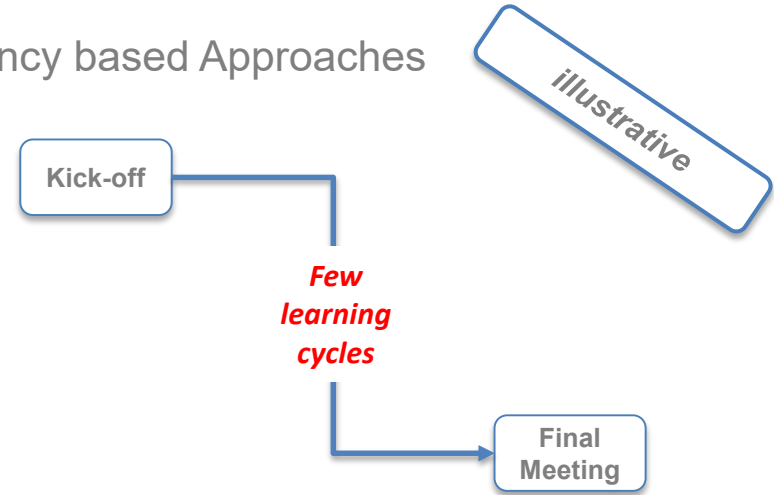


If we are happy with the strength of an argument or rationale, this gives us the chance to move on and solve another question

Rationale based vs. Process/Consistency based Approaches

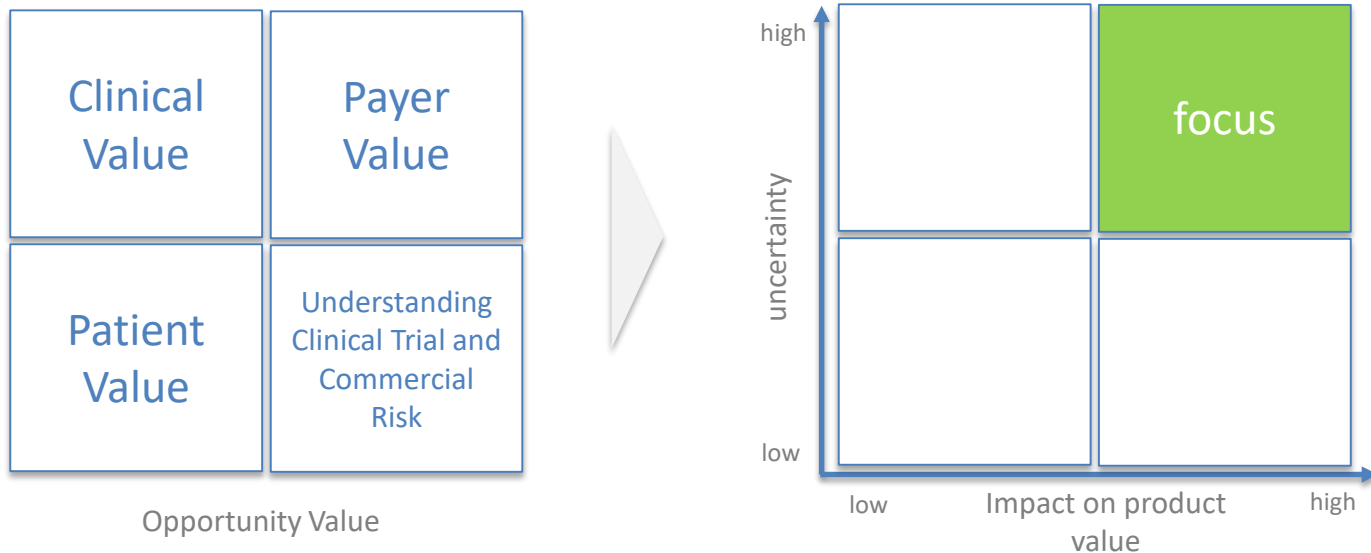


Vs.

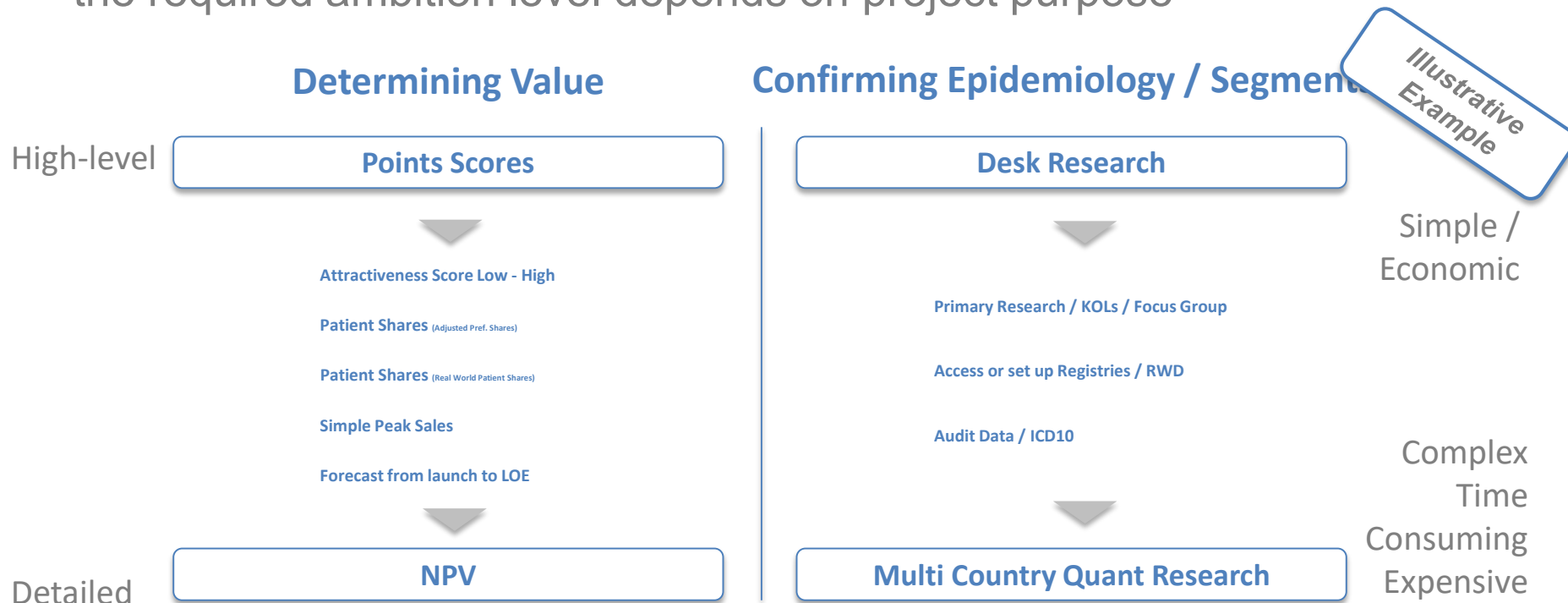


Adding **value** in a project context also means keeping the focus on high-uncertainty / high impact topics

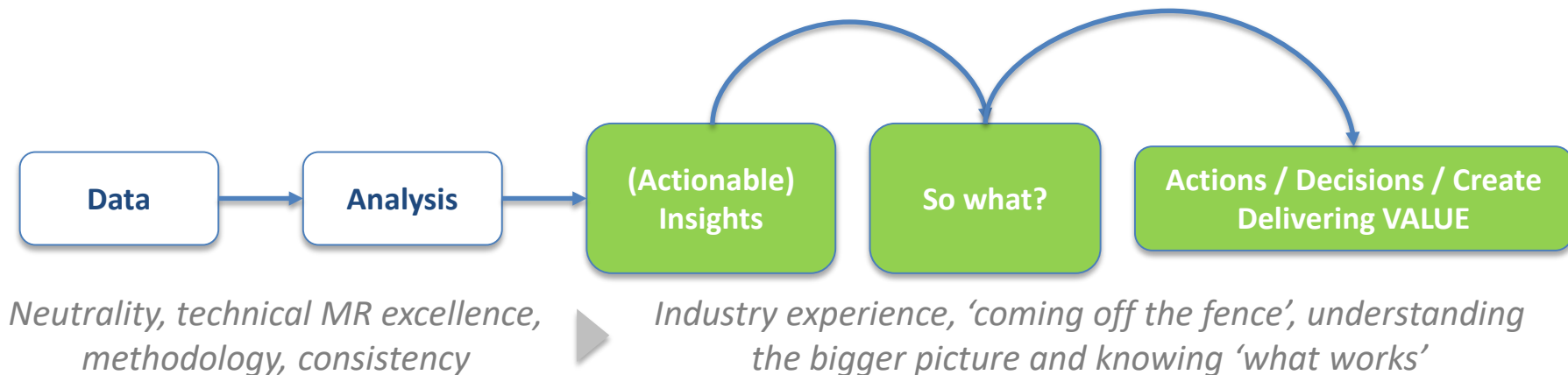
Focus on High Uncertainty / High Impact



For determining value or for work on epidemiology and segmentation, the required ambition level depends on project purpose



How to address some of the issues in Rare Diseases through emphasising *Consulting* techniques in the project



"It may well be that in Rare Diseases lack of data, or of KOL consensus leads to a lack of or non-consensus insights. In this case the So What? means that the project team builds/drafts whatever is lacking and doing this in a convincing and logic way" (e.g. patient segments, endpoints, TPPs)

We ran a short survey asking 20 questions to find out what differentiates Market Research from Consulting

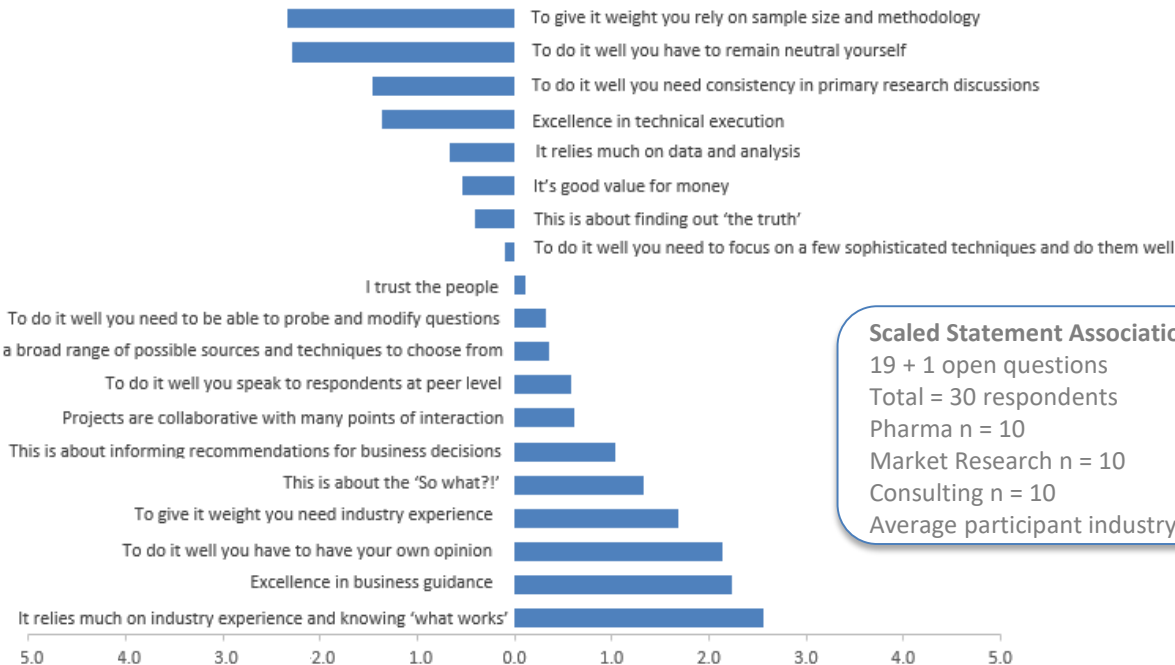
Market Research

Average Ratings from All Participants (n = 30)

More associated with
Market Research

Associated with
Both

More associated
with Consulting



Scaled Statement Association Survey

19 + 1 open questions

Total = 30 respondents

Pharma n = 10

Market Research n = 10

Consulting n = 10

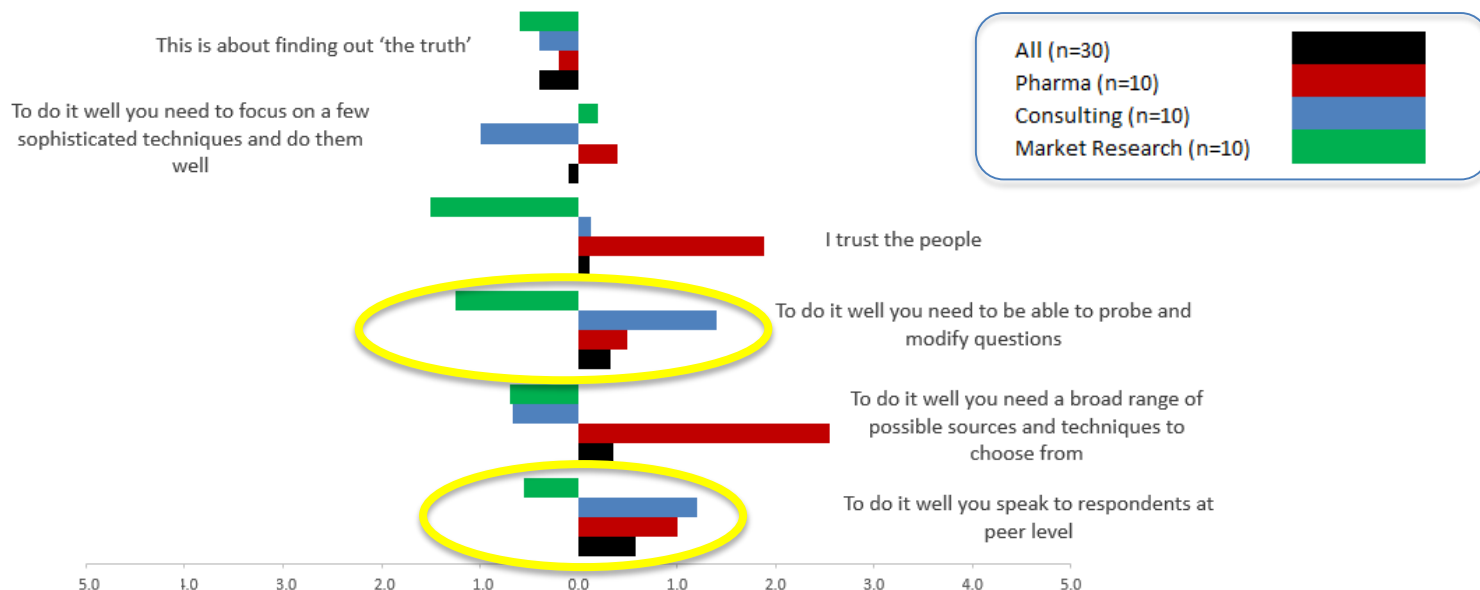
Average participant industry experience = 18.2y

Consulting

While consulting and MR respondent feedback was similar on most questions, in some areas there were differences in opinion

Market Research

Ratings by Respondent Background (n = 30)

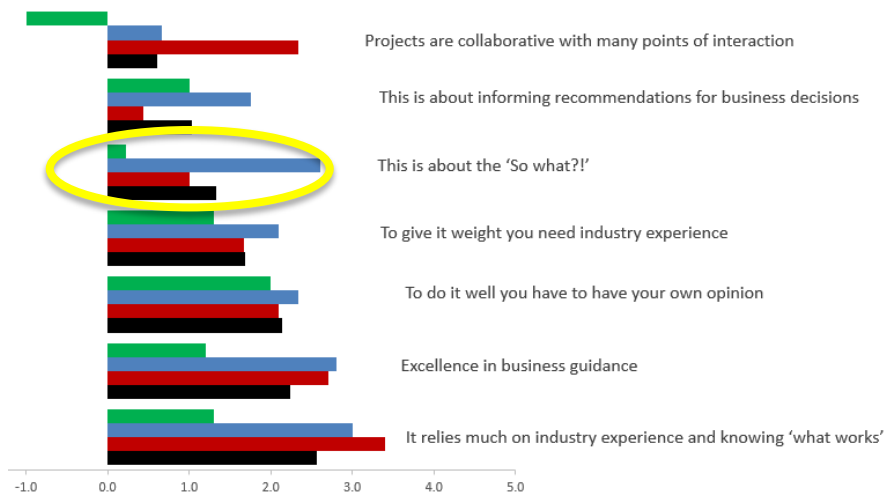


Consulting

Views on the 'So what?' also diverged when comparing MR with consultancy respondents

Ratings by Respondent Background (n = 30)

MR



Consulting

MR



Consulting

All (n=30)
Pharma (n=10)
Consulting (n=10)
Market Research (n=10)



Source: groupH research & analysis, more details available upon request:

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A majority of respondents thought there was a difference between MR and Consulting today – some underlined the synergies, others pointed to project purpose driving agency or team choice

Typical Views by **Pharma** Respondents

“...Consulting can use market research as an input, but it is more about business problem identification and solution identification..., not just customer questions.” – Large EU Pharma, Global Forecasting, >22years Industry Experience

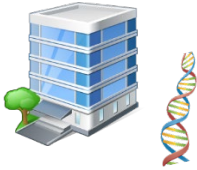
“Market research is conducting a study to address a particular issue with a particular methodology. Consulting requires adding in knowledge from multiple sources (primary or secondary) to create a solution. Most of your questions are not either/or ... ” – US Biotech, Director Product Strategy & Commercial Planning, >20 years Experience

“... MR, to me, is more technical and focused - it's about digging deep for insights, such as underlying behavioural drivers and barriers, making sense of data by connecting the dots to find patterns or disconnects ...

... Consulting, I see more as bigger picture thought partnership for development of strategic options. MR delivers the foundation (insights) and assessments (value measures), consulting fuses these outputs into meaningful strategic options.” – Large EU Pharma, Director Scientific Communications, >15 years industry experience

Source: groupH research & analysis, more details from other respondent groups available upon request:

Case study 1



Biotech developing novel treatments for rare ophthalmology indications



Among the diseases studied some are orphan such as Retinitis Pigmentosa (RP). RP is very heterogeneous in symptoms and course of disease for any individual patient

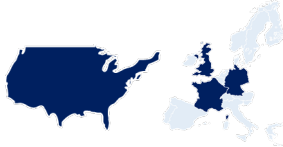


Case study 1

No existing Rx market, no approved SoC, no effective treatments, retinal implants approved and in development, Luxturna (Sparks Therapeutics) approved Dec. 2017 for RPE65 population (<1% of RP)



To understand the commercial value and associated uncertainties in RP to inform clinical development



US and key-EU markets



4-step approach relied heavily on qualitative PMR with doctors and payers + 2ndMR in two phases to support TPP scenarios and commercial value models

Segmentation of Retinitis Pigmentosa (RP) based on WHO visual impairment categories

Aspect / Segment	Line	0	1	2	3	4	5
WHO categories	1	0	1	2	3	4	5
Category		Mild/no visual impairment	Moderate visual impairment	Severe visual impairment	Blindness	Blindness	Blindness
BCVA in the better eye	2	20/70 or better	<70/200 to 20/200	<20/200 to 20/400	<20/400 to 20/1200	<20/1200 to LP	NLP
Visual angle in the better eye	3						
Prevalent RP patients	4						
% of prevalent RP patients (total 100%)							
'Incident' patients becoming legally blind in a given year	5						
% ultimately progressing to (total 100%)							
Time from legally blind to progression	6						



Example for a **rationale based** patient segmentation and a short learning cycle

Case study 1

Interview Stimulus Material – RP Segmentation

Segmentation of Retinitis Pigmentosa (RP) with focus on later stage disease

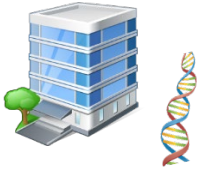


“The project team moved from one original draft patient segmentation to a final segmentation after only 3 discussions with KOL RP ophthalmologists and subsequently validated the new approach in a second PMR step with >10 RP KOLs”

Legally blind (US): <20/200 and/or <20°									
Aspect / Segment	Line	0	1	2	3	4A	4B	4C	5
Segment characteristics	1	20° or better	<20° - 10°	>10°-5°	<5°				
Typical remaining VF									
Typical BCVA range	2				? to CF	CF (20/1000 – 20/2000)	HM (20/2500 – 20/5000)	LP	NLP
Typical other aspects	3								
Proportion among prevalent legally blind* RP patients (total 100%)	4								
Typical time from becoming legally blind to progress to segment	5								
% of legally blind* ultimately progressing to Segment (total 100%)	6								

NOTE: (*) Legal blindness according to definition in your country

Case study 2



Biotech at pre-clinical stage developing novel peptides for the treatment of auto-immune diseases exhibiting too high levels of pathogenic IgG in circulation

>150 classified autoimmune disorders

~20 indications where IgG plays a mayor role in disease ethiology

Many autoimmune indications classified as Rare Disease or orphan

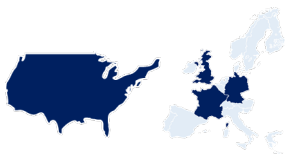


Case study 2

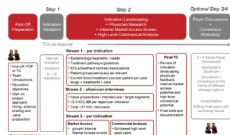
Existing market: Oral corticosteroids, IVIG, Plasmapheresis and pipelines, some more and some less busy, depending on indication.



To choose a total of top-6 most attractive indications for potential clinical development with a focus on commercial value and associated risks and uncertainties



US and key-EU markets



3-step approach relying on indication landscaping and treatment algorithms based on agreed attractiveness criteria, 37 discussions with expert physicians in 2 phases taking a value proposition to TPP stage, performing a Market Access screen **without** payer PMR using a modified and applied version of MAPPI and peak-sales

6 high potential indications have been taken forward to Phase 2

Consensus indications in **green**

Case study 2

	Dermatology		En do	Hematology		Nephrology				Neurology				Rheum.	TP	
Epidemiology / Target Popul.																
Unmet Needs																
Competition / Pipeline																
Reaction to MOA / Concept																
Anticipated Ease of PoC Trials																
Going for the Indication, groupH consensus																

C = existing (unquantified) prevalence pool / chronic maintenance treatments in majority of patients
 = IVIG 1st or 2nd line
 = IVIG few patients

Very High High Medium Low Very Low

High Level Peak Sales Potential – Pemphigus Vulgaris

Case study 2


		Epidemiology PV (2030)***				Launch Date	Ex-man. Price per patient per treatment	Peak Share (penetration potential)	Peak Sales, 2030, €m
	Positioning	US		EU Top-5			*9 month **12 mon		
Pemphigus Vulgaris	Initial Use	Incidence 2,516 all	Treated, mod/severe 1,698	Incidence 2,339 all	Treated, mod/severe 1,579	2025	US: €21,951* EU5: €13,125*	US: 50% EU5: 30%	US: 1m EU5: 4m
	Relapsing ~70%****		1,189		1,105		US: €21,951* EU5: €13,125*	US: 50% EU5: 30%	US: 13m EU5: 4m
	Maintenance (50 x incidence) ****	Maintenance 125,790 all		Maintenance 116,957 all			US: €29,268** EU5: €17,500**	US: 20% EU5: 10%	US: 1m EU5: 4m
Upsides	Higher maintenance penetration High incidence geographies such as Israel, RoW Other dermatological blistering diseases						Total Peak Sales Potential, €m		€

- Peak penetration assumed to be achieved after 5 years due to magnitude of unmet need in PV
- Peak penetration assumed relatively high due to ease of administration and anticipated relative lack of competition
- Competitive threat can't easily be estimated at this point but assumed that xxx is one of two competitors in this market, in maintenance generic rituximab and antimetabolites are also likely to retain a fair share for patients who tolerate it well
- Use of xxx in other dermatology autoimmune indications remains an upside
- Patient registries with more exact US patient numbers could be available from Victoria Werth at UPenn Dermatology and/or Pemphigus Foundation
<http://www.pemphigus.org/research/pemphigus-pemphigoid-registry/>

Source: groupH research & analysis, ***Incidence assumed at 0.7/100,000 (BMJ 2017;357) in US/EU, Maintenance = 50 x newly diagnosed from groupH primary research, assumed US Population 2030: 359,402,194 (US Census.gov), EU5 Population 2030: 334,163,024, US PV Prevalence = 136,654, Incidence: 4,672, EU Prevalence: 127,058, Incidence: 4,344, assume: 90% diagnosed/treated, mod/severe = 75%, exchange rates used: 06/03/18 €/US\$ = 1.23, GBP/€ = 1.12, ****Source: groupH research & analysis (PV KOL physician estimates), see appendix for more details on assumption maintenance = 50 x incidence

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Insights from our work in Rare Diseases

- Understanding differences in **value** for different Rare Diseases stakeholders
 - **Flexible process**
 - **Broad range of sources and triangulation**
 - **Market Research AND Consulting techniques depending on project purpose**
 - **No one-size-fits-all**, it all depends on...
- 
- **Peer-level conversations** with doctors and payers that allow to challenge held beliefs or assumptions
 - **Coding of experience** and using payer models simulating the real world can be used in the early stages

Thank you!

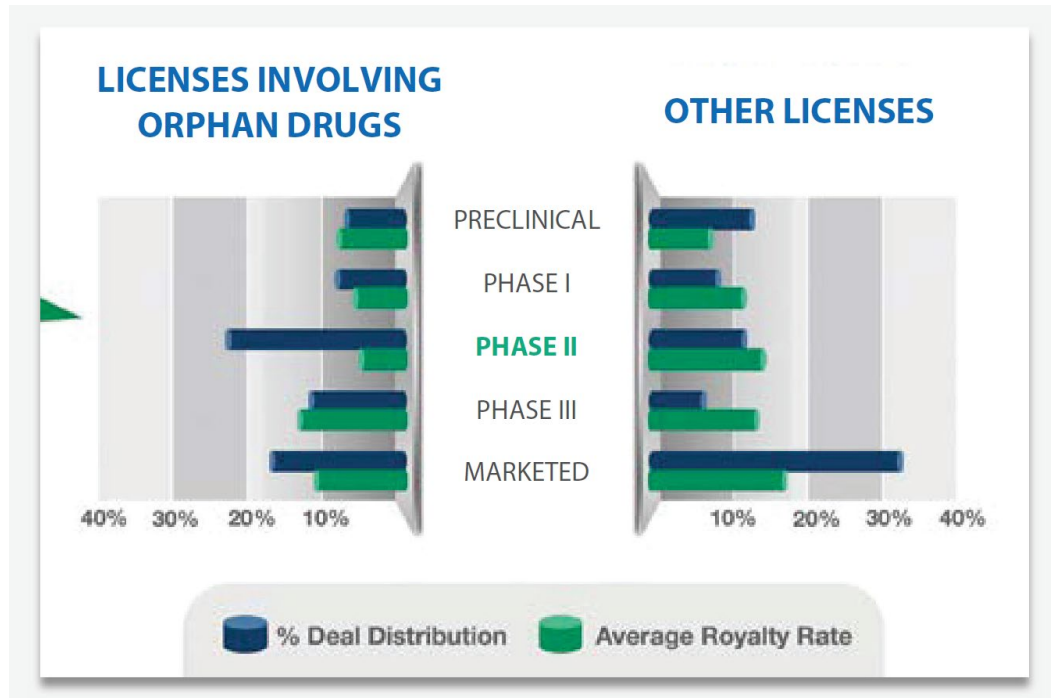
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Appendix

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Appendix

Source: Medtrack / Informa, The Art of the Deal,
Licensing Trends in Orphan Drugs



Appendix

Rare disease patient populations are defined in law as:

- USA: <200,000 patients (<6.37 in 10,000, based on US population of 314m)
- EU: <5 in 10,000 (<250,000 patients, based on EU population of 514m)
- Japan: <50,000 patients (<4 in 10,000 based on Japan population of 128m)

Financial incentives by law include

Orphan drug exclusivity

- During the period of marketing exclusivity, the regulatory bodies are barred from approving the same
- product for the same orphan indication. A product holding several separate orphan designations for
- different indications can have several separate market exclusivities, which can run concurrently.
- USA: Seven years of marketing exclusivity from approval.
- EU: Ten years of marketing exclusivity from approval.
- Japan: Ten years registration validity period (also known as re-examination period).

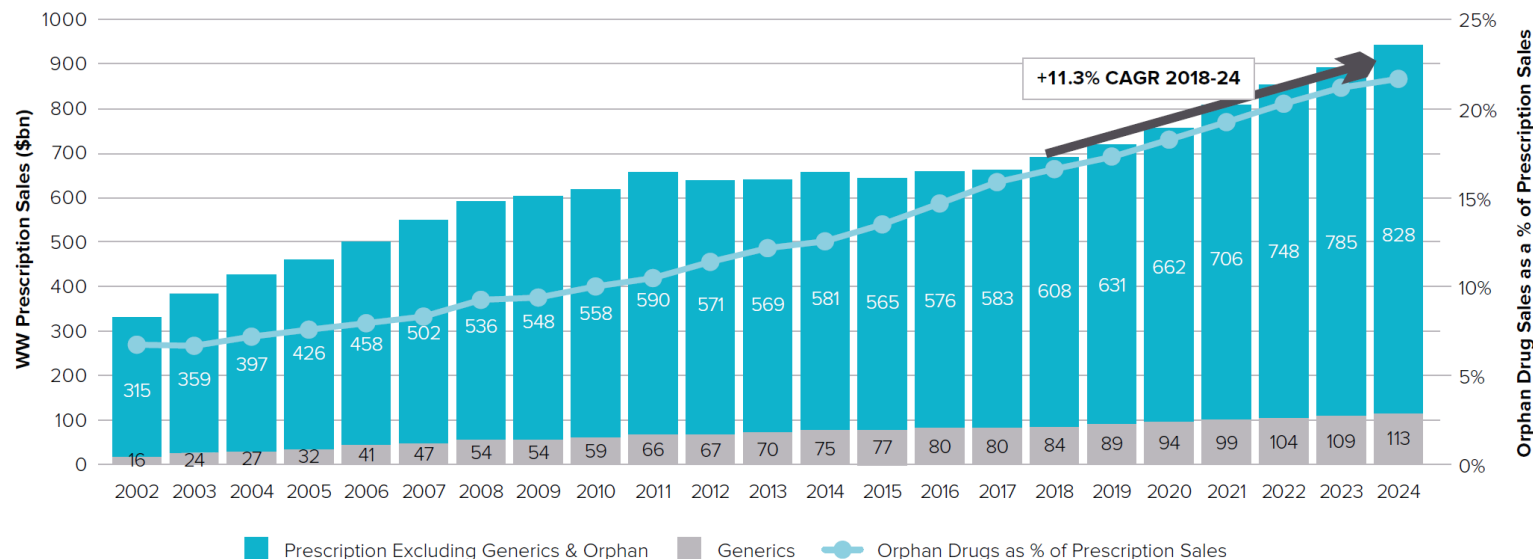
Reduced R&D costs

- USA: 50% Tax Credit on R&D Cost (owing to new tax legislation, is expected to decrease to 25%).
- USA: R&D Grants for Phase I to Phase III Clinical Trials.
- USA: User fees waived (FFDCA Section 526: Company WW Revenues <\$50m).
- EU: EMA protocol assistance at a reduced cost.
- EU: Administrative and procedural assistance at a reduced fee for small and medium sized enterprises.
- EU: The EMA does not offer research grants but funding is available for the European Commission
- (EC) and other sources, such as Horizon 2020 and E-Rare.
- Japan: Orphan products can be subsidised through the National Institute of Biomedical Innovation (NIBIO).
- Japan: Guidance and consultations from the Pharmaceuticals and Medical Devices Agency (PMDA) at a lower user fee.
- Japan: 12% of study expenses incurred during the NIBIO payment period can be reported as a tax credit.

Appendix

Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2002-2024)

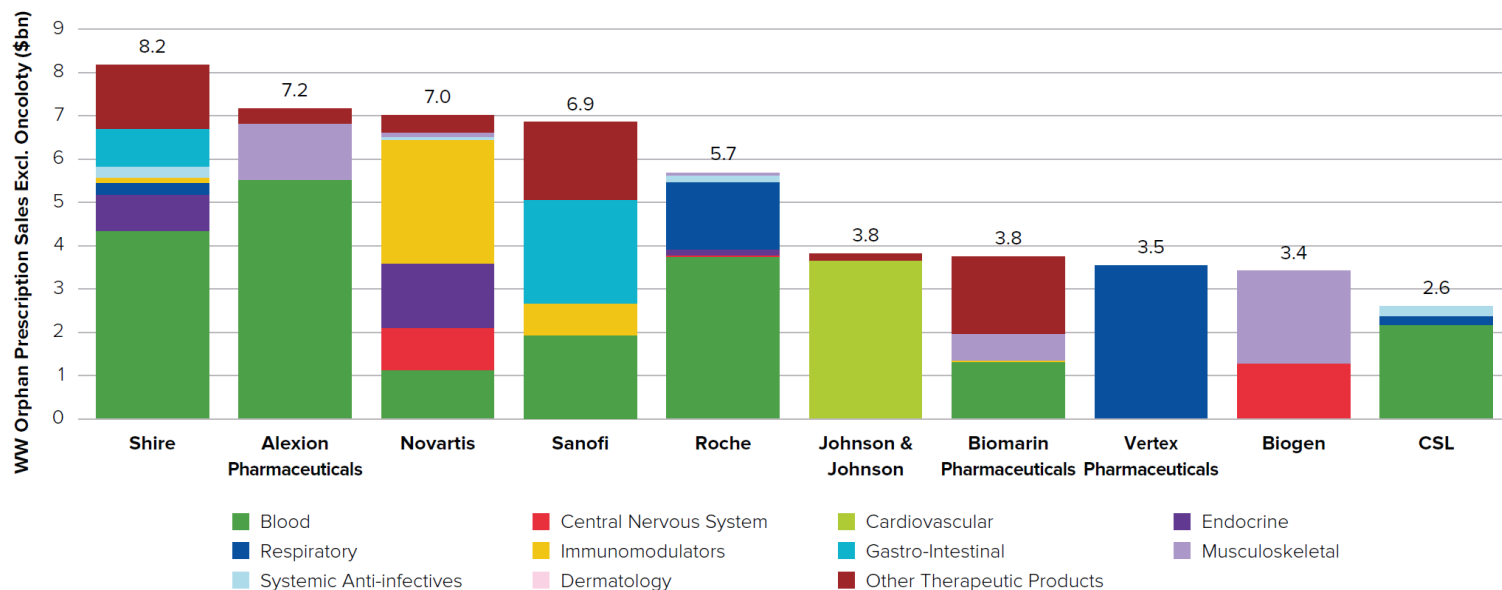
Source: EvaluatePharma* May 2018



Appendix

WW Orphan Drug Sales in 2024 by Therapy Category (Excluding Oncology): Top 10 Companies

Source: EvaluatePharma* May 2018



Appendix

Conceptual

The right blend of MR rigour and process excellence and Consulting experience

Trade offs in individuals as both skill sets take many years to develop and mature

Customised teams can. however, mix individuals with different background in MR and Consulting depending on project purpose

