BLOG NOTE

NEW WAYS TO PAY FOR ANTIBIOTICS

What manufacturers should know when bringing new products to Europe

The antibiotic paradox

01

The incentives that normally make pharmaceutical investment attractive to drug developers are not present for antibiotics. New antibiotics can rarely achieve return-on-investment (ROI) compared to other potential investments into drugs developed for cancer or rare genetic diseases. Most European markets confer premium prices to new drugs only if an incremental value is demonstrated. However, the clinical evidence package for new antibiotics is normally based on controlled clinical trials designed to demonstrate non-inferiority versus current SoC. And even if higher efficacy or much better safety profile was demonstrated, we would still be talking about very modest premiums, given that the large majority of antibiotics currently being sold are generic and only cost few cents per day. Second, in an attempt to reduce the development of AMR, new antibiotics are often shelved and reserved for the multi-drug resistant cases, of which there will be relatively few, while existing antibiotics will always be considered as first-line treatment for less severe cases. This means that new antibiotics are condemned to be restricted to very specific, severe patient sub-populations. That is, both lower price and low unit volumes. Finally, the acute and sporadic nature of most infectious diseases implies that antibiotic treatment courses are usually short in length, further restricting their potential sales volumes. These disincentives have caused an exodus of capital in the field of antibiotics, the bankruptcy of many companies that have successfully brought novel antibiotics to market, and ultimately, an even larger AMR threat.

Supporting R&D to incentivize investment on the antibiotics field: helpful but insufficient without other policy interventions at the commercialization stage

02

As mortality and morbidity rates due to AMR rise, several countries have developed a variety of incentives to encourage investment in antibiotics tackle the AMR problem. Two main types of incentives can be identified: Push and pull incentives. “Push” incentives refer to funding aids that support and facilitate research and development (R&D) activities, whereas “Pull” incentives relate to rewards for bringing to market a product of clinical and public health value; including special reimbursement policies that consider the particular situation of antibiotics during HTA and P&R negotiations.

Significant public and private efforts have been made to finance push funding. With regards to pull incentives, only few European countries have P&R policies that are specific for new antibiotics. And although there has been a large amount of research done to develop new pull incentive models, few of these have led to any practical implementation. The most recent efforts can be found in United Kingdom and Sweden, which are currently exploring the feasibility of novel tailored HTA that consider other elements of value in addition to clinical efficacy and safety, as well as payment models that de-link price setting and reimbursement from volumes sold.

The French and German cases: current policies confer potential for higher price, but not necessarily for positive profit margins

03

In France, antibiotics with minor added therapeutic benefit (ASMR IV) are guaranteed the pricing benefits of getting a moderate benefit (ASMR III). This means that they are guaranteed a price not lower than the lowest price across the other four main markets in Europe (Germany, Italy, Spain and United Kingdom). However, not many manufacturers

would find not being lower than the Italian and Spanish prices a good recognition of value. This policy also increases the chance for new antibiotics to be included in the French DRG carve-out list ("Liste-en-sus") and thus be reimbursed separately. This is an essential condition for ensuring successful market uptake of high-cost drugs in the inpatient hospital setting, which otherwise will have to be funded from the fixed DRG tariff assigned to cover all costs incurred during the hospital admission.

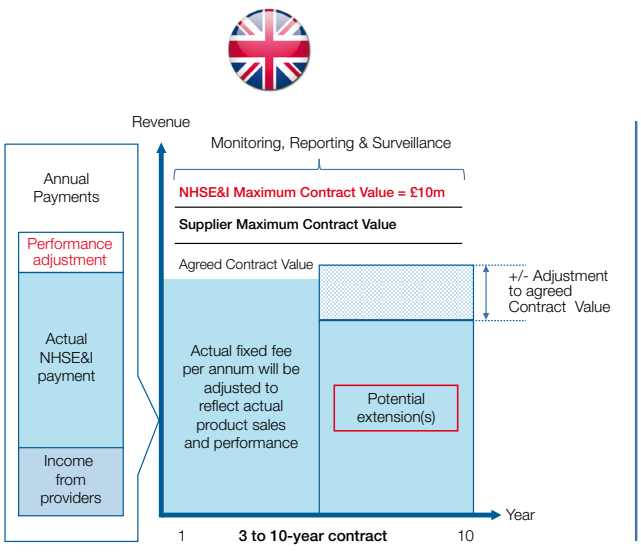
In Germany, new legislation was approved in early 2021 to exempt drugs officially classified as reserve antibiotics by G-BA from the benefit assessment process according to specific criteria predefined by G-BA in alignment with RKI and BfArM. This is similar to the process for orphan drugs where the product is automatically granted a non-quantifiable additional benefit and free pricing. However, as reserve antibiotics are usually restricted to most severe cases and thus, to inpatient hospital use, the attractiveness of this incentive becomes debatable when looking at the way hospital drugs are reimbursed in Germany. As in France, the German healthcare system uses a Diagnosis Related Group (DRG) system to reimburse hospitals and add-on lists (NUB or ZE) for separate reimbursement of medicines which cannot be properly covered from the established DRG tariff. Unfortunately, most applications to add-on payments made for antibiotics approved in the last years have not been successful. With a high price tag and without such add-on payments, extremely high reluctancy of hospitals to use of a reserve antibiotic is to be expected, even in cases where it would be the most appropriate choice for a patient. Said differently, you may get price, but not volume.

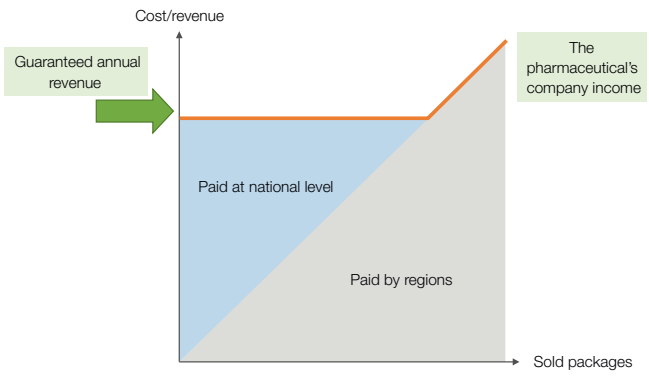
The case of United Kingdom and Sweden: Potentially deep policy changes to HTA and reimbursement rules, but still in a theoretical stage

04

Other countries such as United Kingdom and Sweden are exploring new payment models that de-link price setting and reimbursement from volumes sold: In exchange for a guarantee of good and prompt availability, the manufacturer receives a guaranteed, regular income per product, even if actual sales fall below such pre-defined revenue. In the case of UK, the economic evaluation will consider other elements of value in addition to the direct health gain to patients treated, such as diversity value, transmission value, enablement value, spectrum value and insurance value. However, so far such payment and HTA models remain exploratory and include only a few products in this testing phase (Zavicefta and Fetcroja in the case of United Kingdom, Fetcroja, Zerbaxa, Recarbrio, Vaborem and Fosfomycin-infectopharm in the case of Sweden). It is yet not clear when and how these new payment models are going to be broadly implemented, but more importantly, it remains to be seen whether they will be sufficient to incentivize investment.

Schematic illustrations of the new reimbursement models proposed in United Kingdom and Sweden





Are the current and proposed P&R policies for antibiotics really a sustainable solution for manufacturers?

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It is evident that European countries have made only minor adjustments to their HTA and pricing rules for antibiotics. These policy adjustments are often more than offset by policy disincentives that impact volume, price or both. Guarantees of a premium price and granting of a reserve status does not necessarily translate into a guarantee of positive revenues for manufacturers. In fact, an antibiotic's reserve status may mean zero revenues in many cases, especially when such status is not accompanied by a removal of barriers that prevent an appropriate reimbursement and discourage its use, even in situations where its administration is perfectly justified from the clinical point of view.

Further, antibiotic trials generally are powered for non-inferiority of for "reserve line" therapy. In contrast to late line cancer treatments, the pricing for reserve antibiotics is nowhere near what late-line oncology products can command. If the process to review and fund medicines does not address these issues, antibiotics will continue to be a less attractive investment when compared to products in oncology and rare diseases. Policy changes will only be effective when created via a holistic view of the clinical and economic context for both healthcare systems and drug manufacturers. Certainly, incentives should not promote indiscriminate use of antibiotics and therefore, must co-exist with stewardship policies that prevent their inappropriate use. But also, policy makers must not forget to look through the eyes of the investor to understand when incentives are really sufficient to encourage development.

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About the author:

- Natali joined LatticePoint in December 2016. She has supported several market access strategy projects and the development of payer value communication tools for different European healthcare systems.

- During her tenure at LatticePoint, she has become knowledgeable in various disease areas and medicinal products, including antibiotics. Her passion to ensure patient access to personalized and innovative medicines has led her to focus on the market access, reimbursement, and cross-border healthcare challenges for advanced therapeutic medicinal products.

About LatticePoint Consulting:

- LatticePoint is a boutique consulting firm that focuses on pricing and market access for innovative medicines and medical devices. LatticePoint is led by former industry market access leaders who understand how to plan for the political, scientific, and financial realities that will be pivotal in negotiating product access. We work with biopharma companies and investors to help define, negotiate, and defend the value of their products in key markets around the world. The LatticePoint team has over 40 years of pharmaceutical and biotechnology industry experience. Led by former industry market access leaders and a high-caliber team with significant experience in the sciences, licensing, M&A due diligence and integration, venture capital and international affiliate operations, we have a depth of experience, both at the global and regional levels. Our multilingual staff of native German, French, Italian, Spanish, Portuguese and English speakers is experienced at handling negotiations in many key countries while keeping an eye on cross-border implications. We engage with payers, providers, hospitals, HTA bodies and EMA for early access, give feedback on clinical program design, and create and execute in-country reimbursement strategy negotiations in key markets around the world. We retain a Global Payer Panel for market research interviews.