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Examining Challenges to Antibiotic Commercialization in International Markets

1201 Pennsylvania Ave NW, Suite 500 • Washington, DC
November 6, 2019 • 11:30 am – 5:00 pm

Discussion Guide

Introduction

The public health threat of antimicrobial resistance (AMR) is growing and global, and multifaceted strategies to combat its rise are necessary. The United Nations (UN) highlighted the challenge of AMR at their General Assembly meeting in 2016, only the fourth time the General Assembly has discussed a health issue.[1] This meeting followed the release of a World Health Organization (WHO) Global Action Plan, which provided a strategy to tackle AMR worldwide.[2] This action plan stressed the need for a "one health" approach that involved coordination between multiple sectors, including industry, agriculture, and health systems, and aimed to improve awareness and understanding of AMR, strengthen evidence on the topic, reduce incidence of infection, improve use of current medicines, and build an economic case for sustainable investment in new antimicrobial products.[2]

The lack of economic sustainability is an important factor in the currently limited development of antimicrobial products. A limited return on investment (ROI) for antimicrobial products discourages developers from investing in robust product portfolios. A variety of solutions have been proposed to address this problem, including enhanced funding and support for discovery and preclinical development. However, revenue generation remains a major barrier to sustainability, and until mechanisms are implemented to address this gap, industry investment will remain sparse.

For those companies still developing antimicrobial products, the United States (US) represents the largest market in terms of sales and revenue.[3] However, as different countries consider implementing payment reforms and incentive mechanisms, it will be important to examine barriers to entry in non-US markets; ensuring that innovative antimicrobial products remain accessible to patients around the world is critical.

This discussion guide describes specific circumstances contributing to antimicrobial product commercialization, with a focus on Europe and Japan, which comprise a significant portion of the non-US global market. During the accompanying workshop, participants will expand on these concepts, identify key challenges limiting access to antibiotics in specific regions, and discuss policy approaches that may reduce barriers to antimicrobial development, approval, and access.

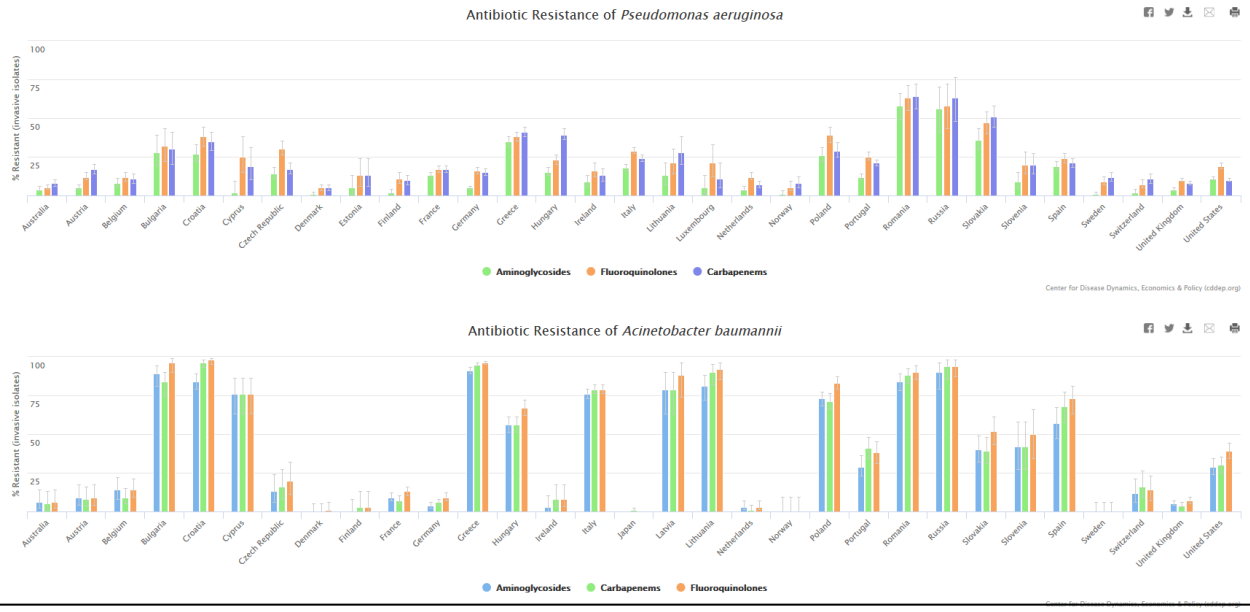
Pre-market Considerations and their Impact on Commercialization

The ROI for pharmaceuticals, including antibiotics, continues to be driven primarily by volume sales. As a result, the incidence of infections among varied populations influences how developers approach commercializing products in different regions and countries. For example, Norway is relatively unburdened by resistant bacterial organisms, and inexpensive generic products like penicillin effectively cure most infections.[4] Accordingly, Norway does not demand a large volume of novel branded

antibiotics, like those active against carbapenem-resistant organisms, and it is often an unlikely market for immediate product commercialization. In other instances, weak stewardship of antimicrobial products creates risk for developers interested in commercializing globally, and income disparities limit where novel antibiotics may be available.

Regional differences in epidemiology are also impacted by antibiotic stewardship programs and their variance among countries and within their healthcare facilities. These programs and how they are implemented can significantly influence how antibiotics are utilized in patient care and whether resistant organisms are likely to spread as a result. In some countries, older antibiotics retain their activity against organisms that are resistant to the same drugs in other locations. Robust antibiotic stewardship may be contributing to these regional differences, and where these programs are lacking, resistance is more likely to occur and spread (Figure 1).

Figure 1. Resistance patterns vary widely among regions and countries. The graphs below are from the Center for Disease Dynamics, Economics & Policy "Resistance Map". Each graph illustrates the rate of resistance of *Pseudomonas aeruginosa* (top) or *Acinetobacter baumannii* (bottom) to aminoglycosides, fluoroquinolones, and carbapenems in the listed countries.



While the prevalence of infectious disease underlies commercialization strategies, regulatory considerations and requirements can further challenge developers applying for marketing approval within multiple countries. The US and Japan have independent regulatory agencies—the Food and Drug Administration (FDA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), respectively—while member states of the European Union (EU) rely on the European Medicines Agency (EMA) for pre-market product evaluation and marketing approval. Among these regulators, diverse trial designs, endpoints, and patient populations can influence how decisions about evidence and benefit-risk assessment are made for the same investigational products.

While harmonized regulatory standards and requirements exist among certain countries, differences in process can be expected. Starting in 2016, the FDA, EMA, and PMDA held a series of meetings to discuss

approaches to evaluating antimicrobial products, aiming to identify areas of potential alignment.[5] These discussions resulted in movement toward consensus regarding patient selection criteria and recommended endpoints for urinary tract and intra-abdominal infections. In other areas, such as appropriate endpoints for community-acquired bacterial pneumonia and skin infections, differences in opinion remain.[6] Ultimately, regulatory harmonization can standardize and streamline product registration among multiple countries by establishing technical guidelines for use across multiple agencies. Extending the impact and benefits of harmonization remains a promising opportunity for industry and public health alike.

Pricing, coverage, and reimbursement

In addition to regulatory standards, pricing, coverage, and reimbursement policies vary considerably across different countries, including among member states of the EU where a common regulatory system for marketing authorization exists. The World Health Organization (WHO) performed a survey and subsequent assessment of European pricing and reimbursement policies, which offers a thorough analysis and foundation for the discussion below.[7]

Among the 28 EU member states and 25 additional countries in the WHO European Region, a diverse array of payer schemes exists. In 2017, the WHO survey collected data on 45 of these 53 countries, all of which deliver health care through either a national health service (22), social health insurance (21), or mixed system (2). Thirty-four of these health care systems are characterized as single payer, and the remaining eleven are multi-payer. Typically, populations covered under national health services can access health care regardless of whether they contribute financially, whereas those covered under social health insurance systems are obligated to contribute for access.

Public payers for medicines differ among countries and vary based on whether medicines are for inpatient or outpatient use. Payers may include a national health service, social health insurer(s), the ministry of health, or some form of regional council. Similarly, procurement varies for inpatient medicines and may involve centralized tendering at the national level, decentralized procurement among individual hospitals or health care systems, or even procurement led by regional organizations (e.g. county councils in Sweden) or a health insurance fund. Among multiple countries, direct contact between hospitals and pharmaceutical developers or insurance funds to negotiate procurement is not uncommon.

In Japan, statutorily mandated health insurance covers different population segments through hundreds of insurers, many mandatorily operated by large employers, and others operated directly by the government, municipalities, and national occupational societies.[8] No matter the payer, access to new medicines through the country's national health insurance system is typically rapid.[9] Developers apply for reimbursement approval through the Ministry of Health, Labor, and Welfare (MHLW) and patients are subject to co-insurance and pay a percentage of the set reimbursement rate.[8]

How medicines qualify for reimbursement (and for how much) depends on varied authorities among different countries. Frequently, the ministry of health is responsible for such decisions (as in Japan), but authorities such as social health insurer(s), a national health service, centralized national councils or agencies, or regional authorities may be responsible for reimbursement and/or pricing decisions. The authorities responsible for decisions regarding reimbursement typically consider therapeutic benefits,

relative benefits, medical needs, safety, cost-effectiveness, and budget impacts. And in 34 of the 45 European region countries surveyed by the WHO, systematic health technology assessment (HTA) informs these reimbursement decisions.

HTA assesses medicines and interventions to better understand their value and recommend if and when public sector resources should be allocated to provide access. HTA is widespread in Europe and is employed around the world in countries such as Mexico, Brazil, South Africa, Malaysia, Singapore, South Korea, Japan, and others.[10] Systematic assessments commonly consider a medicine's safety, clinical effectiveness, economics, budget impact, equity, ethics, feasibility, and acceptability to providers and patients.[11] While each HTA authority or organization may differ, efforts to standardize assessments within and among organizations have resulted in several multilateral collaborations.[10,12,13]

Among European countries, the European Network for Health Technology Assessment (EUnetHTA) was created to encourage agency collaboration and knowledge sharing.[13] The network comprises over 80 organizations from 30 countries. HTA organizations within the network contribute to the production of structured HTA core information, and to a platform for information exchange. To-date, the EUnetHTA has not produced an assessment of antibiotics generally, but an evaluation of cefiderocol (which targets Gram-negative infections) is planned.[14] If applied widely, these assessments have the potential to decrease the variability developers face when launching products in multiple countries, potentially improving future patient access.

While HTA can be attractive for its systematic assessment of value, antibiotics may not be equitably evaluated when compared to other medicines. This is because HTA typically does not consider certain elements of value intrinsic to antibiotics, particularly those that accrue to population health in the context of AMR.[15] Unlike most pharmaceuticals, antibiotics provide value not only to the patient, but to those among a population who are spared subsequent exposure to infectious disease.[16] This so-called transmission or contagion value represents an important and distinct aspect of antibiotic value.[15] Other population health values afforded by antibiotics include their enablement and insurance values. The ability to safely perform infection-prone medical procedures like surgery represents the enablement value of antibiotics and is not typically quantified. Furthermore, in the event resistant infection were to spread suddenly and threaten widespread mortality, having an effective antibiotic treatment available represents an insurance value, also not typically quantified.[17] These population or public health values underpin a broader assessment of antibiotic value, but remain challenging to measure and model.

Following or in tandem with qualification for reimbursement, reference pricing is employed among 30 of the 45 European region countries surveyed. In a reference pricing system, medicines are grouped based on their active substances, chemical subgroups, or interchangability, and priced according to varied rules. Some systems set the price according to the lowest-priced medicine in a group, whereas others rely on an average, weighted average, or average of *n* lowest-priced medicines in a group. In Japan, the Ministry's Drug Pricing Organization (DPO) determines the price of new medicines by referencing the price of comparable products and applying premiums for innovation, supporting small markets, and pediatric indications.[9] When comparable products are unavailable, the price is set based on the costs of manufacturing, marketing, administration, distribution, and a variable operating profit percentage.[9]

These reference pricing systems may update prices biweekly, quarterly, semiannually, annually, or otherwise. While reference pricing is designed to generate savings for public payers, not all countries

agree that its administrative complexity justifies its potential savings, and in countries like Sweden, the United Kingdom, and Austria, other pricing strategies exist.

As outpatient medicines are reimbursed, the amount a public payer covers may depend on the products themselves, the diseases for which they are prescribed, the populations for which they are provided, or the total pharmaceutical expenditure of a patient. These different reimbursement schemes may be combined such that aspects of multiple systems determine the final per-patient reimbursement (e.g. a child or person with chronic illness may reach a threshold of expense at which medicines are covered entirely before an adult without chronic illness) (Table 1).

Table 1. Reimbursement Strategies Applied in Europe.

Reimbursement Strategy	Purpose	How it works	Frequency of use (45 surveyed)[7]
Reimbursement Lists **- Positive** **- Negative** **- Both**	Defining which medicines can be reimbursed by public payers	Medicines included on a positive list can be reimbursed by a public payer, those on a negative list cannot.	*Positive* Widespread *Negative* Rare (1/45) *Both* Rare (2/45)
Health Technology Assessment	Assessing medicines and interventions to determine their value and to recommend resources be used to provide only those that are efficient and effective	A systematic process is designed to objectively inform coverage decisions based on various criteria which commonly include: safety, clinical effectiveness, economics, budget impact, equity, ethics, feasibility, acceptability to providers and patients, etc.[11]	Widespread (34/45)
Reference Pricing	Determining the price of a medicine based on the retail prices of other similar medicines	A group of medicines, typically including the originator and off-patent medicines, comprise a reference group based on their similarity. Countries then set the reference price according to varied criteria, but commonly at the price lowest-priced medicine within a group or an average of certain lower-priced medicines within the group. Revisions to the reference prices are commonly frequent.	Common (30/45)
Managed Entry Agreements	Providing access to therapies when uncertain clinical	Contracts between developers and payers or providers allow patients to access therapies,	*Outpatient* Common (24/38)

	evidence precludes traditional reimbursement approval	conditional upon continued evidence development, limited treatment continuation, research requirements, outcome guarantees, risk-sharing, etc.	*Inpatient* Less Common (17/38)
Product-Specific Eligibility	Determining whether a medicine will be reimbursed by a public payer	A medicine's reimbursement eligibility and rate are based on an evaluation of varied criteria.	*Primary Mechanism* Common (32/45)
Disease-Specific Eligibility	(see above)	A medicine's reimbursement eligibility and rate are based on the disease indicated.	*Primary Mechanism* Uncommon (8/45) *Supplementary* Uncommon (6/45)
Population-Specific Eligibility	(see above)	A medicine's reimbursement eligibility and rate are based on whether a patient is part of a defined population (e.g. child, pensioner, pregnant, etc.).	*Primary Mechanism* Rare (3/45) *Supplementary* Common
Consumption-Based Eligibility	(see above)	A medicine's reimbursement eligibility and rate are based on patients' pharmaceutical expenditures. Coverage rates typically increase as patient expenditures rise.	*Primary Mechanism* Rare (2/54)
Outpatient Co-Insurance / Co-Payments	To discourage unnecessary use of medicine and reduce costs for public payers	Patients cover a percentage of the cost of medicine at the point of sale and/or pay a prescription fee.	*Percent Co-Payment* Common (32/45)
• Japan employs a positive reimbursement list and utilizes HTA and reference pricing strategies that are influenced directly by the average prices of medicines in the US, UK, Germany, and France.[9]			

Under typical fee-for-service (FFS) reimbursement schemes, high-volume utilization generates maximum revenue for developers. Yet reimbursement strategies like reference pricing limit antibiotic reimbursement to a price that reflects a variety of inexpensive, off-patent products, many of which are threatened by rising AMR. Key features of antibiotic value and their potential benefits in the context of AMR are not considered and reflected in reimbursement decisions among public payers. Because of this, antibiotic developers are incentivized to register products for which markets are large and ROI can be driven by volume. This strategy runs counter to stewardship goals and to developing innovative

antibiotics for unmet and future medical needs. Accordingly, investment in developing and commercializing novel antibiotics has become critically inadequate.

Ultimately, if developers forego commercializing novel antibiotics in countries whose markets may be small and where authorities may not approve their products for reimbursement, patient access suffers. Among existing marketed antibiotics, not all are widely available across the globe. Only four antibiotics introduced since 1981 have been registered in more than half of 106 low- and middle-income countries, and among newer* antibiotics, registration occurs in fewer than five countries on average.[18] Developing novel antibiotics while supporting both stewardship and appropriate patient access is critical.

New payment approaches

Recognizing that current reimbursement mechanisms for antimicrobials are unlikely to drive the innovation needed to combat emerging resistance, some countries are considering payment reform mechanisms to better align reimbursement for antibiotics with their value to public health and society. Many of these models are focused on ensuring access for patients and range from payment based on a fee-for-service structure to those that are delinked from volume used.

In the US, the Centers for Medicare and Medicaid Services (CMS) recently revised the way that some antibiotics are reimbursed within Medicare in the inpatient setting. For hospital payments, CMS reimburses based on episodes of care, through diagnosis-related groups (DRGs), which cover care, drugs, and devices associated with a given patient episode. New antibiotics, which are priced at a higher amount than generics, will often lead to costs that exceed the DRG reimbursement, potentially delaying inclusion of these drugs on hospital formularies, which may result in not using the new antibiotic when it is the most appropriate treatment.[19] This reimbursement issue occurs for other new, high-cost therapeutics that are administered in the hospital, and CMS has a mechanism that is designed to offset some of the deficits that a hospital might face, called the New Technology Add-On Payment (NTAP). In the new Fiscal Year (FY) 2020 rule, CMS increased the additional NTAP reimbursement amount from 50% to 75% for qualifying antibiotics.[20] To enable more antibiotics to qualify for this enhanced reimbursement mechanism, CMS also waived the requirement for demonstrating substantial clinical improvement over other treatments. This requirement was challenging for antibiotic products to meet due to use of non-inferiority trials in clinical development. In addition, CMS adjusted payment codes so that some types of resistant infections would be reimbursed at a higher rate, ideally enabling additional resources to be spent on newer antibiotic products if needed. These changes by CMS are not expected to make a significant impact in the revenue for new antibiotics, but it is an encouraging sign that the US government is taking action to try to address some of the financial hurdles that antibiotic manufacturers face.[21] Other legislative efforts are ongoing to remove antibiotics from the DRG altogether.[22]

These payment changes in the US would keep antibiotic reimbursement within a volume-based system. Other countries are experimenting with delinked payment models. In the United Kingdom (UK), the National Health Service and National Institute for Health and Care Excellence (NICE) will be testing a new type of delinked payment model for antibiotics. The UK will be employing a subscription-like payment mechanism that will pay for antibiotics based on availability and value rather than the number of doses that are used. This reimbursement mechanism will use new modeling parameters with the HTA to catch

* Approved by the US FDA, EMA or PMDA, or reported by the developer as introduced in or after 2012.

elements of value that are not normally considered (e.g. enabling other procedures, reduction in transmission, and having a drug available for newly emerging resistance mechanisms). This model will initially be tested with a limited number of antibiotics, and actual reimbursement amounts are unknown. However, implementation will be closely watched, and if successful, stakeholders in other countries may consider adopting a similar approach.

In Sweden, the Public Health Agency has developed a value-based insurance model that would guarantee a certain level of revenue from the government to an antibiotic manufacturer regardless of the volume of antibiotic used.[23] The purpose of this model is to encourage market entry and enable access to the new antibiotic if needed. There are three aspects to this model. The first is the premium that is paid to the manufacturer based on the assessed value of the antibiotic without regards to volume. The second is the cost per unit of drug that is actually used, which would enable the antibiotic to be used and reimbursed without disruption to the current healthcare system. The third component is the ceiling spend for an antibiotic; in essence, Sweden would not pay more than a set amount if need for the antibiotic significantly increased over the set time period. This model has yet to be implemented, so it is unclear if the total payment would provide the needed incentive. However, it is feasible that if this model was implemented by multiple countries, then the accumulated premiums may provide a substantial return to the antibiotic manufacturer.

Norway, like Sweden, has low levels of AMR and limited antibiotic consumption, but has devised a model that attempts to ensure access if resistant infections were to emerge. The Norwegian Institute of Health undertook a study to design a reimbursement model that would ensure availability of critical antibiotics based on clinical need, and to augment HTA processes.[4] They concluded that consideration of a delinked model was constrained by the current pricing and reimbursement system, since changes would likely be complex. Instead, the Norwegian Institute of Health recommended that critical antibiotics should receive a premium price that would be paid by the hospital systems, then the government would provide an additional top-up payment. This model was not constructed as a means to encourage additional antibiotic development; due to the size of the country, it was determined that they would not be able to provide a financial incentive large enough to influence manufacturer behavior. However, like the Swedish model, if multiple small countries were to contribute, it could impact manufacturer decisions.

Overview of workshop

Moving forward, access to new antibiotics is important to maintain public health, particularly as AMR increases across the globe. Changes to how new antibiotics are paid for will have broad implications for commercialization and access across healthcare systems, and success of these antibiotics may benefit from better alignment of payment approaches. This workshop is convened to consider circumstances impacting the commercialization of novel antibiotics among different nations and opportunities to align policy approaches for antibiotic reimbursement reform and development incentives. During this workshop, the following topics will be discussed:

Exploring pre-market considerations for antibiotic development

Before bringing a drug to market, manufacturers must consider factors unique to the country of interest, including epidemiology and resistance trends, as well as regulatory decision-making and expected available evidence. This session will explore:

- How do expectations about the evidence generation of an antibiotic's effectiveness vary among nations?
- What are the opportunities to advance regulatory harmonization between different nations?

Understanding the factors that impact commercialization success

Once an antibiotic has received regulatory approval, country-specific factors can impact expected return on investment, which may in turn affect patient access. Return on investment may be influenced by value assessments, market size, and reimbursement systems, as well as by manufacturing capabilities and distribution channels. This session will explore:

- What are the barriers to registering products beyond the most 'core' markets – i.e. the extent to which these are commercial vs. administrative?
- How do current pricing and reimbursement policies impact patient access?
- Where are there opportunities to streamline country-specific assessments or negotiations for the reimbursement of novel antibiotics?

Examining potential policy and payment reforms

To capture the full value of antibiotics in reimbursement, new approaches to payment may be needed, including revised health technology assessments, alternative payment models, and incorporation of pre- and post-market evidence. This session will explore:

- What considerations could underlie a framework recommending alternative payment models among high-income countries with varied payers and populations?
- How should fixed or subscription payments adjust based on ongoing evidence development, and what is an appropriate time frame?
- What evaluation criteria should be used to determine the success of a new payment model?

Identifying areas for alignment

There is a need for better alignment and coordination for the success of reimbursement and access approaches and questions about the need and plausibility of development consensus principles that could be broadly applied and that would be equitable in innovation and access. This session will explore:

- On what issues is there opportunity for greater collaboration?
- How might multiple nations contribute toward an internationally coordinated pull incentive?
- What expectations regarding access and stewardship could apply globally toward eligibility for new payment models or a substantial pull incentive?

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