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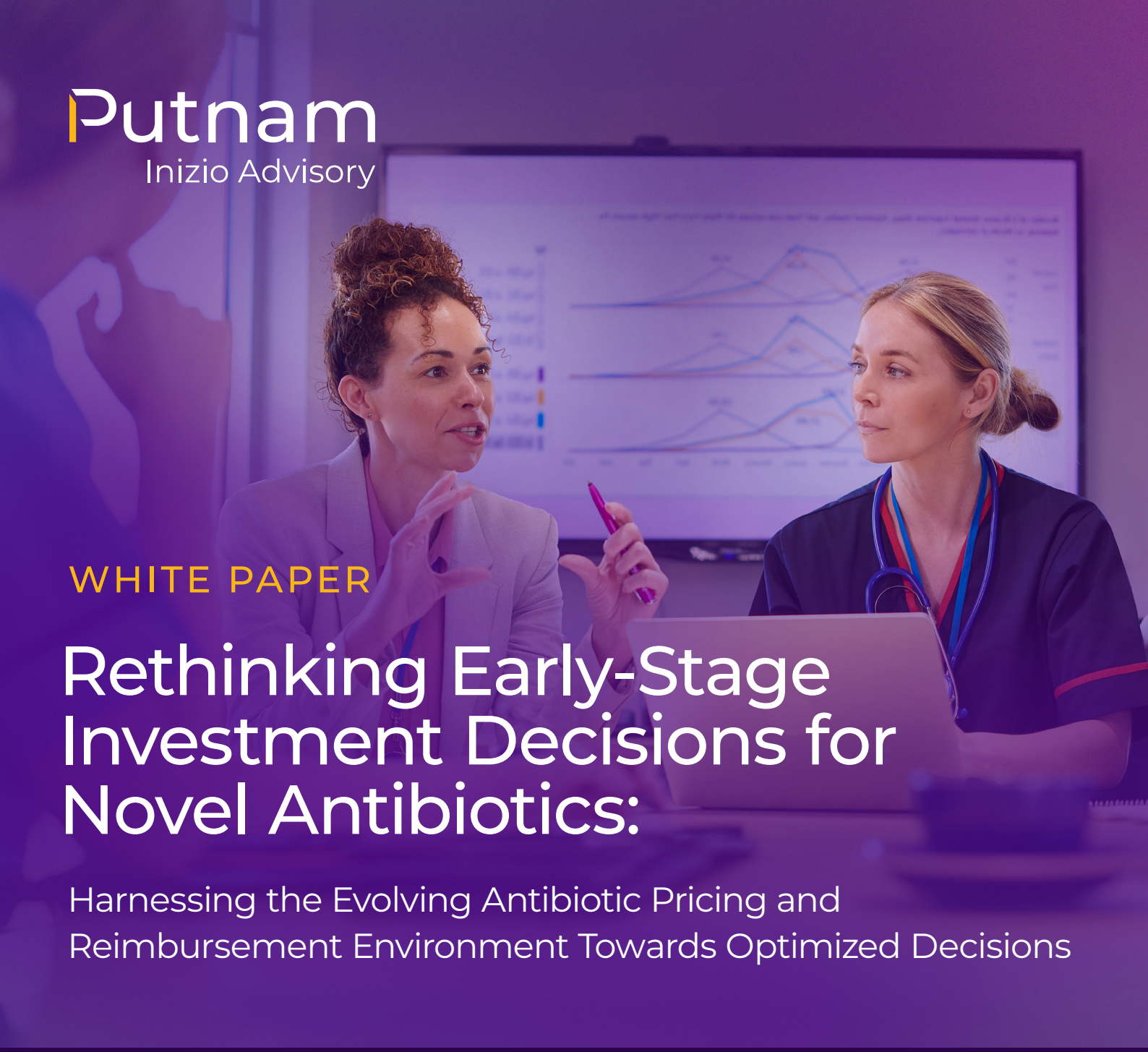

WHITE PAPER

Rethinking Early-Stage Investment Decisions for Novel Antibiotics:

Harnessing the Evolving Antibiotic Pricing and Reimbursement Environment Towards Optimized Decisions

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ABSTRACT

The pharmaceutical industry faces a call to action for a more sustainable pipeline of novel antibiotics to ensure the availability of effective treatment against the ever-increasing threat of bacterial antibiotic resistance (AMR). However, traditional early-stage investment frameworks rely on commercial proxies that break down in the antibiotic market. In this work, we argue that the evolving global pricing and reimbursement (P&R) environment, in which there is an increasing prevalence of novel pull incentives seeking to reward innovation and address stewardship challenges, can also serve as a blueprint for rethinking early-stage asset evaluation and provide a new framework to guide early-stage investment decisions to maximize commercial opportunity. We explore four core commercial indicators: unmet need, patient volumes, pricing potential, and evidence requirements, to illustrate how emerging P&R frameworks help resolve uncertainty and guide asset prioritization.

Introduction

Antimicrobial resistance (AMR) is ever-increasing, threatening a global public health crisis projected to claim 39 million lives over the next 25 years[1]. Current management strategies cannot fully address AMR and demand innovation in antibiotic therapy. However, the antibiotic pipeline has stagnated due to unique market dynamics which make it increasingly challenging for manufacturers to generate viable return on investment, driven by:

- **Low sales volumes** – new antibiotics are kept in "reserve" to treat only the most challenging drug-resistant infections to mitigate further development of AMR
- **Low pricing benchmarks** – new antibiotics are typically benchmarked to older genericized products with pricing unaligned to their clinical value

These challenges also cloud early-stage investment decisions and their accuracy. Typically, early-stage investment decisions are guided by high-level, proxy indicators of commercial opportunity which are well-correlated with commercial outcomes under standard market assumptions. However, the unique antibiotic market dynamics invalidate many of these assumptions, making it challenging to prioritize the assets that are likely to match clinical value with a meaningful commercial return, as shown in **Figure 1**.

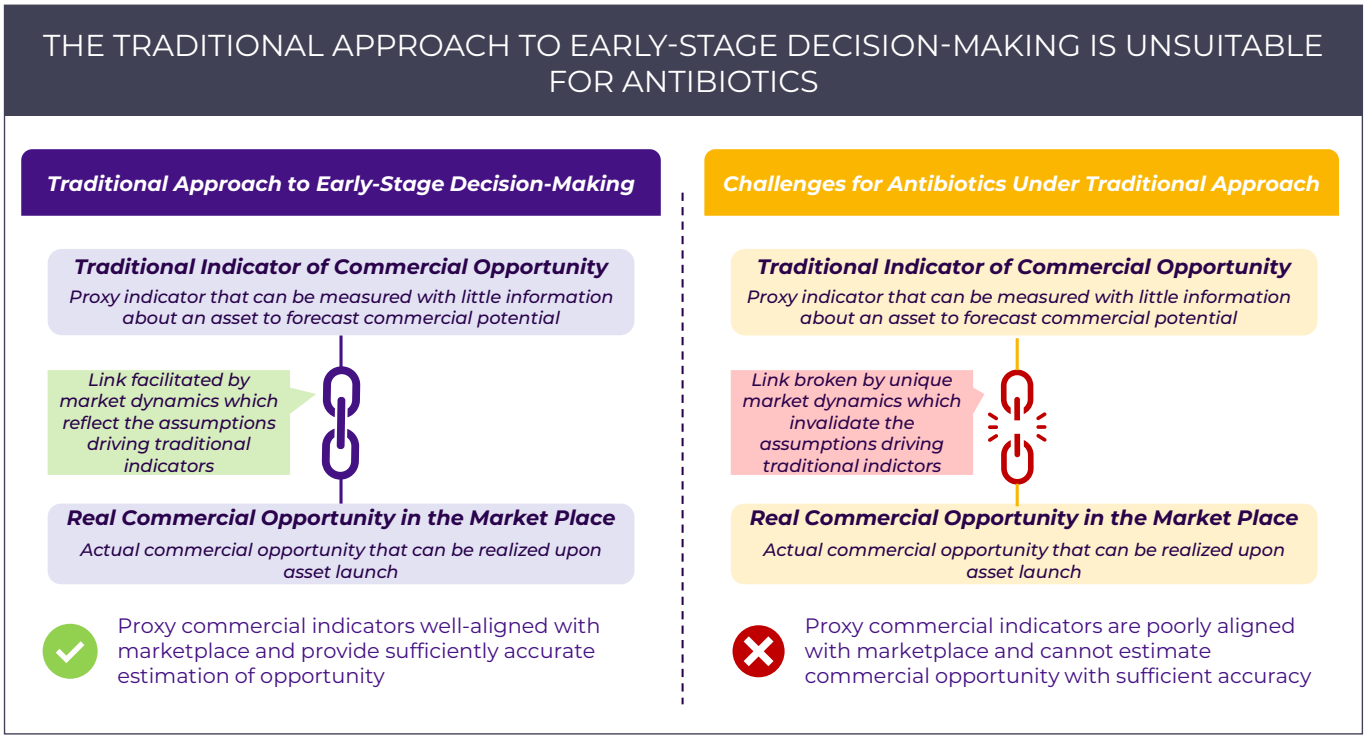

Figure 1:
The traditional approach to early-stage decision-making is unsuitable for antibiotics

For example, consider the following four proxy indicators which are often used in early-stage decision-making:

1. **Unmet Need** – the identification of patient groups where there is a meaningful opportunity for clinical innovation to provide improved outcomes
2. **Patient Volumes and Market Size** – the volume of eligible and likely treated patients
3. **Approximations of Pricing Potential** – the estimation of a cost-effective sales price
4. **Evidence Requirements** – the necessary evidence to demonstrate product value for market entry and uptake

The utility of these indicators for an early-stage antibiotic is decreasing as the market evolves. **Table 1** highlights how the unique dynamics of the antibiotic market invalidate the assumptions that enable the traditional early-stage decision-making framework.

THE UNIQUE ANTIBIOTIC MARKETPLACE INVALIDATES THE ASSUMPTIONS ASSOCIATED WITH TRADITIONAL COMMERCIAL INDICATORS

← *Traditional Approach to Early-stage Decision Making* →			← *Challenges for Antibiotics Under Traditional Approach* →
Indicator of Opportunity	**Use in Early-stage Assessment**	**Core Assumption Upholding Indicator**	**Are These Assumptions Valid for the Antibiotic Market?**
Unmet Need	Understand current clinical outcomes and identify unmet needs requiring innovation	Significant unmet need facilitates commercial opportunity and will remain until innovation launched	✘ • **Unpredictability** in unmet need due to **endemic foci** and **evolutionary nature** of AMR pathogens and **inconsistencies** in hospital AMR practices (AMS, diagnostic) • Unmet need driven by antibiotic **chemical structure** and **MoA** • Existing efficacious options and theoretical **unmet need for "reserve" treatments**
Patient Volume and Market Size	Define and quantify the likely treated population based on epidemiology and uptake assumptions	Volume of the treated population is likely to be proportional to clinical value of product	✘ • Antibiotic stewardship requires **low volumes of utilization**, independent of clinical value • Inconsistent stewardship practices drive **unpredictability** and regional disparities in volume
Approximations of Pricing Potential	Consider proxy metrics such as % of GDP spend on indication or economic burden of indication	Stable relationship between price/value and price/volume	✘ • **Poor correlation** between clinical value of antibiotic and price • **Poor correlation** between volumes of antibiotic and price • Commercial challenges driven by **low bundled payments** to providers calibrated for older, low-price antibiotics
Evidence Requirements	Understand evidence requirements for regulatory approval and plan CDP accordingly	Achieving regulatory approval will facilitate a meaningful market access opportunity	✘ • HTA frameworks poorly set up to acknowledge clinical value demonstrated in **non-inferiority trial** • **Broader value elements** of antibiotics not captured in traditional HTA

Table 1:
The unique antibiotic market invalidates the assumptions associated with traditional commercial indicators

Abbreviations:
AMR = Antimicrobial Resistance; AMS = Antimicrobial Stewardship; CDP = Clinical Development Plan; GDP = Gross Domestic Product; MoA = Mechanism of Action; HTA = Health Technology Assessment

These uncertainties have resulted from a decision-making framework which is no longer aligned with the market it seeks to interpret. To overcome these challenges, we consider how manufacturers can harness the evolving antibiotic market to redirect their early-stage decision-making and generate greater certainty over the likelihood of commercial return.

The Evolving P&R Environment as Guidance for Early-Stage Commercial Decisions

To incentivize antibiotic development and address the market dynamics which have made antibiotic development unattractive, a wave of national and supranational "pull" incentives have emerged in major markets in recent years, as shown in **Figure 2**[2-18]. This includes an array of approaches, from national P&R reforms which seek to address the inherent failure of the price-volume relationship in the antibiotic market, to pan-continental "one-time" financial rewards given to manufacturers upon launch of an eligible antibiotic.

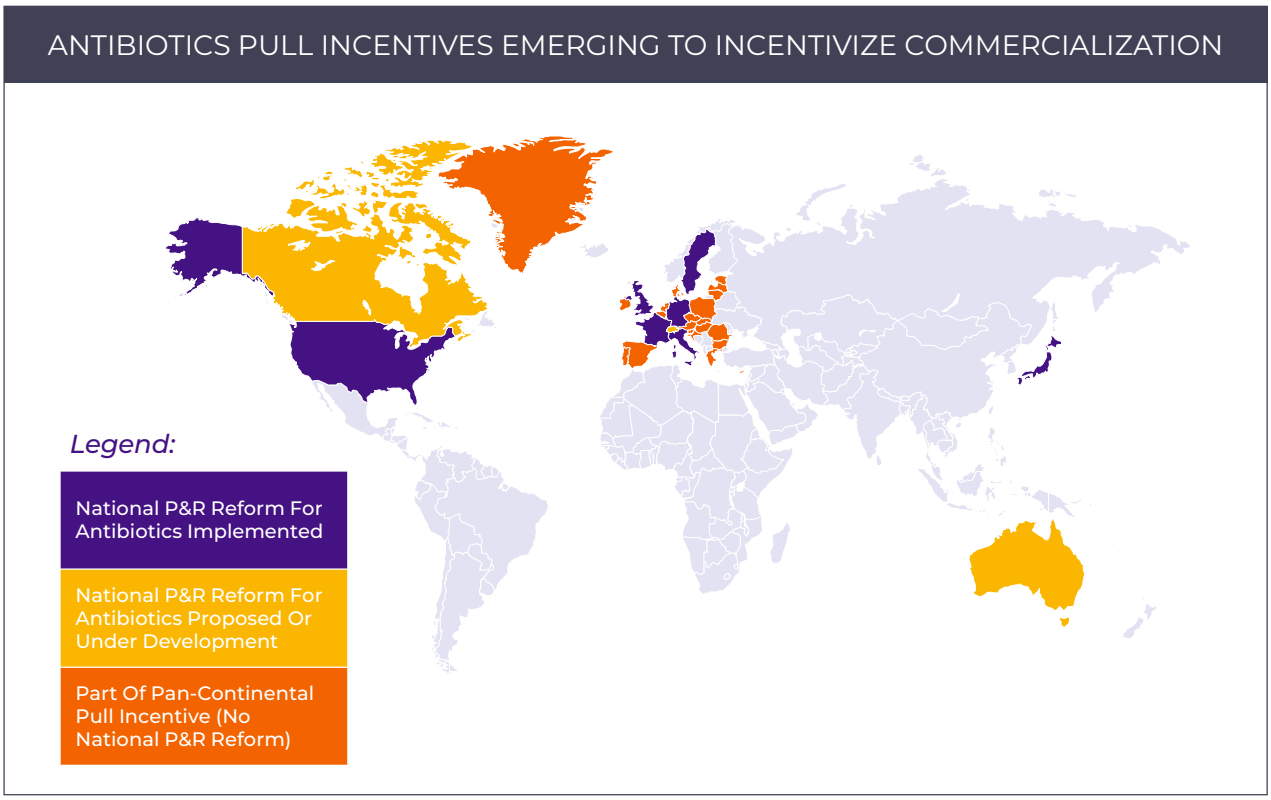

Figure 2:
Novel pull incentives for antibiotics are emerging to incentivize sustainable commercialization[2-18]

Abbreviations:
P&R = Pricing & Reimbursement

In-depth discussion of these various pull incentives, their financing and their implications for antibiotic access per se has been conducted extensively in the literature[19-23] and is not the focus of this article. However, it is relevant to note how efforts to increase the bi-directional value of these incentives to both industry and payers mean that they are increasingly attached to antibiotic-specific valuation criteria and consequent evidence generation requirements atypical to traditional health technology assessment (HTA).

For example, one of the most advanced pull incentives is the UK's Antimicrobial Products Subscription Model, now fully implemented after an initial pilot program[2]. Rather than relying on volume-based revenue, the model assigns antibiotics to fixed annual payment bands based on a detailed, points-based scoring system. Products are evaluated across 17 criteria grouped into three categories, capturing value elements that are specifically tailored to antibiotics:

- **Relative effectiveness and unmet clinical need** – capturing clinical value of the antibiotic in the context of current microbiological unmet needs
- **Pharmacological benefit** – capturing the unique chemical and pharmacological profile of the antibiotic and its associated value against the emergence of resistance
- **Health system benefit** – capturing wider benefits of the antibiotic to the patient and health system

Primarily, these incentives encourage the development of novel antibiotics by offering a more sustainable commercial reward. However, by addressing the market failures with a high degree of specificity in their valuation and reward criteria, novel pull incentives also offer alternative solutions to the core uncertainties that lie in the traditional early-stage decision-making process.

We will take the commercial indicators of opportunity in turn. We first consider Patient Volumes and Market Size, then Approximations of Pricing Potential, as the indicators which are impacted directly by the primary objective of pull incentives to remedy the market failures and, consequently in some cases, can be eliminated entirely from early-stage decision-making. We then consider Unmet Needs and Evidence Requirements, showing that pull incentives provide clear guidance for manufacturers to maximize their commercial reward by creating prescriptive, antibiotic-specific valuation criteria. Together, these considerations show how novel pull incentives reduce uncertainty in early-stage decision-making across the four domains.

Patient Volume and Market Size

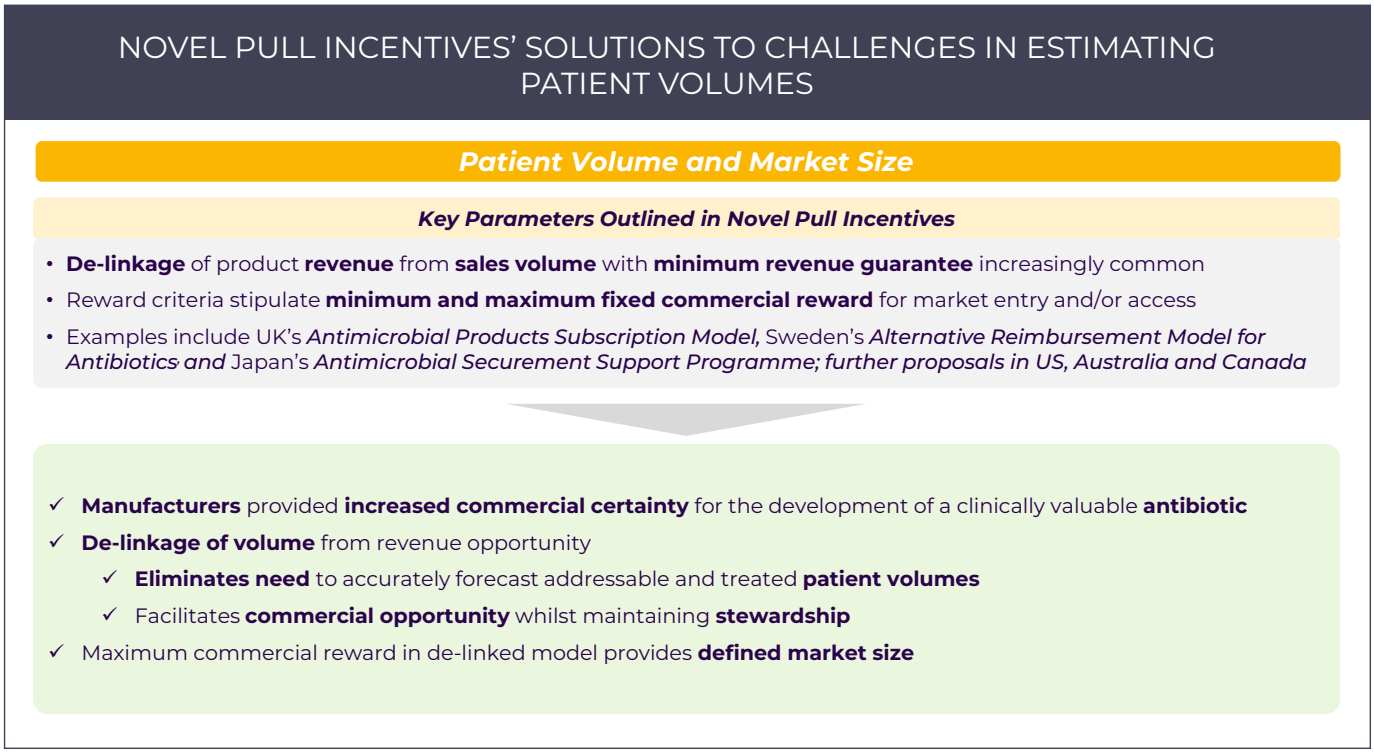

Figure 3:
Novel pull incentives' solutions to challenges in estimating patient volumes

As the need to address the underlying revenue-volume imbalance driving the antibiotic market failure is recognized, the de-linkage of product revenue from sales volume is becoming increasingly common. Alongside the UK's archetypal subscription model, other incentives such as Sweden's Alternative Reimbursement Model for Antibiotics[5,6], Japan's Antimicrobial Securement Support Programme[7,8] and the US's proposed PASTEUR Act[9] seek to offer a minimum guaranteed revenue return irrespective of volume sold. Earlier stage proposals are also under review in Canada[12,13] and Australia[14,15]. By de-linking the size of the financial reward from product sales, these incentives remove the necessity to define market size through patient volumes and re-define market sizes upfront through minimum revenue guarantees. Therefore, the satisfaction of the reward criteria outlined for the maximal financial reward in these approaches becomes the primary driver of the market size estimation.

Approximations of Pricing Potential

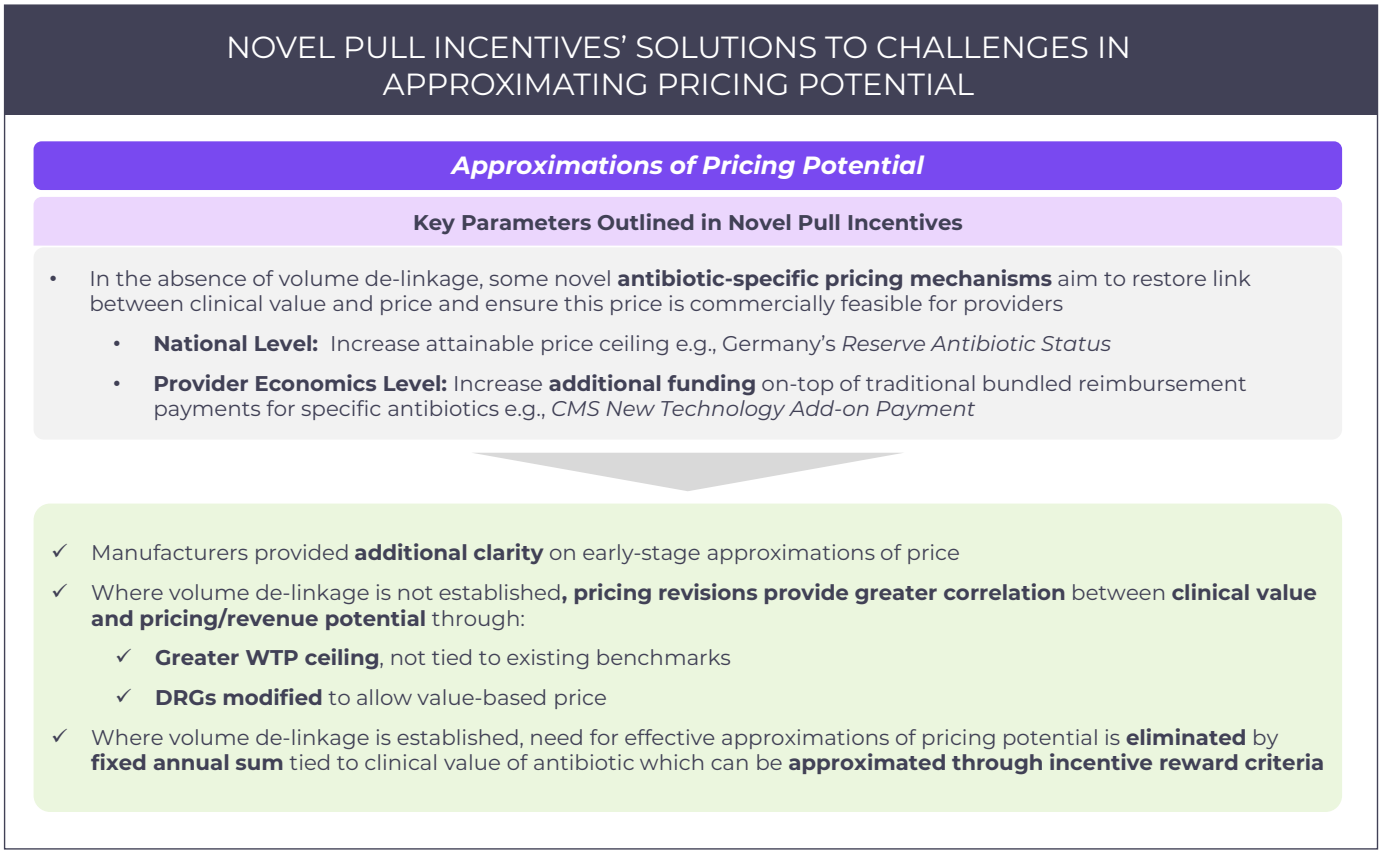

Figure 4:
Novel pull incentives' solutions to challenges in approximating pricing potential

Abbreviations:
DRG = Diagnosis-Related Group; WTP = Willingness To Pay

While volume-de-linkage also serves as a solution to these challenges, in several markets where volume de-linkage has not been implemented, novel and antibiotic-specific pricing mechanisms have been designed to restore, at least partially, the relationship between product value and pricing potential. A number of differing approaches exist, either addressing pricing ceilings at the national level, or relieving pressure imposed by DRG-based or bundled payment models.

For example, in Germany, eligible antibiotics under the Reserve Antibiotic Status are exempt from the G-BA's Benefit Assessment process and are thus able to maintain pre-AMNOG pricing indefinitely[4]. France offers relaxed clinical criteria for antibiotic products to access their European Price Guarantee when establishing national list prices[10]. In the US, the Center for Medicare and Medicaid Services' New Technology Add-On Payment (NTAP) offers more relaxed qualifying criteria and a greater reimbursement carve-out for novel antibiotics explicitly[11], facilitating access to antibiotics at prices that greater reflect the value of the product.

Therefore, for products that are eligible for pull incentives which remedy the early-stage commercial uncertainties in either Patient Volumes & Market Size, or Approximations of Pricing Potential, there is a potentially less burdensome decision-making process open to manufacturers. However, to ensure that this is attainable, manufacturers must understand how to align their early-stage development pathways with the requirements to access these. We now consider how uncertainties within Unmet Need and Evidence Requirements have been solved by pull incentives, providing manufacturers with clear guidance on how to maximize commercial reward.

Unmet Need

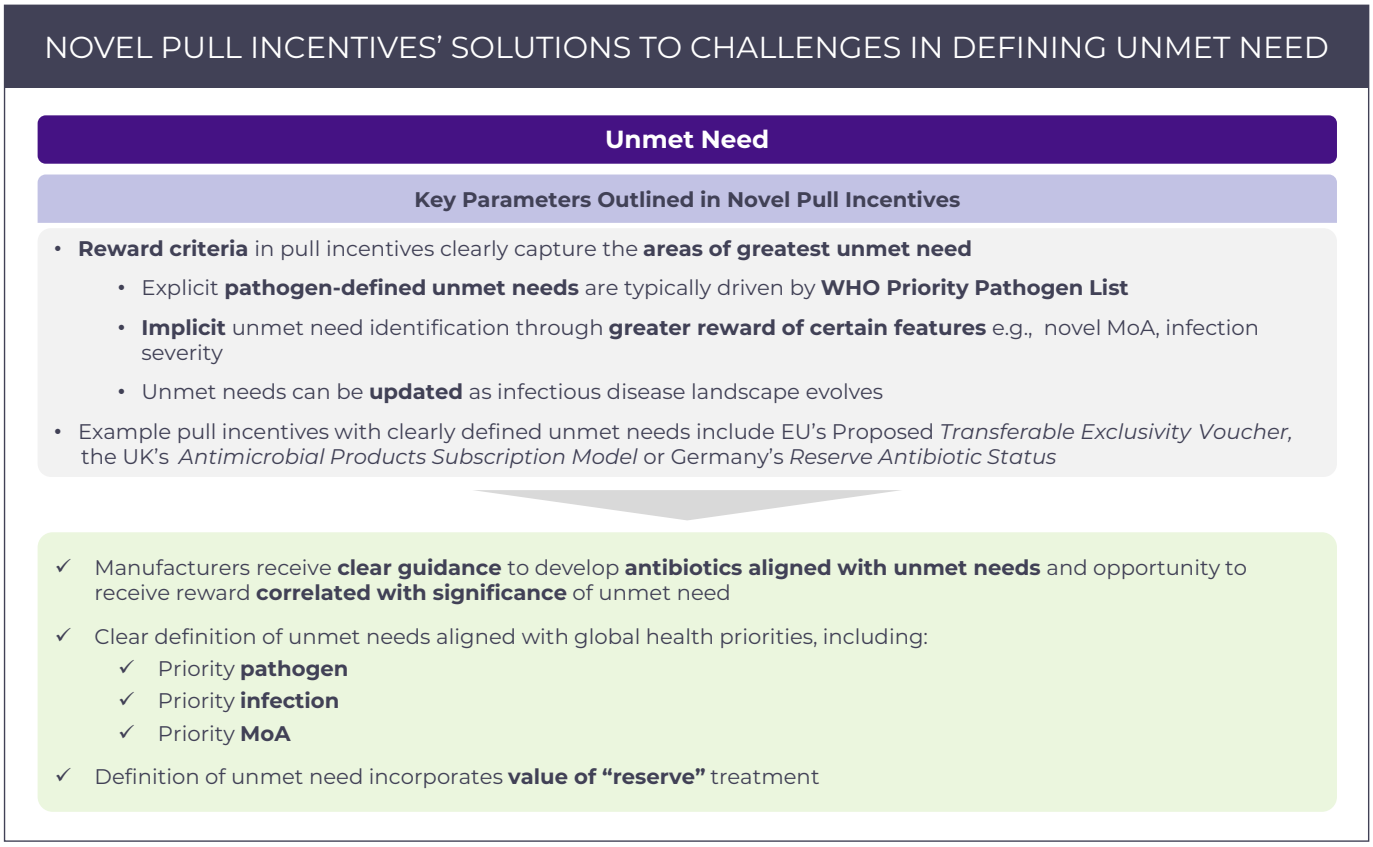

Figure 5:
Novel pull incentives' solutions to the challenges in defining unmet need

Abbreviations:
MoA = Mechanism of Action; WHO = World Health Organization

Unmet needs, whilst classically illusive in bacterial diseases, are now defined across many pull incentives, either explicitly through calls for particular antibiotics or implicitly through the greater reward of antibiotics with specific clinical features. These unmet needs are typically pathogen-focused, often in alignment with the WHO's Priority Pathogen List, but also place emphasis on the severity of infection with regard to its morbidity and mortality outcomes. This aims to help manufacturers align development programs with public health priorities.

For example, the European Union's proposed Transferable Exclusivity Voucher (TEV) is a proposed market entry reward whereby the manufacturer of an eligible antibiotic may receive a voucher for an additional period of patent protection that can be transferred or sold to other manufacturers. The current draft TEV legislation explicitly prioritizes eligibility based on priority pathogen, type of infection and chemical MoA[3]:

"An antibiotic shall be considered 'priority antibiotic' [i.e., eligible for TEV] if preclinical and clinical data underpin a significant clinical benefit with respect to antibiotic resistance and it has at least one of the following characteristics:

- ***It represents a new class of antibiotics;***
- ***Its mechanism of action is distinctly different from that of any authorised antibiotic in the Union;***
- ***It contains an active substance not previously authorised in a medicinal product in the Union that addresses a multi-drug resistant organism and serious or life threatening infection.***

In the scientific assessment of the criteria referred to in the first subparagraph, and in the case of antibiotics, the Agency shall take into account the 'WHO priority pathogens list for R&D of new antibiotics', or an equivalent list established at Union level."

Article 40, Paragraph 3 of the European Commission Reform of the EU Pharmaceutical Legislation 2023

These themes can be found in defining eligibility for other pull incentives, such as the UK's Antimicrobial Products Subscription Model[2] or Germany's Reserve Antibiotic Status which offers the bypass of traditional HTA and maintenance of pre-AMNOG pricing for antibiotics which meet strictly defined criteria[4]. By providing these stringent eligibility criteria, pull incentives effectively bear the onus of the identification of unmet needs, and guide manufacturers explicitly towards the development of antibiotics which are likely to generate the greatest commercial reward. Importantly, challenges identified regarding the continually evolving and geographically diverse nature of pathogen-defined unmet needs are likely to be addressed as these incentives are updated to respond to changing unmet needs, and by the inclusion of reward metrics which are not subject to evolution, such as the novelty of chemical class.

Evidence Requirements

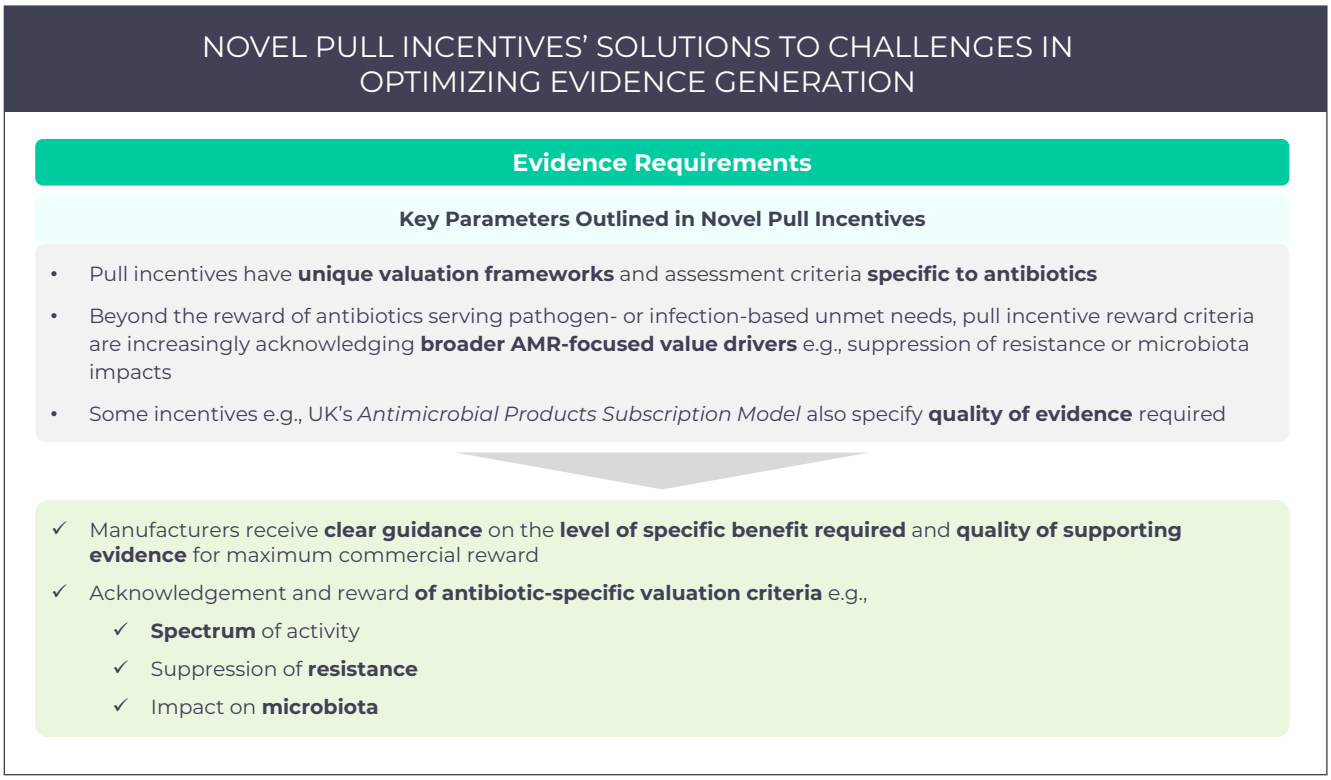

Figure 6:
Novel pull incentives' solutions to challenges in optimizing evidence generation

Abbreviations:
AMR = Antimicrobial Resistance

Pull incentives are increasingly designed with unique valuation frameworks and assessment criteria specific to antibiotics, to capture their broader value to an extent not possible in current HTA. For example, the UK's Antimicrobial Products Subscription Model employs a bespoke assessment matrix that rewards unique value dimensions, each of which is accompanied by clear requirements for the quality and methodology of supporting evidence[2], including:

- **Spectrum of activity** – including activity against WHO priority pathogens and clinical relevant mechanisms of resistance
- **Suppression of resistance** – absence of cross-resistance and absence of rapidly emerging resistance
- **Impact on microbiota** – minimization of collateral damage to patient's microbiota

By clearly defining novel and specific valuation criteria which will result in maximum financial reward, pull incentives provide an opportunity to remedy the broken link between regulatory approval and HTA success for antibiotics, and provide clear guidance for manufacturers to tailor early-stage evidence generation to guarantee commercial return.

As increasingly robust and ambitious reforms to antibiotic HTA and P&R are in development across markets like Canada[12,13] and Australia[14,15] which cite the UK's approach as a model example, these evidence requirements are likely to become more prevalent across the global landscape.

The Solution: A New Framework for Early-Stage Investment Decisions in Antibiotics

By facilitating a sustainable commercial opportunity and detailing specific requirements to achieve maximum commercial reward, novel pull incentives have redefined the parameters of commercial success and provided meaningful clarity to the uncertainties facing early-stage antibiotic development. It follows then, that they have also redefined how manufacturers should conceptualize and prioritize early-stage investment decisions for antibiotics and gradually move away from traditional considerations of unmet need, patient volumes and approximations of pricing potential. We consider four refocused drivers of early-stage commercial decisions which can maximize commercial opportunity in the development of a novel antibiotic. (**Figure 7**).

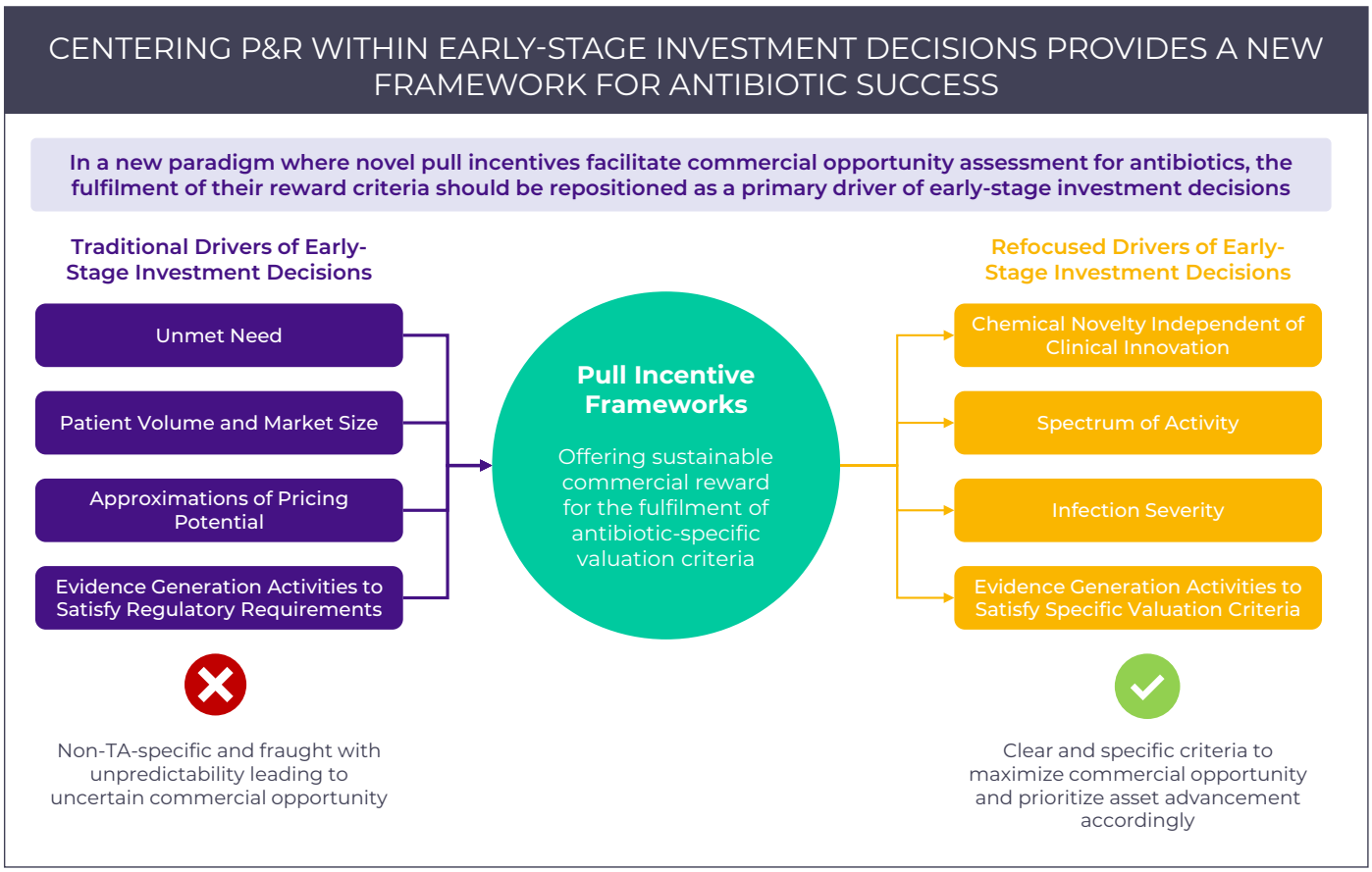

Figure 7:
Centering P&R within early-stage investment decisions provides a new framework for antibiotic success

Abbreviations:
TA = Therapy Area

Evaluate Chemical Novelty Independently of Clinical Innovation

When multiple assets are under consideration, manufacturers must prioritize those that offer the most chemical novelty and innovation, as stipulated by novel valuation frameworks and public health organizations. Where possible, priority should be given to assets that represent:

- A novel antibiotic class
- A new mechanism of action
- A unique biochemical target

These attributes should be evaluated independently of any associated clinical innovation, as chemical structure can be rewarded in its own right. While the absolute novelty of new antibiotics is not necessary for commercial viability, it is likely to play an increasingly significant role in long-term commercial viability given their utility against AMR pathogens.

Evaluate Spectrum of Activity Against Priority Pathogens

The motivation driving the introduction of novel incentives, is, at its core, to reward the development of antibiotics against the most clinically demanding pathogens. Therefore, manufacturers should prioritize assets that have a spectrum of activity against WHO "critical" and "high" priority pathogens, including those of the most difficult-to-treat multi-drug resistant strains, where clinical unmet need is greatest. Wherever possible, assets with significant multi-pathogen potential are likely to command the greatest commercial return and thus should be prioritized within early-stage decision-making.

Evaluate Proposed Indications Against Definitions of Infection Severity

Advancing the right indication to optimize commercial opportunity is a decision driven as much by pull incentive eligibility as by clinical or epidemiological considerations. Developers should prioritize indications in accordance with eligibility criteria stipulated in novel addressing serious or life-threatening infections. While terminology within eligibility criteria is still evolving, and what constitutes a "serious" infection may be subject to some debate, it is clear that antibiotics which can tackle disseminated or invasive disease are likely to reap the greatest commercial rewards, while those developed for local infections with minimal disease burden may be excluded from pull incentive eligibility entirely.

Invest in the Robust Demonstration of Wider Elements of Antibiotic Value

The development of novel antibiotic-specific valuation criteria, while offering commercial sustainability for valuable antibiotics, also demands a robust evidence generation strategy. It will become increasingly essential that manufacturers invest early in a clinical evidence package which captures the full spectrum of antibiotic value. For example, beyond trial demonstrations of non-inferior infection eradication and in vitro activity assessments, valuation frameworks are likely to reward the demonstration of an absence of cross-resistance, the absence of rapid onset of resistance and the impact of the product on the gut microbiome. In some valuation frameworks, the quality of these evidence requirements will also be a key factor, with grading systems differentiating between evidence derived from laboratory conditions vs. clinical conditions. An evidence generation strategy that anticipates these expectations will be better positioned to achieve premium contract valuations and long-term value in an increasingly access-driven marketplace.

These criteria are challenging, and certainly not all have to be satisfied for a meaningful product to be developed. However, a novel antibiotic that has been prioritized according to these four key criteria is highly likely to see a significantly more sustainable commercial opportunity than one that has been developed to satisfy traditional indicators of commercial attractiveness.

Conclusion

Novel pull incentives offer an attractive promise to reshape the antibiotic market and provide sustainable commercial opportunity for manufacturers. For early-stage decision makers, they offer both an opportunity and a challenge. Those willing to adapt traditional frameworks to align with these incentives will be best placed to develop assets that not only clear regulatory hurdles, but also thrive commercially in a market increasingly driven by access, value, and public health impact.

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