

Stewardship & Access Plan (SAP) Development Guide



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UK Government



CARB-X
Combating Antibiotic-Resistant Bacteria



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This Guide is endorsed by:

The Access to Medicine Foundation (ATMF)

The Bill & Melinda Gates Foundation (BMGF)

**Combating Antibiotic-Resistant Bacteria
Biopharmaceutical Accelerator (CARB-X)**

**The Global Antibiotic Research & Development
Partnership (GARDP)**

UK Government (Department of Health and Social Care)

**US Department of Health and Human Services (HHS)
Office of Global Affairs (OGA) & Biomedical Advanced Research
and Development Authority (BARDA)**

Wellcome Trust

This document has been produced at the request of CARB-X awardees, to provide guidance on how to meet the stewardship and access obligations for CARB-X-funded diagnostics, vaccines/other preventatives and treatments.

We hope that the information is of use to other Product Developers (PDs), as well as the wider scientific and global health community.

The Guide was developed collaboratively by a working group comprising of CARB-X, several of its funders (the United States Department of Health and Human Services (HHS) Office of Global Affairs (OGA) and Biomedical Advanced Research and Development Authority (BARDA), the Global AMR Innovation Fund (GAMRIF), UK Department of Health

and Social Care (DHSC), the Bill & Melinda Gates Foundation (BMGF), and Wellcome Trust), as well the Global Antibiotic Research and Development Partnership (GARDP) and the Access to Medicine Foundation (ATMF), with valuable consultative input from the Biotechnology Innovation Organization (BIO).

The SAP Development Guide is available online from the CARB-X website:

www.carb-x.org/about/stewardship-and-access

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www.carb-x.org/about/stewardship-and-access

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Abbreviations

AMR	Antimicrobial Resistance
API	Active pharmaceutical ingredient
ATMF	Access to Medicine Foundation
AWaRe	Access, Watch, Reserve
BARDA	Biomedical Advanced Research and Development Authority (US)
BMBF	The German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung)
BMGF	Bill & Melinda Gates Foundation
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDMOs	Contract development and manufacturing organisations
COI	Conflict of interest
DHSC	The UK Department for Health and Social Care
EMA	European Medicines Agency (EU)
FDA	Food & Drug Administration (USA)
FIND	Foundation for Innovative New Diagnostics
GAMRIF	Global AMR Innovation Fund (UK)
GARDP	Global Antibiotic Research & Development Partnership
GLASS	Global Antimicrobial Resistance Surveillance System
HHS	US Department of Health and Human Services
IP	Intellectual property
LMIC	Low and middle-income country
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MPP	Medicines Patent Pool
ODA	Official Development Assistance
OGA	US Office of Global Affairs
OECD	Organisation for Economic Co-operation and Development
OT	Other Territories
OTC	Over the counter
PD	Product developer
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PNECs	Predicted no-effect concentrations
PTE	Pass through entity
SAA	Sub-Award Agreement
SAP	Stewardship and Access Plan
TT	Targeted Territories
WHO	World Health Organization

Introduction

Summary of the Stewardship & Access Plan Requirement

Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) is a global non-profit partnership, with a portfolio that supports the world's largest early development pipeline of new antibiotics, vaccines, rapid diagnostics and other products to prevent, diagnose and treat life-threatening bacterial infections. Under Attachment 6, Section 5.01(c) of the CARB-X Subaward Agreement (SAA) ([See Annex A](#)), all CARB-X funded PDs are required to create a non-confidential Stewardship & Access Plan (SAP). The SAP explains the PD's strategy to meet the stewardship and access obligations contained in the SAA. PDs must submit an initial SAP within 90 days of their product entering pivotal clinical trials (generally Phase III trials, or equivalent for diagnostics).

The PD must also update the SAP: (1) upon first regulatory health authority approval for marketing by any of the FDA, EMA (or national authorities), MHRA or PMDA, and (2) following any significant market or product changes (SAA, Attach. 6, s. 5.01(d)). Events that may qualify as significant market or product changes include: product label expansions, new approvals obtained from a regulatory health authority, a contract is executed that satisfies a major obligation under the SAP, or changes to the World Health Organization (WHO) antibiotics Access/Watch/Reserve (AWaRe) categorisation for the product.

The stewardship and access provisions survive the termination or expiration of the SAA (SAA, Attach. 6, s. 5.01(f) (iii)). Additionally, the commitments follow the product and continue until the expiration of the last patent or exclusivity period in the United States, European Union/UK, or Japan related to Project IP. [See Annex A](#) for the full SAA excerpt in relation to stewardship and access.

Purpose of this Guide

The objectives of this Guide are to:

- 1) Assist PDs to write SAPs which fulfil the requirements of the SAA, meet the expectations of CARB-X funders, and facilitate faster and broader access to innovative antibacterials (antibiotics and non-traditional treatment approaches), preventatives (vaccines, phages, microbiome etc) and diagnostics, but without damaging the product's viability or sustainability in the market;
- 2) Help PDs think strategically and comprehensively to create practical and functional SAPs in timeframes and levels of detail appropriate to their product;
- 3) Suggest some of the activities, strategies and processes that could be adopted in order to support both stewardship and access, and provide links to additional guidance and organisations who might offer support. We hope to add to these resources over time, as all of us gain experience with this process.

The document includes a series of questions to stimulate PDs to think strategically and comprehensively about stewardship and access ([Annex B](#)), and provides an overview of some of the strategies and activities that could be adopted ([Annex C](#)). We have also provided a list of recommended organisations with specific knowledge and expertise who may be willing to provide non-binding confidential advice and support to your organisation, if this would prove helpful ([Annex D](#)). Finally, there is a checklist of stewardship and access activities that PDs should be able to easily consider at an early stage of product development ([Annex E](#)).

Defining Antimicrobial Stewardship & Access

‘Antimicrobial stewardship’ (which is also commonly referred to as **‘appropriate use’**) can be defined in many ways, but has recently been defined by the WHO as:

“a coordinated and coherent set of tailored actions to promote access and appropriate use of quality and affordable antimicrobials, including the selection of the optimal drug regimen, dosing, duration, and route of administration, following proper diagnosis, to improve patient outcomes across the continuum of care and prevent drug-resistant and healthcare-associated infections.”^{1 2}

‘Access to medicines’ has been defined by the WHO as:

“having medicines continuously available and affordable at public or private health facilities or medicine outlets that are an hour’s walking distance from the home.”³

The WHO identifies the following four factors that determine access to essential medicines:

- Rational selection of medicines
- Affordable prices
- Sustainable financing
- Reliable healthcare and supply systems⁴

The above factors apply very broadly to access to medicines, and it is recognised that PDs cannot feasibly tackle all these areas in their SAPs.

Therefore, more specific to **‘access to antimicrobials’**, there are four main components for PDs to consider:

- **Accessibility**

- Is the product registered and accessible in a country?
- Can patients reach the product/health services?

- **Availability**

- Is there a sustainable supply of the product available?
- Does the product meet a genuine public health need, as well as the specific needs of different patients? (e.g., children, pregnant women, etc)

- **Affordability**

- Is the product priced affordably for payers in low-income settings?
- Are suitable reimbursement models in place to reflect the product’s public health value?

- **Acceptability**

- Are the characteristics of the product compatible with patients’ attitudes, perceptions and expectations of the product?
- Is health promotion or education needed to support product use?

¹ WHO, *Policy Guidance on Integrated Antimicrobial Stewardship Activities* (2021)

² At time of publication, an updated WHO definition was being developed, but was not yet available. The definition will be updated in subsequent versions of this document.

³ WHO, *Access to affordable essential medicines. In: Millennium Development Goals* (2004). Available from:

<http://www.who.int/medicines/mdg/MDG08ChapterE/MedsEn.pdf>

⁴ WHO, *Equitable access to essential medicines: a framework for collective action* (2004). Available from: <https://apps.who.int/iris/handle/10665/68571>

The SAP Development Guide

Section 1. Product description

The first section of the SAP should define the specifications of the product.

Some questions to consider are:

- Which bacteria is the product active against?
- What is the initial indication of the product?
- Do you plan development for additional indications?
- Is your product designed for hospital or community use?
- Are you targeting the product for particular populations?
- Will the conditions of use be different across countries and regions?
- Are there special circumstances related to when it can/can't be used? (toxicity, use in combination with other drugs, specific populations such as pregnant women or children)

See [Annex B.1](#) for a full list of questions to aid PDs.

Section 2. Identify Obstacles and Constraints to Stewardship and Access

(Satisfies SAA, Attach. 6, s. 5.01(c)(ii))

Section 2 should include an early-stage analysis of the obstacles and constraints that exist which could hinder the PD achieving stewardship and access. In doing so, think practically, focusing on obstacles and constraints within the PD's control, as well as those which are not.

You should also consider the anticipated position of the product on the WHO AWaRe categorisation list, and the impact this may have on stewardship and access.

See [Annex B.2](#) for a list of guiding questions. Some of these questions may not apply to the initial PD but could apply to the product licensee or acquirer accountable for implementing the SAP.

These factors should therefore be considered as part of later iterations of a product's SAP. However, effective access and stewardship measures should be thought about at an early stage of product development, so PDs should think ahead as much as possible.

Section 3. Strategies to Ensure Marketing Approvals are Received in a Timely Manner in the Targeted Territories

(Satisfies SAA, Attach. 6, s. 5.01(c)(iv))

Receiving market approval from a regulator is an important first step to ensuring access to a medical product in a country. **The SAP should include the strategies that the PD will deploy to secure market approvals.** See [Annex B.3](#) for a list of guiding questions.

Some aspects to include are:

- List the expected sequence of marketing applications by groups of countries within the Targeted Territories (TTs) (as defined in the SAA Section 6.04 (a)(i)). Include general timelines if not commercially confidential.
- Include information about any plans to conduct additional clinical trials for phase IV and for other indications or specific, vulnerable populations (e.g., children, neonates, and pregnant or lactating women).
- If you are intending to utilise accelerated registration mechanisms, such as the Collaborative Procedure between the WHO Prequalification of Medicines Programme and National Medicines Regulatory Authorities, provide as much detail as you are able.
- Similarly, if you are considering additional availability mechanisms (e.g., EMA Article 58, special importation waivers, WHO Collaborative Registration Procedure, WHO Prequalification, GAVI, Global Antibiotic Research & Development Partnership (GARDP), Global Fund, etc.), provide as much information as possible. See [Annex D](#) for additional resources.

Section 4. Strategies to Support Stewardship and Access in the Other Territories

(Satisfies SAA, Attach. 6, s. 5.01(c)(i))

Outline which strategies the PD intends to deploy to support stewardship and access in the Other Territories (OTs) where the PD does not intend to market the product. Aspects to consider include:

- Pricing and marketing strategies (actual prices need not be disclosed)
- Out-licensing and tech transfer to third parties
- Global partnerships with purchasing organisations
- Supply chain and manufacturing strategies
- AMR surveillance systems
- Educational programmes
- Diagnostic test development to support stewardship and access

It is recommended that PDs think about stewardship and access strategies separately. The guiding questions in [Annex B.4](#) are divided in such a way. See [Annex C](#) for a non-exclusive list of stewardship and access strategies, compiled by the Access to Medicine Foundation (ATMF). See [Annex D](#) for a list of organisations which may be willing to provide non-binding, confidential advice and support.

Section 5. Strategies for Exploiting Project IP Rights in the Other Territories

(Satisfies SAA, Attach. 6, s. 5.01(c)(iii))

Outline what actions the PD will take to ensure that Project IP is not a barrier to access in OTs, including any plans to explore partnerships or licensing agreements with third-parties to achieve access in OTs. See Annex B.5 for a list of guiding questions.

See Annex D for contact information for potentially helpful resources, such as [Medicines Patent Pool \(MPP\)](#) and [GARDP](#). If you intend to explore partnerships or licensing agreements with such entities, include these details in the SAP.

Also indicate what further initiatives you consider to be required from governments, funders, regulators, NGOs and the private sector in relation to stewardship and access.

Section 6. Strategies for Monitoring Effectiveness of Stewardship and Access Activities

(Satisfies SAA, Attach. 6, s. 5.01(c)(v))

Provide details about what strategies the PD intends to use to monitor the effectiveness of stewardship and access activities, both for TTs (where the PD is undertaking the marketing) as well as for OTs. For OTs, the monitoring and evaluation could be part of the arrangements described in Sections 4 and 5 above.

Once a SAP is published on the CARB-X website following first registration, [ATMF's AMR Benchmark](#) will capture whether specific strategies have been implemented or not - provided that the product is in scope of the Benchmark.⁵ Any other organisation will be able to access your SAP via the CARB-X website and make their own assessment. ATMF are, however, a leading independent organisation in this field, and we encourage you to engage in a constructive dialogue with them and other organisations like them who might be able to provide advice and guidance before SAP publication.

See [Annex B.6](#) for a list of guiding questions, and [Annex D](#) for contact details for ATMF.

⁵ Please note that there is no formal relationship between CARB-X and ATMF, and they are not an 'official' evaluator of SAPs

Additional Considerations

Important disclaimers

- **This document provides advisory guidance only**, and no PD is bound by the suggested strategies and actions contained within. The SAA obligates PDs to produce an SAP in line with five broad principles (see [Annex A](#)), but the content of the SAP is at the discretion of PDs alone, consistent with their contractual obligations to CARB-X.
- It is important to highlight that **PDs are not expected to necessarily provide high levels of detail in their SAPs for every area covered in this Guide, particularly for the initial version of the SAP**. Not every question will be relevant for every SAP, due to differing product characteristics. Later versions of this Guide may provide further specific guidance for diagnostic and preventative PDs. During the time of CARB-X funding, most products will be many years away from potential first market approval, and although we encourage PDs to consider stewardship and access as early as possible, we understand that it will not always be possible to provide exhaustive answers before market approval. Instead, additional details and further access and stewardship strategies should be considered in subsequent versions of the SAP that PDs will be updating as product or market conditions change.
- **It is not the intention of this Guide to compel PDs to commit to stewardship and access strategies that would have a damaging impact upon the viability and sustainability of their product in the market**, nor damage the prospect of the product being acquired, obtain further investment or enter into other forms of collaboration. In this respect, it is recognised that PDs currently face unfavourable market conditions in many countries, even higher-income ones.
- **The SAP will be publicly available on the CARB-X website once the product has obtained its first regulatory approval, and so no confidential information should appear in the SAP**. However, we urge PDs to share as much information regarding the strategies and actions they intend to adopt in relation to stewardship and access. For example, if you sign a contract for sub-licensing a product in certain low-income territories, the details of the contract need not appear in the SAP, but the plan to engage with third parties and/or the existence of a contract could be, as this demonstrates the efforts the PD is making to support access. [Annex F](#) has some examples of the type of information that should be included in the SAP for different areas of stewardship and access, versus information which is considered commercially sensitive and should not be included.

Interplay between SAP and Official Development Assistance (ODA) Funding Requirements

The following considerations will only be relevant to PDs who receive [Official Development Assistance \(ODA\)](#) contributions from the UK Government. Under the International Development (Official Development Assistance Target) Act 2015, the UK has a legal requirement to spend 0.7% of its Gross National Income (GNI) as ODA and must ensure these funds are dispersed according to the Organisation for Economic Co-operation and Development (OECD) Development Assistance Committee rules for ODA spending.⁶ Global AMR Innovation Fund (GAMRIF) funding towards CARB-X and relevant PDs are for R&D activities which are designed to be primarily and directly for the benefit of people living in low and middle-income countries (LMICs). This requires that products developed using these funds are designed to support applicability, affordability and availability in the LMIC contexts for which they are intended.

PDs who have secured GAMRIF funding should be aware of the specific requirements placed on them through the application process, feedback from the CARB-X team or contact with the ODA Consultant at CARB-X. However, it is worth reiterating here that to meet ODA requirements, there needs to be demonstrable *intent* from PDs to ensure their product is applicable to the context of one or more LMICs – including burden of disease – as well as to explore ways to secure affordable access to their product in LMICs. This should be clear to PDs awarded ODA funds, as this intent – the ‘pathways to impact’ for LMICs - and the ODA-eligible activities will have been agreed in the project approval process.

Given these conditions associated with GAMRIF funding, it is expected that PDs receiving ODA funds will give an increased consideration to their stewardship and access plans for these products, with a particular focus to affordable access for LMIC markets.

For more information about ODA funding, see the [guidance on the CARB-X](#) website.

AMR Industry Alliance Roadmap

The [AMR Industry Alliance’s Industry Roadmap for Progress on Combatting Antimicrobial Resistance](#) lays out four main commitments to reducing antimicrobial resistance:

1. Reduce environmental impact from production of antibiotics
2. Help ensure antibiotics are only used by patients who need them
3. Improve access to current and future antibiotics
4. Explore new opportunities for open collaboration between industry and the public sector.

The Roadmap serves as a minimum standard for stewardship and access, and therefore **PDs should agree to the commitments laid out by the AMR Industry Alliance.**

⁶ Due to the impact of the Covid-19 global pandemic on the economy and, as a result, the public finances, the UK Government will temporarily move to a target of spending 0.5% of GNI on ODA in the financial year 2021/22. This is not expected to impact CARB-X-supported PDs receiving UK aid funding where this has been previously agreed.

WHO AWaRe categorisation

If your product is an antibiotic, which of the three [WHO AWaRe categories \(Access, Watch or Reserve\)](#) you expect it to be initially categorised under will have a significant impact on the stewardship and access strategies you may need to include in the SAP.

Most recently-approved antibiotics have been placed into the 'Reserve' category. The appropriate stewardship and access measures will be significantly different for a product that is categorised as an 'Access' antibiotic, suitable for wide availability and broad use in human health, as opposed to a 'Watch' or 'Reserve' antibiotic, which should be prescribed under much stricter circumstances when other first and second line treatments fail.

The SAP of a 'Reserve' drug may require going a step further on the topic of stewardship, but have different lower expectations on access compared to Access or Watch antibiotics. For example, PDs may want to outline how the use of a 'Reserve' drug will be reported and monitored, commit to engaging with national and international stewardship and surveillance programmes, and reflect the importance of stewardship in any educational or promotional activities related to the product. It would also increase the importance of activities such as the decoupling of sales incentives from sales volumes.

Therefore, **the first step that antibacterial PDs should take when considering stewardship and access is to have an informal technical discussion with WHO to determine which category their product will likely fall under.** WHO indicated that they are willing to have these informal discussions at an early stage of product development, and contact details can be found in [Annex D](#). CARB-X can assist in this process if requested.

Annexes

ANNEX A

Excerpts from CARB-X Sub-Award Agreement

Attachment 6, Section 5.01 Access, Not Excess

- (a) The purpose of CARB-X is to protect humanity from the most serious threats from drug-resistant bacterial infections by accelerating antibacterial product development. Over the long term, the new products invented or developed with CARB-X funding (the “Products”) must be sustainably managed and used to promote “Access, Not Excess,” including:
- (i) Thoughtful and effective stewardship of new Products whose utility is diminished by resistance, to prevent inappropriate use and therefore premature resistance, in line with the [Global Action Plan on Antimicrobial Resistance](#) developed by the World Health Organization;
 - (ii) Through planning for and ensuring appropriate access to new Products, especially in low- and middle-income countries; and
 - (iii) Avoidance of misaligned commercial incentives, which go against the above-stated goals.
- (b) Therefore, the Subrecipient agrees that Products will be manufactured, marketed, and sold under practices consistent with the applicable principles of the Davos Declaration on Antimicrobial Resistance – January 2016 or the [Industry Roadmap for Progress on Combatting Antimicrobial Resistance – September 2016](#).
- (c) The Stewardship and Access Plan. When its Product enters Phase III trials (or Phase IIb trials, if they are intended as the pivotal trials to support registration, or otherwise, when the Subrecipient is preparing a Product that is not a therapeutic or preventative for First Approval as defined in Section 5.01(d) below), the Subrecipient shall create and provide to the Pass Through Entity (PTE) [Trustees of Boston University] within ninety (90) days, a plan reasonably describing how it intends to meet the above stewardship and access obligations for the Product, (the “Stewardship and Access Plan”). The Stewardship and Access Plan shall not include confidential business information and shall include:
- (i) Strategy to support access and stewardship (e.g. proposed reliable production with sufficient capacity, supply systems, the broad approach to product labelling, and the broad approach to ensure economic barriers to access are as low as reasonably possible);
 - (ii) Identifying obstacles and constraints to access and stewardship;
 - (iii) Exploitation strategy for Project IP Rights, including whether it is planned for the Project IP Rights to be transferred to a third party;
 - (iv) Strategy to ensure marketing approvals are received for key territories in a timely manner; and
 - (v) Strategy for monitoring effectiveness of access and stewardship, including proposed metrics to measure success.

- (d) The Subrecipient shall update the Stewardship and Access Plan and provide it to the PTE when the Product is first approved by any of the FDA, EMA (or national authorities), or Japan's PMDA (the "First Approval"). After First Approval, the Stewardship and Access Plan shall be updated if there are significant market or product changes, or if events so require. The Subrecipient shall use best reasonable efforts to comply with its Plan at all times.
- (e) The Stewardship and Access Plan will be a non-confidential document and will be publicly posted on the PTE website.
- (f) Obligations Follow the Product
 - (i) If control of the Subrecipient's Project IP Rights resulting from the Project changes, whether through sale, transfer, license, assignment or otherwise, the Subrecipient will require the obligations of Sections 5.01, 5.03 and 6.04 to follow the Product and be incorporated into any such sale, transfer, license, assignment or otherwise to the new company (the "Acquirer"). Prompt notice will be provided by the Subrecipient to the PTE of any such event. If the Acquirer accepts obligations under Sections 5.01, 5.03 and 6.04, the Subrecipient is discharged from further obligations from Sections 5.01, 5.03 and 6.04.
 - (ii) If the Subrecipient fails to provide the Stewardship and Access Plan as provided in Section 5.01, within ninety (90) days, the PTE can demand the same in writing within sixty (60) days).
 - (iii) The obligations of this Section 5.01 survive the termination or expiry of this Subaward Agreement and shall continue in force until the expiration of the last patent or exclusivity periods in the United States, the European Union or Japan for any Project IP Rights (the "Project IP Expiration").
- (g) If the PTE informs the Subrecipient that it is no longer receiving CARB-X funding and no longer operates CARB-X, then Wellcome Trust will assume the rights reserved to the PTE in this Section 5.01, and, for purposes of this Section 5.01, the Wellcome Trust is an intended third-party beneficiary of this Subaward Agreement, and is entitled to enforce its rights as described in this Section 5.01 as if it were a party hereto.

ANNEX B

Guiding Questions for SAP Drafters

Section	Guiding Questions
1. Product Definition	<ul style="list-style-type: none"> • Which bacteria is the product active against? • What is the initial indication of the product? • Do you plan development for additional indications? • Is your product designed for hospital or community use? • Are you targeting the product for particular populations? • Will the conditions of use be different across countries and regions? • Are there special circumstances related to when it can/can't be used? (toxicity, mode of administration, use in combination with other drugs etc) • Has your product been developed in a way that this might support rapid or low-resource deployment (e.g. single dose, topical application, oral route, no cold-chain requirements)?
2. Identify Obstacles and Constraints to Stewardship and Access	<ul style="list-style-type: none"> • For new antimicrobials, what is the anticipated category that your product will be placed on the WHO AWaRe list? How does that category impact stewardship and access for your product? • Are there aspects of stewardship and access that are within the control of the PD that may be difficult to achieve? If so, why? (E.g., financial, technical, resource capacity, unfamiliarity with systems and processes) <ul style="list-style-type: none"> ○ Have you considered specific strategies to overcome these challenges or amplify opportunities (e.g. existing public funding, strong experienced national regulatory authority or political support for AMR therapy implementation)? • What is the split between public and private healthcare in targeted LMICs, and will this result in specific obstacles or opportunities to stewardship and access in some countries? • Are there unique product considerations that may present obstacles to broad and rapid product deployment? Examples might include: <ul style="list-style-type: none"> ○ Raw materials (active ingredients, adjuvants, excipients) availability and cost ○ Formulation adaptations to specific populations and environments ○ Manufacturing/scale-up challenges ○ Finished product stability and/or quality control (e.g., heat, humidity, light sensitivity) ○ Supply chain management (e.g., a need to maintain cold chain which requires closer monitoring of the supply chain) ○ Procurement and pricing (as a barrier to access) ○ Provider (dispensing from pharmacies or hospitals will make the stewardship plan look different) ○ End user and prescription practices/enforcement (OTC drugs may benefit from packaging adaptations directed at patients)

	<ul style="list-style-type: none"> • Do you foresee particular product manufacturing, supply chain management or cost of goods issues that could impact stewardship and access? • Are there specific health system capacity considerations (e.g., for community-based infections and treatment vs. hospital-based infections and treatment) that you are aware of? • Are there specific challenges to ensuring effective stewardship of new products? (e.g., lack of tools to define the proper use of a drug, absence of diagnostics, insufficient national capacity to conduct stewardship) • Do you foresee stewardship measures negatively impacting the market viability of your product? If so, are you able to provide details of which stewardship measures would negatively impact the market? This will help us to better understand the challenges PDs/owners face, and support the future development of this Guide • Are there wider barriers to achieving stewardship and access of this product that you are aware of that are beyond the control of your organisation?
<p>3. Strategies to Ensure Marketing Approvals are Receiving in a Timely Manner in the Targeted Territories</p>	<ul style="list-style-type: none"> • List the expected sequence of marketing applications by groups of countries within the TTs. Include general timelines, if not commercially confidential. • For the TTs, have you explored regulatory requirements with appropriate experts (i.e., national requirements related to clinical trials)? • Do you plan to carry out additional clinical trials for phase IV and for other indications or specific, vulnerable populations (e.g., children, neonates and pregnant or lactating women)? • Are you considering accelerated registration mechanisms or additional availability mechanisms (e.g., EMA Article 58, special importation waivers, WHO Collaborative Registration Procedure, WHO Prequalification, GAVI, GARDP, Global Fund, etc.)? Please elaborate. See Annex D for additional resources.
<p>4. Strategies to Support Stewardship and Access in the Other Territories</p>	<p><u>Related to Access</u></p> <p>Pricing:</p> <ul style="list-style-type: none"> • Do you have plans to price the product equitably in OTs to take into consideration differing economic circumstances? (e.g., differential price points that consider the unique ability to pay of specific countries or population groups, as determined through the use of socioeconomic factors, such as average household income)? • Will these strategies be applied only in OTs, or will some of these strategies also be used in some TTs? • Are equitable pricing strategies linked to company/organisational policies and marketing plans (e.g., reducing prices in some markets when economies of scale and more cost-effective manufacturing are achieved)? • Have you considered the different payers in OTs, and designed pricing strategies that are relevant and suitable to support access?

- If the product is intended for public markets or for use by humanitarian aid organisations/large multilateral global procurers, do you plan to offer discounts based on affordability or advanced market commitments?
- If the product is intended for private markets, do you plan to offer differential prices per country, and/ or a segmented approach based on unique ability to pay for those paying out of pocket?

Licensing:

- Have you considered licensing the product to a third-party organisation to achieve access in OTs (e.g., [Entasis granted GARDP an exclusive license with sublicensing rights in most LMICs](#))?
- If appropriate for your product, have you considered partnerships with purchasing organisations to support access in OTs (e.g., GAVI for vaccines)
- Would you be interested in guidance, support or a possible partnership with a non-governmental organisation or funder to facilitate registration and distribution of your product in OTs? See [Annex D](#) for a list of suggested organisations to contact.

Investigational & early access programmes:

- Is your product suitable for making investigational treatments available to eligible patients in OTs (e.g., Managed Access Programmes such as Compassionate Use and Special Access Schemes)?
 - If so, do you have plans to offer the product under such schemes? Which schemes are being considered, and why?
 - In which countries would patients be eligible for the programmes, and have you already received any such requests?
 - What is the rationale for why these countries have been selected (e.g., high disease burden, resistance rates, socioeconomic indicators such as type of health system financing, etc.)?
 - What types of patients will be eligible for these programmes, and how will they be defined and identified?
 - Companies such as [Novartis](#) and [Pfizer](#) have guidance and resources on their websites for physicians to request an investigational product prior to regulatory approval.

Supply chains and manufacturing:

- Are you considering methods to reduce or keep track of mark-ups along the supply chain (e.g., contracts with known reputed distributors, the use of third-party logistics or direct shipment to control mark ups, and where applicable, the inclusion of contractual obligations that limit mark-ups)?
- Are you considering efforts to strengthen supply chains (e.g., existence of shortage mitigation strategies, buffer stock, purchasing from multiple sources to keep suppliers of active pharmaceutical ingredients in business, supporting pool procurement mechanisms)?
- Are you considering strategies to ensure compliance with stringent quality standards along the supply chain?

- Are you planning to implement responsible manufacturing processes (e.g., development of an environmental risk-management strategy that assesses the manufacturing processes as well as how the company disposes of waste)?
 - At a minimum, do you intend to meet the standards outlined in the [AMR Industry Alliance Responsible Manufacturing Framework](#)?
 - At a minimum, do you intend to meet the discharge targets outlined in the [AMR Industry Alliance's list of Predicted No-Effect Concentrations \(PNECs\) document](#)?
 - What elements of the environmental risk management strategy (e.g., discharge targets, discharge levels, auditing results, list of suppliers) are being considered for public disclosure to enable responsible procurement and best practice sharing?
 - Have you considered supply management from an environmental perspective (e.g., what are the local conditions to ensure unsold and unused products are appropriately disposed of)?
- Do you have a manufacturing strategy to support access in OTs and avoid shortage issues? Activities could include working on lowering Cost of Goods and complexity in manufacturing, identifying appropriate API Contract Development and Manufacturing Organisations (CDMOs) or out-licensing strategies (For further guidance, see Access to Medicine Foundation's '[Shortages, Stockouts and Scarcity](#)' white paper, which offers detailed actions companies can take to ensure supply and avoid shortages.)
- Do you plan to facilitate local manufacturing in OTs or alliances with manufacturers to help lower prices and/or strengthen supply-chains? Please elaborate on which countries, if possible.

Related to Stewardship

Responsible promotion & sales strategies:

- Are you considering appropriate promotion and responsible sales strategies to prevent overselling (e.g., distributed through national programmes, avoiding marketing materials, decoupling sales incentives from sales volume)? The [AMR Benchmark](#) references best practices, which may be useful.
 - If so, which strategies are being considered?
 - In which countries/sectors will these efforts be applied?
 - Are you planning to adapt your promotion activities by country?
 - Do you intend to comply with the AMR Industry Alliance's commitment to meet responsible standards on marketing, sales and promotion, as outlined in the [AMR Industry Roadmap](#)?

	<p>Surveillance and data sharing:</p> <ul style="list-style-type: none"> • Do you plan to restrict the product’s use solely for human health (e.g., no animal or agricultural use), as recommended by the WHO? • Are you considering an AMR surveillance programme, or is there one already in place for the pathogen that this product targets that you intend to contribute to, in order to ensure resistance will be recorded? • Describe post-approval AMR surveillance studies likely to be required by regulatory authorities in connection with marketing approvals. • Are you considering additional AMR surveillance studies? • Do you intend to work with existing surveillance systems such as the WHO Global Antimicrobial Resistance Surveillance System (GLASS)? • Are you planning to share the raw surveillance data with open access databases, such as the AMR Register? <p>Educational activities:</p> <ul style="list-style-type: none"> • Do you intend to undertake any educational activities (e.g., clinical educational tools)? <ul style="list-style-type: none"> ○ If so, how do you intend to mitigate conflicts of interest? ○ Which strategies are being considered to mitigate conflicts of interest (e.g., receiving accreditation from an independent body that evaluates potential COI or providing an unrestricted grant to an independent third party to develop the activities)? ○ Have you considered working with others, such as through the AMR Industry Alliance, to deliver educational activities? <p>Diagnostics:</p> <ul style="list-style-type: none"> • If applicable, would your product benefit from the deployment of a diagnostic test, so that clinical use of your drug is more appropriate? <ul style="list-style-type: none"> ○ Is such a diagnostic in development? ○ If so, when will this diagnostic test be on the market, and in which territories? • The Foundation for Innovative New Diagnostics (FIND) may be willing to offer advice and support related to the development of diagnostics. You can find their contact details in Annex B.
<p>5. Strategies for Exploiting Project IP Rights in the Other Territories</p>	<ul style="list-style-type: none"> • For OTs, do you have plans to partner with other stakeholders to ensure appropriate access and effective stewardship (e.g., transferring the Project IP Rights and providing access to FDA/EMA regulatory dossiers and development data, to third parties such as Medicines Patent Pool or GARDP)? <ul style="list-style-type: none"> ○ If so, what are these plans (e.g., negotiating a collaboration or license agreement)? ○ If such plans do not cover all OTs, for which countries are these plans being considered?

	<ul style="list-style-type: none"> • If a voluntary license is being considered, will additional stewardship plans be built into licensee agreements to safeguard against over production and over use? <ul style="list-style-type: none"> ○ If so, which stewardship plans are being considered for licensee agreements? ○ Will the overall terms of the license agreements be made publicly available? • If there are barriers or challenges related to exploring a partnership with NGOs, governments or funders to ensure access and stewardship in OTs, what are they? • What specific support measures would you welcome from these actors to assist your access and stewardship strategies in OTs?
<p>6. Strategies for Monitoring Effectiveness of Stewardship and Access Activities</p>	<ul style="list-style-type: none"> • Do you have a strategy for reporting the actual implementation and effectiveness of stewardship and access activities? <ul style="list-style-type: none"> ○ If so, do you intend to report annually in a public document? ○ If you have out-sourced aspects of licensing, manufacturing, supply, marketing and sales, have you included reporting requirements in your agreements with partner organisations? • ATMF runs a Benchmark for antibiotic companies. It would be helpful if your company cooperated with them with respect to: <ul style="list-style-type: none"> (i) their multi-stakeholder and expert consultation process to update the methodology of the AMR Benchmark, including metrics to measure success of access and stewardship activities (ii) the data collection process for their reporting of the AMR Benchmark • Have you established a relationship with ATMF to explore what more you could be doing in order to achieve a high score on access and stewardship? See Annex D for contact details.

ANNEX C

ATMF List of Stewardship and Access Strategies

Availability components

Component	Why it helps	Example of detail in this component
Widespread and fast 1) country-level registration and/or 2) utilisation of additional availability mechanisms (e.g. special importation waivers)	<p>Ensures earlier availability of new products in high-burden markets in a timely manner.</p> <p>Provides availability for special populations that may be less likely to be prioritised (e.g., neonates and infants [paediatrics in general]).</p>	<p>Prioritise filing for country-level registration where disease burden/resistance is highest. E.g., private companies should file for registration in a predefined set of markets, including LMICs, (typically within one year of first market approval, which usually takes place with Stringent Regulatory Authorities, e.g., United States Food and Drug Administration [USFDA], European Medicines Agency [EMA]). Progressively file in more countries over time.</p> <p>Additional mechanisms to expedite availability may include:</p> <ul style="list-style-type: none"> • Special importation waivers; • WHO Collaborative Registration Procedure, if applicable; or • EMA Article 58, if applicable.
Managed access programmes for high-burden countries (prioritising LMICs)	<p>Makes certain investigational or unapproved treatments available to eligible patients. These patients may not be eligible to enrol in a clinical trial and may have life-threatening diseases or conditions, with no comparable or satisfactory alternative therapy to monitor or treat the disease or condition available.</p>	<p>Implement programs such as Compassionate Use or Special Access Schemes/Programmes.</p>

Access components

Component	Why it helps	Example of detail in this component
Equitable pricing	<p>Increases affordability to different and poorer market segments/countries.</p>	<p>Tailor equitable pricing strategies for LMICs, which are often overlooked. These strategies can be linked to company policies and marketing plans (e.g. cost-plus strategies). PDs may also consider improving the cost-effectiveness of manufacturing antibiotics.</p> <p>Price-caps ensuring limits on mark-ups by third parties, aligning final price with the intended price.</p> <p>Price-volume agreements, providing incentives and predictability with the supply of products while at the same time considering the risk of potential overuse.</p>

Sustainable manufacturing and supply	Facilitates predictability of supply to meet forecast global demands. Avoids stockouts and shortages.	Existence of shortage mitigation strategies (e.g., buffer stock, local/regional manufacturing, etc.). Local manufacturing commitments to help keep costs low and shorten supply chains, while recognising that this approach can add complexity to already weak supply chains. Short-term and long-term forecasting to accurately schedule demand, ensure continuity and avoid production loss. Purchase from multiple sources to keep the suppliers of active pharmaceutical ingredients (APIs) active and in business.
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Stewardship components

Component	Why it helps	Example of detail in this component
Supply chain strengthening	Helps make products available globally through supply chain strategies with plans to cover unexpected demand increases, as well as streamlined supply processes that reduce mark-ups and ensure quality as well as appropriate use.	Supply only through certified channels: Permissible buyers may include partners in the public sector (or monitored and controlled by the public sector) that can implement systems to detect and collect adverse effects and resistance emergence to the product. Depending on the status of the medicine (e.g., on the WHO's AWaRe list), it may need to be supplied under certain conditions e.g., only in a hospital setting or in centres with surveillance capacity to monitor resistance.
Appropriate promotion	Prevents overselling and subsequent over-prescription and overuse of antibiotics.	Sales staff should not promote antibiotics and any sales staff deployed in such markets for multiple products should not be incentivised by sales volume. Supply through national programmes, avoiding marketing materials.
Mitigation of COI in educational activities directed at healthcare professionals	Find the right balance between building health system capacity about AMR and mitigating the risks that that may arise from providing information about how specific products should be used.	Comprehensive COI mitigation can be done by: (1) receiving accreditation from an independent body that evaluates potential COI; or (2) providing an unrestricted grant to an independent third party to develop a programme; or (3) implementing three COI mitigation strategies simultaneously. These are: (a) developing content independently from the marketing department, (b) pledging not to provide financial or material incentives to participants, and (c) not using branded materials.

Packaging and product information addressing resistance and usage	Ensures that healthcare providers and patients are aware and well informed on the risks of resistance.	Product labelling accounts for different language/literacy needs. Product labelling includes adequate information on storage and transportation needs in different environments (temperature/light stability), sometimes going beyond national legal standards.
Avoid expansion of use in unnecessary indications	This may have an important impact on stewardship. Similar restrictions for non-human use could be considered.	Any development for a hospital-based indication/serious pathology will be discussed and agreed upon by both PDs and users. Facilitate additional trials to support guidelines for stewardship and use. Ban all non-human use, when appropriate.
Surveillance	Ensures that any resistance will be recorded and solved appropriately so that treatment remains effective.	Surveillance programs set up or in the absence of a program, PDs ensure adequate monitoring of resistance emerging. When surveillance programs are in place, data is shared through open data platforms.
Availability of susceptibility tests and diagnostics	Ensures appropriate usage of antibiotics only in the correct diagnosis. Thus, antibiotics are prescribed or given by HCPs only to the right patients at the right time.	Susceptibility testing of pathogens. Adequate availability of diagnostics.
Responsible manufacturing	Transparent implementation and auditing risk-management strategies reduce the likelihood of manufacturing practices contributing to the emergence of AMR.	Existence of an environmental risk-management strategy that assesses the manufacturing process as well as how the company disposes of antibacterial waste. This strategy should be applicable to any licensee and third parties as well. Both the strategy and the auditing results should be disclosed to ensure accountability.

Exploitation of IP rights components

Component	Why it helps	Example of detail in this component
Responsible IP arrangements, licensing arrangements	Ensures multiple sources of quality-assured medicines for use in LMICs. Contributes to equitable pricing, sustainable manufacturing and supply and registration in LMICs, which may be challenging for the original PD to achieve but could be prioritised by a licensee.	Waiver of patent rights and/or non-enforcement of rights in selected geographies. Voluntary licensing arrangements that include terms on royalties or royalty-free agreements, non-exclusivity for generic manufacturers, broad territorial applicability and supply commitments.

ANNEX D

Contact Details for Supporting and Partnering Organisations

Organisation	Topic	Contact name	Email address
World Health Organisation (WHO)	AWaRe Categorisation; Prequalification	WHO EML Secretariat	emlsecretariat@who.int
Access to Medicine Foundation (ATMF)	Market approvals; Access & Stewardship strategies	Margo Warren Marijn Verhoef	mwarren@accesstomedicinefoundation.org mverhoef@accesstomedicinefoundation.org
Medicines Patent Pool (MPP)	Market Approvals; Access & Stewardship strategies	Sandra Nobre	snobre@medicinespatentpool.org
Global Antibiotic Research & Development Partnership (GARDP)	Access & Stewardship strategies; Licensing	Jean-Pierre Paccaud	jppaccaud@gardp.org contact@gardp.org
Wellcome Trust	Stewardship & Access policy AMR Register	Oliver Williams Francesca Chiara	o.williams@wellcome.org f.chiara@wellcome.org
Foundation for Innovative New Diagnostics (FIND)	Diagnostics	Cecilia Ferreyra	cecilia.ferreyra@finddx.org
AMR Industry Alliance	Manufacturing and environmental standards; Educational activities; Sales and Distribution strategies	Melissa Mitchell	mmitchell@amrindustryalliance.org info@amrindustryalliance.org
Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)	All	Rose Garson	rgarson@bu.edu

ANNEX E

Checklist of Recommended Early Stage Stewardship and Access Actions

Recommended early stage Stewardship and Access actions	✓
Speak to WHO about: - which AWaRe category the product falls into - WHO Prequalification Programme - WHO Collaborative Review Procedure for accelerated registration	
Commit to the AMR Industry Alliance Roadmap and related voluntary standards	
Speak to FIND about the development of diagnostics to support stewardship and access	
Speak to GARDP about long-term partnerships for your product to facilitate access in OTs	
Commit to contributing raw surveillance data to the AMR Register and GLASS	
Speak to Access to Medicine Foundation early and maintain constructive dialogue	
Plan to review and update the SAP regularly	

ANNEX F

Examples of Information in an SAP versus Commercially Sensitive Information

S&A Area	Information that should be included in the SAP	Commercially sensitive information that should not be included in the SAP
Define the product	<ul style="list-style-type: none"> • Non-commercially sensitive product information that will impact the relevant S&A activities included in the SAP 	<ul style="list-style-type: none"> • Commercially sensitive product information
Clinical trials	<ul style="list-style-type: none"> • Which countries clinical trials will be conducted in • Plans for additional clinical trials 	<ul style="list-style-type: none"> • Confidential clinical trial data
Registration	<ul style="list-style-type: none"> • If not commercially sensitive, sequencing of registration in TTs • Which countries are designated TTs/ OTs • Any plans to register in OTs 	<ul style="list-style-type: none"> • Commercial strategy for registration in TTs
Pricing	<ul style="list-style-type: none"> • Commitment to adopt equitable pricing strategies in OTs • Description of an equitable pricing mechanic (COGS + percentage, without revealing COGS) 	<ul style="list-style-type: none"> • Commercially sensitive pricing plans in different territories
Licensing/IP	<ul style="list-style-type: none"> • Commitment to engage with partners to transfer/sublicense IP • The existence of licensing agreements that cover OTs • If possible, the name of third-parties involved in licensing agreements in OTs • Whether access to critical third-party IP/background technologies are included within licensing agreements 	<ul style="list-style-type: none"> • Commercially sensitive details within licensing agreements
Manufacturing	<ul style="list-style-type: none"> • Commitment to explore local manufacturing to reduce costs/supply chain in OTs • Commitment to responsible manufacturing processes 	<ul style="list-style-type: none"> • Contractual details of manufacturing for product, including location, costs and parties involved
Marketing and sales	<ul style="list-style-type: none"> • Commitment to responsible marketing and sales practices 	<ul style="list-style-type: none"> • Details of marketing and sales strategies in TTs and OTs
Surveillance	<ul style="list-style-type: none"> • Commitment to share surveillance data through own programmes or with existing surveillance systems 	<ul style="list-style-type: none"> • Confidential product data