SUMMARY OF THE DESCRIPTION OF THE ACTION

Ensuring availability of off-patent antibiotics

TABLE OF CONTENTS

ACRONYMS

ANMV	National Agency for Veterinary Medicines
AMR	antimicrobial resistance
ANSES	National Agency for Food, Environmental and Occupational Health Safety
ANSM	French Drug Agency (human medicine)
BPG	Benzathine penicillin G
DALY	disability-adjusted life year
DGAL	Directorate General for Food
DGE	Directorate General for Enterprise
DGOS	MSS Directorate General for Healthcare Organisation
DG Reform	Directorate General for Structural Reform Support
DGS	MSS Directorate General for Health
DSS	MSS Directorate for Health & Social Security
EAHP	European Association of Hospital Pharmacists
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FTE	full-time equivalent
FWG	French Working Group
HAS	National Authority for Health
HMA	Heads of Medicines Agencies
IACG	Interagency Coordination Group on Antimicrobial Resistance
LEEM	French Pharmaceutical Companies Association
M&E	monitoring and evaluation
MSS	Ministry for Solidarity and Health
MTES	Ministry for the Ecological and Inclusive Transition
NWC	National Working Committees
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
RFSA	French Network for Animal Health
SDG	Sustainable Development Goal
SIMV	French Veterinary Pharmaceutical Companies Association
UN	United Nations
UNEP	United Nations Environment Program
WHO	World Health Organization

1. CONTEXT AND OBJECTIVES OF THE ACTION

1.1 Context

The mission of the Directorate-General for Structural Reform Support (DG REFORM) of the European Commission is to provide support for the preparation and implementation of growth-enhancing administrative and structural reforms by mobilising European Union (EU) funds and technical expertise. France has requested support from the European Commission under Regulation (EU) 2017/825 on the establishment of the Structural Reform Support Programme ("SRSP Regulation"). The request has been analysed by the Commission in accordance with the criteria and principles referred to in Article 7(2) of the SRSP Regulation, following which the European Commission has agreed to provide support to France together with World Health Organization (WHO) in the area of human health, animal health and the environment (One Health approach), with the purpose of **addressing the root causes of the recurrent shortages and lack of availability on the market of off-patent antibiotics in France (in humans and animals, while taking into account the environment) and identify effective countermeasures** under the conditions set in the Contribution Agreement.

How severe are shortages and lack of availability of off-patent antibiotics?

Antimicrobial Resistance (AMR) poses a major threat to global human health, to the financial sustainability of healthcare systems, and it implies high economic costs to society internationally. Also in the animal health sector AMR poses a major problem that affects human health and the economic development of countries.

The World Bank in 2019 reported that "*by 2050, in a high-case scenario of antimicrobial resistance (AMR) - where antibiotics and other antimicrobial drugs no longer treat infections the way they are supposed to - could cause low-income countries to lose more than 5% of their GDP and push up to 28 million people, mostly in developing countries, into poverty by 2050*[1]. The European Centre for Disease Prevention and Control (ECDC) estimates that in EU/EEA countries infections with multi-resistant bacteria accounted for 33 000 attributable deaths, and 874 541 Disability-adjusted life years (DALYs) in 2016, which is comparable to the combined disease burden of influenza, tuberculosis and HIV/AIDS[2]. The US Centers for Disease Control and Prevention estimated that in the USA each year more than 2.8 million people get an antibiotic-resistant infection, causing more than 35 000 deaths[3]. While infections with antibiotic-resistant bacteria affect all age groups, the elderly and infants are disproportionally affected and suffer from a significantly higher burden of disease. One study estimated that globally,

[1] "By 2050, drug-resistant infections could cause global economic damage on par with 2008 financial crisis". World Bank, September 20th, 2016. Available at: https://www.worldbank.org/en/news/press-release/2016/09/18/by-2050-drug-resistant-infections-could-cause-global-economic-damage-on-par-with-2008-financial-crisis

[2] "33000 people die every year due to infections with antibiotic-resistant bacteria". ECDC, November 6th, 2018. Available at: https://ecdc.europa.eu/en/news-events/33000-people-die-every-year-due-infections-antibiotic-resistant-bacteria.

[3] "Antibiotic Resistance Threats in the United States". CDC, 2019. Available at: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

each year 214 000 neonatal sepsis deaths are attributable to resistant pathogens, a vast majority occurring in lower- and middle-income countries[4].

Until recently, an overlooked issue in the fight against AMR is the frequency of supply chain disruptions of off-patent antibiotics (also addressed as 'old or generic antibiotics'). Supply chain disruptions (often leading to shortages[5]) occur for different reasons, for instance when an antibiotic cannot be produced or distributed. The IACG[6] in its report to the UN Secretary-General pointed out that fragile production and supply chains for existing antimicrobials due to the small number of producers are leading to frequent shortages around the world increasing the risk of AMR in both humans and animals. Moreover, there is an increasing risk that existing antibiotics disappear from the market if remaining suppliers discontinue their production. Combatting shortages of antibiotics and strengthening supply systems are basic enabling conditions of successful stewardship programmes to foster appropriate use. In addition to the shortages issue, off-patent antibiotics are also not available because of a lack or a discontinuation of marketing. In this case, off-patent antibiotics are available in other markets but specific countries are unable to access them.

Shortages for human use have been reported for different formulations, in particular for intravenous formulations used in hospitals. These antibiotics are a key part of the therapeutic arsenal and their constant availability is of utmost importance to ensure that hospitals and health personnel can follow recommended standards of care. Shortages can lead to patients receiving suboptimal treatment including delayed treatment, intravenous injections rather than oral forms, and greater side effects. Economic costs include costs to manage shortages as well as increased costs for procurement of alternatives.[7]

A survey of the European Association of Hospital Pharmacies (EAHP) showed that the percentage of hospital pharmacists in European hospitals reporting antibiotics shortages increased from 57% to 77% between 2014 and 2018, respectively.[8] Moreover, hospital pharmacists reported that antimicrobials are the therapeutic class most frequently affected by shortages. In France, the number of alerts of drug shortages notified in human medicine to the French Drug Agency (ANSM) increased 10-fold between 2008 and 2013. In 2017, a 30% increase was reported. In this context, antimicrobials are one of the three therapeutic classes that are the most affected and represent 21% of all reported drug shortage alerts. Antibiotics shortages have been observed for piperacillin – tazobactam, benzathine penicillin G (BPG), amoxicillin – clavulanic acid (intravenous form) and intravenous penicillin M in particular.

In the veterinary sector, safeguarding the availability of established veterinary antibiotics is even more important as very few (if at all) new antibacterial active substances will be developed for use in veterinary medicine. Rising concerns about AMR in humans and animals, lead to limitations for the veterinary use of those antibiotics considered critical for humans (e.g. fluoroquinolones, 3rd- and 4th-

[4] "Access to effective antimicrobials: a worldwide challenge". Laxminarayan et al., Lancet, 2016. Available at : https://doi.org/10.1016/S0140-6736(15)00474-2 . LSH stands for Latin Hypercube Sampling (LHS).

[5] Acosta et al. (2019) point out that countries have adopted different definitions for medicine shortages. Acosta A, Vanegas EP, Rovira J, Godman B and Bochenek T (2019)Medicine Shortages: Gaps Between Countries and Global Perspectives. Front. Pharmacol. 10:763.doi: 10.3389/fphar.2019.00763

[6] Interagency Coordination Group on Antimicrobial Resistance. No time to wait: Securing the future from drug-resistant infections, Report to the Secretary-General of the United Nations (2019) https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf?ua=1

[7] WHO. Meeting Report, Antibiotic Shortages: Magnitude, Causes and Possible Solutions (2019) https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf?ua=1

[8] EAHP. Survey on Medicines Shortages to improve patient outcomes (2018) https://www.eahp.eu/sites/default/files/report_medicines_shortages2018.pdf

generation cephalosporins, and colistin). For the same reasons, new antibiotics developed for human use in general will not be authorized for use in animals. Hence, the continued availability of older veterinary antibiotics is essential to keep a range of safe and effective treatment options for bacterial diseases in animals in France and the EU. While shortages as such as are less of a problem in the veterinary sector, antibiotics for animals are more often withdrawn from the market or lack marketing authorisation. The lack of antibiotics for the treatment of minor species and potential restrictions of use of specific antibiotics are also issues of concern for the animal sector. In 2018, the French National Agency for Veterinary Medicines (ANMV) reported that antibiotics shortage remained stable with respect to those reported in previous years and amounted to 11% of all shortages alerts[9].

What policies have been implemented so far to tackle shortages and lack of availability?

The EU legal framework for human medicines sets standards to ensure a high level of public health protection and the quality, safety and efficacy of authorised medicines. The requirements and procedures for marketing authorisation are primarily, including harmonised provisions for the manufacture, wholesale or advertising of medicinal products for human use are laid down in Directive 2001/83/EC and in Regulation (EC) No 726/2004. There are additional ongoing initiatives aiming at analysing the causes of drug shortages in-depth and at identifying possible solutions. The European Medicines Shortages Research Network (CA15105) aims at stimulating and developing scientific research, as well as proposing solutions by end of 2020.[10] The network will look at causes of shortages and their impact on patients and propose short and long-term solutions to address them. The project will cover all pharmaceuticals, but antimicrobials have been identified as a priority.

In veterinary sector, a new Regulation (EU) 2019/6 on veterinary medicinal products, published on 7 January 2019, repeals Directive 2001/82/EC and introduces new rules and concepts for reducing the administrative burden, stimulating innovation, incentives to increase the availability of veterinary medicinal products and strengthening the EU action to fight AMR.

The European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) also created the Task Force on the Availability of Authorized Medicines for Human and Veterinary Use (EMA/HMA). The Task Force looks at: i) ways to minimize supply disruptions and avoid shortages; ii) strategies to improve prevention and management of shortages caused by disruptions in the supply chain; and iii) pathways improving timely access to up-to-date information on availability issues, for all actors within the network as well as users of medicines[11].

Concerning the causes leading to antibiotics shortages, a WHO report highlights that they include the low return on investment and the dependency on few actors involved in the production chain (e.g. limited number of firms that produce raw materials)[12]. It was also highlighted that regulatory aspects also lead to absence of marketing, since obtaining market authorization requires a high investment that is unlikely to be compensated by the low expected benefits on the market. While different governments have started to implement measures to tackle antibiotics shortages, they have not been successful in building comprehensive strategies to address these root causes (long-term). Governments have focused

[9] https://www.anses.fr/fr/system/files/ANMV-Ra-Pharmacovigilance2018.pdf

[10] https://www.cost.eu/actions/CA15105/#tabs|Name:overview

[11] https://www.hma.eu/522.html

[12] WHO (2018) Meeting Report Antibiotic Shortages: Magnitude, Causes and Possible Solutions. Norwegian Directorate of Health, Oslo, Norway 10-11 December 2018 https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf?ua=1

on setting up measures to manage and mitigate the impact of shortages such as implementing early warning systems and requiring companies or other actors to improve reserves stock-pilling. There is evidence that the number of marketed antibiotics in Europe, Canada, Australia and the United States has decreased in human medicine in recent years.[13] These initiatives will provide options to address shortages and lack of availability of off-patent antibiotics but governments will need to implement them and follow-up their impact.

Policies implemented so far in France

France started to introduce measures to address pharmaceutical shortages in human medicine in the early 2010s. In 2012, the government implemented new rules making pharmaceutical companies responsible for ensuring appropriate and continuous supply of wholesalers and for informing pharmacists, wholesalers and authorities of possible shortages. Additionally, wholesalers must comply with specific deadlines for delivering products and provide most dosage forms of a product (9 out of 10). In 2016, the 'health system modernisation law' introduced further reforms to ensure greater accountability of pharmaceutical companies through the implementation of shortages' management plans for medicines with a major therapeutic interest, notably antibiotics (measures about security, registration of raw materials' alternative manufacturing sites, identification of equivalent drugs, etc.). The obligation for industrials to have such management plan came into force in June 2017. The assessment of 20 management plans of antibiotics' shortages has been performed as well as the mapping of some antibiotics' manufacturing sites.

All the actions implemented in France so far have not yet reduced the number of antibiotics' shortages. Moreover, several projects, notably the inventory and root cause analysis led by the French Drug Agency (ANSM) and the French Pharmaceutical Companies Association (LEEM), were initiated but were not finalised.

One of the main reasons for the limited impact of these measures is the complexity and multifactorial nature of the problem, the need for involvement of many actors including pharmaceutical industry representatives, and the need to consider all national measures addressing the same issue within a European context. In line with this, a recent study raises the question on whether setting up legal obligations and sanctions for pharmaceutical companies and pharmacy wholesalers is sufficient to address 'a multifactor and worldwide issue'[14].

Regarding lack of marketing or discontinuation of marketing, the ANSM has repeatedly tried to work with the pharmaceutical industry and other stakeholders to keep off-patent antibiotics on the French market or to reintroduce them, ticarcillin-clavulanic acid being a recent example.

Against this background, France requires the support of experts to provide concrete actions to tackle antibiotics shortages and lack of availability and facilitate their implementation. Experts will compile the complex, scattered information on the reasons behind antibiotics shortages and lack of availability in France and reflect on those affecting other European Countries. Experts will also combine different methodological approaches to identify evidence-based policies and to engage stakeholders to fine-tune

[13] C. Pulcini, S. Mohrs, B. Beovic, I.C. Gyssens, U. Theuretzbacher, O. Cars. Forgotten antibiotics: a follow-up inventory study in Europe, US, Canada and Australia. Int J Antimicrob Agents, 49 (2017), pp. 98-101

[14] Bocquet F, Degrassat-Théas A, Peigné J, Paubel P. The new regulatory tools of the 2016 Health Law to fight drug shortages in France. Health Policy. 2017 May; 121 (5):471-476.

their design and to increase the chance of a successful implementation. Additionally, experts will disseminate the knowledge gained through this Action to other Members States.

At the same time, the French agency for veterinary medicines (ANMV) also developed activities to fight against shortages and lack of availability of veterinary medicinal products. The ANMV adopted a Good Practices Guide to manage shortage in collaboration with all stakeholders (marketing authorisation holders, wholesalers and veterinarians) with objectives of more transparency, better communication and better sharing of information and proposal of alternatives when it exists. ANMV with RFSA (the national network of animal health) realised a mapping of therapeutic gaps by species to increase innovation and availability of veterinary medicines.

WHO activities and expertise related to shortages and lack of availability of essential medicines and antibiotics in particular

In its 13th Global Programme of Work 2019-2023[15], WHO has identified AMR as one of the major challenges for global health and made it one of its priorities. WHO will promote policy and technical dialogue on AMR across sectors in Member States, and will provide strategic support for scaling up comprehensive and sustainable actions to tackle AMR and related specific pathogens, based on the Global Action Plan on Antimicrobial Resistance, the 2030 Agenda for Sustainable Development and the Political Declaration of the high-level meeting of the General Assembly on AMR. These actions will include optimizing the use of antimicrobial medicines, including combatting shortages of existing antibiotics as highlighted by the IACG.

In 2019, the new WHO Antimicrobial Resistance Division was set up to define, advance, promote and monitor comprehensive policies and strategies that prevent, reduce, and mitigate drug-resistant infections and the overall impact of AMR globally based on the Global Action Plan on Antimicrobial Resistance and the 13th General Programme of Work of WHO and the Sustainable Development Goals (SDGs). The Department of Global Coordination and Partnership on Antimicrobial Resistance leads and coordinates the global One Health response to AMR, including the work on research and development of new antibiotics as well as promoting the appropriate use and combatting shortages. In 2018, WHO carried out a project reviewing the magnitude and the root courses of shortages in European countries and organized a meeting with representatives of a number of European countries and key stakeholders to discuss possible actions.[16]

A one-health approach is needed to control AMR

Use of antimicrobials in food animals can create a source of antimicrobial resistant bacteria that can spread to humans through the food supply. Improved management of the use of antimicrobials in food animals, particularly reducing those critically important for human medicine by maintaining availability of other antimicrobials in the veterinary sector, is an important step towards preserving the benefits of antimicrobials for people. Therefore, WHO works closely with the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) in its endeavours to combat AMR. A

[15] WHO, Thirteenth general programme of work 2019-2023 (2019) https://www.who.int/about/what-we-do/thirteenth-general-programme-of-work-2019-2023.

[16] WHO (2018) Meeting Report Antibiotic Shortages: Magnitude, Causes and Possible Solutions. Norwegian Directorate of Health, Oslo, Norway 10-11 December 2018 https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf?ua=1

multitude of projects have arisen from this collaboration that are managed by the tripartite Secretariat that has been established in WHO in 2019 to manage the close collaboration among the three agencies. WHO thus regularly draws on the expertise of FAO and OIE when it comes to questions on the use of antibiotics in animals or plants and related risks for human health.

On EU level, the European One Health Action Plan against Antimicrobial Resistance (COM(2017)339) and the new Regulation (EU) 2019/6 on veterinary medicinal products are part of the regulatory framework emphasizing the importance of the One health approach.

The OIE in 2016 adopted the Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials that governs its activities on AMR. The OIE is the standard-setting organisation for animal health, including zoonoses. Over the past year, it has developed a wide range of international standards on antimicrobial agents – in particular on responsible and prudent use – that are regularly reviewed and updated. The OIE also is engaged with its Member countries in capacity-building for veterinary services.

With respect to antibiotics, WHO has developed and applied criteria to rank antibiotics according to their relative importance in human medicine that are published in form of the WHO list of critically important antimicrobials (WHO CIA list). [17] Clinicians, regulatory agencies, policy-makers and other stakeholders can use this ranking when developing risk management strategies for the use of antimicrobials in food production animals with the ultimate goal to preserve the effectiveness of currently available antimicrobials.

This work is closely linked with the longstanding programme of WHO on access to essential health products. The WHO Roadmap for access to medicines, vaccines, and other health products, 2019–2023[18] inter alia focuses on improving the capability and capacity to responding to shortages of medicines and vaccines. It foresees the establishment of a global mechanism for early detection of shortages and rapid notification systems and a framework of mitigation actions needed to prevent and respond to shortages.

AMR and the environment

Bacteria can become resistant to antibiotics through a variety of mechanisms, such as mutation or genetic exchange (acquired resistance). This can occur in microorganisms in the body of human or animal hosts, but also in environmental settings. In the environment, bacteria can share genetic material including the genes that code for AMR that can be present in naturally resistant bacteria under selective pressure when antibiotics or other selecting agents, for example heavy metals, biocides, herbicides and pesticides, are present. The presence of antimicrobial agents or their residues in the environment can weaken or deplete the main populations of disease causing bacteria allowing the remaining resistant strains to flourish. The emission of antimicrobial agents or their residues through human and animal excreta, through wastewater including stemming from chemical or pharmaceutical manufacturing facilities as well as the use of antibiotics, biocides in households or medical facilities, herbicides and pesticides in plant protection can all drive the emergence of AMR against existing treatments and ultimately threaten human health. In this context, WHO works hand in hand with FAO, OIE, the United Nations Environment Program (UNEP) and other relevant organizations on access to clean water, sanitation, hygiene and wastewater control.

The European Commission in 2019 adopted a Communication on a Strategic Approach to Pharmaceuticals in the Environment (COM(2019) 128 final) which envisages "measures to be taken at

[17] https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/

[18] https://apps.who.int/iris/handle/10665/330145

Union and/or Member State level to address the possible environmental impacts of pharmaceutical substances, with a view to reducing discharges, emissions and losses of such substances into the aquatic environment, taking into account public health needs and the cost-effectiveness of the measures proposed".

Consequences of the COVID-19 crisis on the availability of antibiotics in the EU

Shortages and availability of essential medicines patented and off-patent has emerged as one of the challenges of the COVID-19 pandemic. Increased demand of off-patent essential medicines such as azithromycin, fentanyl and other products needed in intensive care as well as the challenge to meet global demand for potential cures and vaccines combined with travel and trade restrictions have demonstrated the weaknesses of a global supply chain. These challenges, including environmental issues have been discussed earlier specifically for antibiotics and will be taken into account in this Action.

1.2 Objectives of the Action

The general objective of this Action is to contribute to institutional, administrative and growth-sustaining structural reforms in France. By approving the request for technical support submitted by France, DG REFORM assessed that the proposed Action is in line with Article 4 of the SRSP Regulation; and the Action will contribute to the achievement of the following specific objectives of the SRSP Regulation:

- to support the national authorities in enhancing their capacity to formulate, develop and implement reform policies and strategies and in pursuing an integrated approach ensuring consistency between goals and means across sectors
- to support the efforts of national authorities to define and implement appropriate processes and methodologies by taking into account good practices of and lessons learned by other countries in addressing similar situations

The achievement of the objectives are not solely the responsibility of WHO and will depend partly but not only on France action.

1.3 Relevance of the Action

This Action will be essential to implement the structural measures tackling shortages and lack of availability of off-patent antibiotics, in line with the EU Action Plan against Antimicrobial Resistance, the Global Action Plan on Antimicrobial Resistance, the OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials, the Report of the UN Interagency Coordination Group (IACG) on Antimicrobial Resistance and UN Sustainable Development Goal 3 "Ensure healthy lives and promote well-being for all at all ages". The Action taking place in France will allow to garner experience and best practice that can be extrapolate in other countries as well as on European level.

The proposed Action is in line with policy objectives in France and definition of interventions to reach them. The Action is part of the implementation of the French inter-ministerial roadmap on AMR published on November 21st, 2016, more precisely of:

- Action 24 "To preserve the efficiency of the therapeutical arsenal by implementing incentives which aim to maintain old antibiotics on the market" and

- Action 37 “To raise awareness at the European level in order to create a specific framework dedicated to develop products which control AMR” as well as of the
- French National 2019-2022 roadmap on drug shortages of the French Ministry for Solidarity and Health (Ministère des Solidarités et de la Santé, MSS) and
- Action 16 and 19 of the French Ecoantibio plan two, the sectorial AMR roadmap for animal health that aims to maintain the supply of veterinary antibiotics to support for provisions that foster/protect innovation (including data protection for existing market authorizations and development of older market authorizations).

The pilot measures that will be identified through this Action will be implemented in France to address the root causes of the shortages’ and lack of availability issue, for antibiotics used in both human and veterinary medicine, while at the same time protecting the environment and taking into account the European and national regulation contexts and required evolutions.

1.4 Beneficiary EU Member State Institution(s), Target Groups and Other Stakeholders

The beneficiary Member State of the Action is France and the main beneficiary Member State institution is the Ministry of Solidarity and Health (Ministère des Solidarités et de la Santé (MSS)).

The cross-sectoral approach integrated in the Action will benefit other institutions in France involved in setting policies to counter shortages and lack of availability of essential pharmaceuticals in the human and veterinary sector, in particular the Ministry of Agriculture and Food for the use of antibiotics in the animal sector and the Ministry of the Economy and Finance, as part of the implementation of the national health technologies and industries sector’s strategic agreement. In the human sector, the Action’s main benefit will be for those who are today suffering from recurrent shortages and lack of availability of off-patent antibiotics, hospitals, hospital pharmacies and community pharmacies as well as patients that are in need of off-patent antibiotics and today do not always have access to the recommended treatment. In the veterinary sector, veterinarians, breeders and animal owners will benefit as the lack of availability of certain antibiotics could conduct to inappropriate use of antimicrobials considered as critical for human health. The Action will also benefit the industry by allowing for better forecasting and, in the long term, by assuring a better, more stable and predictable market for antibiotics or for maintaining availability of veterinary medicines containing antimicrobials not critically important for humans.

2. DESCRIPTION AND IMPLEMENTATION OF THE ACTION

2.1 Impact, Outcomes, Outputs and Activities

2.1.1 Impact of the Action: Outcome, Outputs, Activities

While the French government over the past years has already taken actions to mitigate shortages and lack of availability of medicines and antibiotics in particular, these actions so far have not yet reduced the number of antibiotics' shortages. One of the main reasons is that current measures have focused mostly on how to manage occurring shortages and are just starting to address their root causes. The latter is due to the multifactorial nature of the problem, the need for involvement of many actors including pharmaceutical industry representatives, and the need to consider all national measures within a European context also impacted by the same issue.

The overall objective of this Action therefore is to address the root causes of the recurrent shortages and lack of availability of existing off-patent antibiotics in France and identify effective countermeasures at national and European level. The specificity of veterinary sector shall be taken into account as the supply chain is different than that of the human sector and the reasons behind availability gaps are not the same.

The Action is based on the following results framework: activities – outputs – outcomes – impact.

It is expected that all relevant French Ministries, government institutions and stakeholders, having been closely involved in the design and the implementation of the Action and consulted at all major stages will adopt the selected pilot measures through their internal mechanisms and implement them. Subject to this, the outputs are expected to result in the following outcomes:

- **Outcome 1:** The French Authorities have improved knowledge and awareness of factors leading to shortages and lack of availability of off-patent antibiotics in the human and veterinary sector.
- **Outcome 2:** The French Authorities are enabled to take measures to address the root causes of shortages and lack of availability of off-patent antibiotics, and share insights and lessons learned with other stakeholders.
- **Outcome 3:** The French Authorities and stakeholders are enabled to implement and to monitor and evaluate the implementation and impact of the measures.

Subject to other contributing factors, the activities and outputs of this action, and the associated outcomes, should over the longer-term contribute towards the following **impact**:

> **National authorities have initiated and completed several actions that address root causes of shortages and lack of availability on the market of off-patent antibiotics and improve access to antibiotics over time.**

Achievement of the outcomes, and contributing to a longer-term impact of this Action, depends to a large extent on the degree of adoption and implementation of the outputs by France and subsequent enforcement, as well as wider policy conditions, which remain outside the responsibility of the European Commission and WHO. Such implementation remains the exclusive responsibility of France, see Assumptions under Annex 1.

2.1.2 Outputs and Activities

All actions will be taking into account the One Health approach addressing both the human and the veterinary sector. Where appropriate, separate outputs will be delivered for analysis and recommendations on antibiotic shortages and lack of availability on the market for human and animal usage.

Given that, thus far, French authorities have focused mainly on the human sector, the Action's implementation efforts on the veterinary side might encounter different challenges, for instance with respect to data collection.

Environmental aspects will be addressed throughout the Action and in all relevant outputs.

The activities will take into account feasibility of implementation of the different measures building on existing activities related to shortages and lack of availability on the market in general. They will be adapted to each sector taking into account their specificities. Opportunities to harmonise with ongoing and future national, European and international initiatives will be seized and are vital to make use of available material and perform cost-effective and sustainable interventions.

Throughout the Action, WHO will foster a participatory approach to secure ownership and commitment of stakeholders. WHO will host regular meetings, face-to-face or remotely, with the MSS and other relevant ministries and agencies, and shall be invited to participate in relevant National Working Groups (see section 1.1.2 on the project's governance).

The intervention logic is summarised in the logical framework matrix (Annex 1). This section presents the activities and outputs that relate to each expected outcome.

Inception Phase

Output 0: Inception Report

The aim of the Inception Phase is to bring clarity on the Action's objectives, division of labour, division of roles and responsibilities and communication among partners. During the inception phase, the MSS (in collaboration with relevant Ministries and agencies) and WHO will initiate the collection of the information necessary for WHO to prepare a more detailed Action plan. At the end of the inception phase, WHO will review and finalize the action plan as described in the Description of Action and deliver an Inception report. The Inception report will complement the elements presented in the action plan of the Description of the action and include at least: i) a description of the activities carried out during inception phase; ii) the minutes of the kick-off meeting; and iii) the reviewed action plan with description of outputs, activities, resource allocation, team composition, working methodologies and timeline, iv) risks and mitigation measures.

Activity 0.1: Organise a kick-off meeting and finalization of the action plan

WHO will, in close collaboration with the MSS (specifically, in coordination with relevant Ministries and agencies), organise a half-day kick-off meeting in Paris, in the premises of the MSS and with the attendance of the WHO project team and the Steering Committee (no more than 20 people). This meeting will take place within four weeks from the official starting date of the Action.

During the meeting, the Steering Committee will review and agree on the working arrangements: frequency and preparation of meetings, methods of communication, and other relevant details. An agreement on the members and approximate frequency of meetings with the Action Team (see section 1.1.2) will be reached. Based on the Description of Action, WHO will finalise (i.e. within ten days) the minutes of the meeting. After the meeting of the French Working Group (FWG) and taking into account the feedback gathered there, WHO will finalise the action plan – an update of the Description of Action - which will be guiding the Action.

The product of this activity will be the minutes of the meeting and the action plan.

Activity 0.2: Organise a workshop of the French Working Group (FWG) to inform stakeholders and partners about the Action and to establish working relations with key stakeholders

The one-day workshop of the French Working Group (FWG) with main stakeholders and partners (up to 45 participants) will take place at the premises of the MSS. The purpose of the workshop is to introduce the Action and the team to the main stakeholders and partners and inform them about the planned activities to gather immediate feedback and establish working relations with all relevant stakeholders. WHO will be responsible for organising and carrying out the workshop (contacting the participants and preparing any relevant documentation, propose an agenda etc.). The MSS (in coordination with relevant Ministries and agencies) will assist in identifying the participants and be responsible for booking the venue if it is possible to hold the meeting at the MSS.

The product of the activity will be to inform national stakeholders of planned activities and gather immediate feedback and establish working relations with all relevant stakeholders.

Activity 0.3: Identification of existing publications, material and data to assess baseline of knowledge on shortages and lack of availability on the market of both human and veterinary antibiotics

During the inception phase, WHO will identify all relevant existing publications, material and data produced by French authorities and stakeholders, including published literature, grey literature and available data on shortages and lack of availability in general, and on antibiotics for both human and veterinary use more specifically. Confidentiality of data will be ensured contractually either through the contract with the EU or separately with France.

WHO will also identify publications, data and other material from other sources outside France including from the European Union/Commission, European Medicines Agency (EMA), US Food and Drug Administration (FDA), Organisation for Economic Co-operation and Development (OECD), Organisation for Animal Health (OIE), ReAct - Action on Antibiotic Resistance and other relevant sources that should be taken into account. Publications on situations in other European countries will be taken into account on an ad hoc basis; no systematic search will be carried out. This initial screening of existing publications and data sources will form the basis for the analysis carried out in the next phase of the project and its related output (i.e. Output 1).

The product of this activity will be a compilation of material and data sources.

Activity 0.4: Communication tools for the Action

WHO will produce the following communication material:

- Standard PowerPoint presentation to present the project in French and English. This presentation will be further developed throughout the Action to align external communication by all three partners;
- WHO Website covering the Action (subject to WHO rules on website design and content);
- A two pager (flyer) on the Action in French and English that includes the Action's objectives, outputs and activities and partners.

Outcome 1: The French Authorities have improved knowledge and awareness of factors leading to shortages and lack of availability of off-patent antibiotics in the human and veterinary sector

The analysis under Output 1 will enable the French Authorities and other stakeholders to raise their awareness and knowledge of the problem of shortages and lack of availability and enable a better understanding of the factors leading to shortages and lack of availability of antibiotics in France. In turn, this will allow for an identification of possible solutions. Based on the analysis and the identified root causes, possible counter measures will be identified.

The analysis will be carried out in cooperation with all the concerned stakeholders (described in more detail under the different Activities), including from the government, the private sector, professional associations and academics and other non-state actors. This will require direct contacts between the WHO team and various French and European stakeholders, including from industry. Team member visits to different authorities and stakeholders will also be required, including visits to antibiotic manufacturers.

The relevant output will be an analysis of antibiotic shortage and availability situation in France for antibiotics in human and veterinary use in form of a report with several chapters.

Output 1: Analysis of antibiotic shortage and availability situation in France for antibiotics in human and veterinary use

The analysis of antibiotic shortage and availability situation in France, for antibiotics in human and veterinary use, will include a description of the current situation, and a review of quantitative data on shortages and availability. After identifying the products that are most vulnerable to shortages and lack of availability, a detailed mapping of their characteristics should allow for the identification of the root causes leading to disruptions in the supply chain, and problems of availability in the human and veterinary sectors. Finally, possible measures to tackle these root causes will be devised by reviewing previous measures implemented in France and abroad and by designing tailored measures in response to antibiotics characteristics.

Activity 1.1: Review of all existing reports, literature and publications on shortages and lack of availability in France in the human and veterinary sector based on the compilation of material done in the Inception Phase

WHO will review the existing material, partly gathered during the inception phase, on the problem of shortages and lack of availability of antibiotics in France, to be complemented with other material as

identified in the inception phase. Sources and material to be analysed include (in no particular order of importance):

- Relevant National Plans: French National 2019-2022 roadmap on drug shortages of the French Ministry for Solidarity and Health, Paris 2019[19], Ecoantibio 2: plan national de réduction des risques d'antibiorésistance en médecine vétérinaire (2017 - 2021)[20]
- National Agency for Veterinary Medicines: Annual reports on post market authorization surveillance (Rapports annuels de l'Anses sur la surveillance post autorisation de mise sur le marché des médicaments (AMM) des médicaments vétérinaires);
- National Pharmaceutical Academy (Académie nationale de Pharmacie). «Indisponibilité des médicaments» Rapport adopté par le Conseil de l'Académie nationale de Pharmacie le 20 juin 2018[21] and Recommandations «Médicaments: ruptures de stock, ruptures d'approvisionnement» Paris 2013[22]
- French Pharmaceutical Companies Association (LEEM) : « Pénurie de médicaments: le plan d'actions du Leem », Paris 2019[23]
- National Industry Council : « Contrat Stratégique de Filière Industries et Technologies de Santé », Paris 2019[24]

WHO will also review information sources identified in the Inception Phase from international and regional bodies, including the European Medicines Agency (EMA), US Food and Drug Administration (FDA), Organisation for Economic Co-operation and Development (OECD) which will include an overview of production capacities of active pharmaceutical ingredients for antibiotics in Europe, Organization for Animal Health (OIE) and ReAct, and further selected publications from other European countries.

The review will be summarized in one chapter in the Analysis of the situation of shortages and lack of availability of off-patent antibiotics in France.

Activity 1.2: Review and analysis of existing available data on shortages and lack of availability of off-patent antibiotics in France in general and extraction of data related to antibiotic shortage and lack of availability in the human and the veterinary sector

WHO will review available data on shortages and lack of availability of off-patent antibiotics in France in the human and veterinary sector and extract data relating specifically to antibiotic shortages. Based on the analysis of this data WHO will identify:

- Data gaps on antibiotic shortages and lack of availability of antibiotics;

[19] https://www.gouvernement.fr/lutte-contre-les-penuries-de-medicaments-agnes-buzyn-devoile-sa-feuille-de-route

[20] https://agriculture.gouv.fr/le-plan-ecoantibio-2-2017-2021

[21] https://www.acadpharm.org/dos_public/2018_06_20_AnP_RAPPORT_INDISPONIBILITE_MED_VF1.pdf

[22] https://www.acadpharm.org/dos_public/Recommandations_ruptures_de_stocks_et_appro_VF_2013.04.24.pdf

[23] https://www.leem.org/sites/default/files/2019-02/DP-Leem-Pénurie-VF.pdf

[24] https://www.entreprises.gouv.fr/files/files/directions_services/conseil-national-industrie/Contrats_de_filieres/Contrat-de-la filiere-sante-signe-fev2019.pdf

- Those antibiotics that have in the past years been most vulnerable to shortages and lack of availability in France.

Sources and material to be analysed include databases from key institutions: the French Drug Agency (ANSM), National Agency for Food, Environmental and Occupational Health Safety and National Agency for Veterinary Medicines.

In collaboration with the MSS and the Action Team, WHO will decide which data gaps identified should and could be filled within a reasonable time-period. WHO and the Action Team will define an appropriate methodology, including surveys and qualitative methods (interviews, focus groups). It is assumed that WHO will conduct interviews with key stakeholders (15-20) and run a survey among hospitals and users of veterinary antibiotics to confirm findings and fill the identified data gaps.

The review of the data will be summarized in one chapter in the Analysis of the situation of shortages and lack of availability of off-patent antibiotics in France.

Activity 1.3: Mapping the characteristics that make certain antibiotics more vulnerable to shortages and lack of availability

WHO will carry out a more in-depth review of the antibiotics that were identified as being most vulnerable to antibiotic shortage and lack of availability. The analysis shall include the following aspects:

- Where data is available, identification of a range of procurement prices/selling prices for these antibiotics in the hospital sector, and their strategies to mitigate shortages.
    - Methodology: review of existing data sources and survey/interviews among hospitals, veterinarians and the relevant Ministries/agencies (e.g. base de données publique des medicaments). Several elements will be collected, including information on antibiotics' dosages and administration forms, negotiations with procurers and their strategies to address shortages, official price, etc.
- Study to assess the production costs of these antibiotics and complexity of manufacturing.
    - Methodology: To assess the production cost of selected antibiotics (cost of goods), a study will be undertaken taking into account the cost of active pharmaceutical ingredients, manufacturing costs, specific production conditions for certain antibiotics, quality requirements, labour costs, environmental requirements and other cost factors. The results of the study will be cross checked through interviews with European manufacturers. The study in conjunction with the pricing data should provide an approximation of the range of profit margins.
- Assessment of number of suppliers and, where available, of sources of active pharmaceutical ingredient.
    - Methodology: WHO will carry out a survey and interviews among manufacturers, experts and relevant stakeholders to retrieve information on specific challenges, including with respect to the identified products. This survey/interviews may be combined with the interviews under the previous bullet point.

Based on the review, WHO will establish a list of products' characteristics that make products more vulnerable to shortages and lack of availability. Without prejudice to the outcome of the analysis, the latter may include characteristics that are linked to the product (e.g. intravenous vs. orally-ingested

products) as well as market aspects, for example market share and volume, number of suppliers, relationship between production costs and price. Based on this analysis, the review will also identify root causes for recurrent shortages and lack of availability.

The analysis and mapping of the characteristics that make certain antibiotics more vulnerable to shortages and lack of availability will be summarized in one chapter in the Analysis of the situation of shortages and lack of availability of off-patent antibiotics in France.

Activity 1.4: Review existing recommendations to address shortages and lack of availability in France and develop a long list of possible measures

WHO will develop a long list of possible new measures to mitigate shortages and maintain availability of antibiotics to at national and where appropriate European level in the human and veterinary sector taking into account previous work of relevant stakeholders. To establish the long list WHO will:

- develop possible measures in response to the list of characteristics and the root causes identified in Activity 1.3, in collaboration with all relevant stakeholders,
- list all existing recommendations to tackle shortages and lack of antibiotic availability, and suggested or implemented solutions by French authorities and relevant stakeholders,
- list measures recommended in international reports and relevant literature as well as in other European countries (WHO will not carry out a systematic review of all European countries)
- consult the FWG on the long list of possible measures and include their feedback as well as any other measures put forward by the FWG members.

The long list of recommendations will be included in the Analysis of the situation of shortages and lack of availability of off-patent antibiotics in France.

Outcome 2: The French Authorities are enabled to take measures to address the root causes of shortages and lack of availability of off-patent antibiotics, and share insights and lessons learned with other stakeholders

The analysis will enable the French authorities to take measures to address the root causes of antibiotics' shortages and lack of availability of antibiotics in both human and veterinary medicine, and to share insights and lessons learned with stakeholders (both national and international) as well as with other European countries. The identified measures will be implemented in France taking into account the European context.

The relevant output will be the identification of measures to mitigate shortages and will be presented in one report. The report will present the decision framework that will allow to select the most promising measures, leading to a shortlist of possible measures and related action plan to tackle shortages and lack of antibiotic availability at the national and EU level and the conclusions and recommendations compiled during key meetings and events.

Output 2: Measures to mitigate shortages and lack of availability of off-patent antibiotics on national and European level are identified.

WHO will develop a decision framework to select the most suitable measures to address the root causes of shortages in the human and veterinary sectors, for their implementation. Based on the long list of potential measures identified as part of Activity 1.4 and the decision framework, WHO in consultation with relevant stakeholders will establish a shortlist of possible measures to mitigate shortages and lack of antibiotic availability at the national and European level, for discussion with the relevant authorities and stakeholders and the Steering Committee. The final selection of measures to be implemented in France will be decided upon by the MSS and all relevant Ministries.

Activity 2.1: Building a decision framework to select measures to tackle shortages and lack of availability

In collaboration with the Action Team, WHO will develop a decision framework to select the most promising and most feasible measures to be piloted as part of the Action. The decision framework will include criteria allowing to compare the different measures and will cover, among others, the following aspects[25]:

- Legal feasibility: The measures should comply with the national and European legal framework, including overarching principles such as subsidiarity and proportionality;
- Technical feasibility and costs: The action needs to technically implement the measure, for example recognised technical limitations in manufacturing as well as costs.
- Political feasibility: The measures should have a realistic chance of being implemented on a political level.
- Impact: Evidence on effectiveness or efficiency of the policies, including potential short and long-term impact.

The decision framework will include the SMART principles and require that shortlisted measures are: **S**pecific, **M**easurable, **A**chievable**, R**elevant and **T**ime bound.

The product of this activity will be a decision framework and will be summarized in one chapter of the decision framework report.

Activity 2.2: Shortlist of measures and related action plan

Based on the decision framework, WHO will shortlist measures to mitigate shortages and lack of availability on national and European level. The selection of pilot measures will target antibiotics that in the past have been most vulnerable to shortages and lack of availability as identified under Activity 1.3 and address specific root causes identified under Activity 1.3. Without prejudice to the analysis and outcome of the Action, measures could address:

- specific antibiotics, for example how to prevent future shortages of piperacillin/tazobactam or benzathine penicillin,

[25] Partly based on: https://ec.europa.eu/info/law/law-making-process/planning-and-proposing-law/better-regulation-why-and-how/better-regulation-guidelines-and-toolbox/better-regulation-toolbox_en

- specific root causes for shortages, for example certain features in procurement tenders,
- measures to improve the diversity of sources, for example by changing procurement practices - or measures to retain availability of veterinary products in the French market,
- address existing legislative requirements, for example regulatory requirements and costs for regulators dossier changes or setting up new legislative requirements (for example, rules for increased transparency of the supply chain, or rules for data protection in innovation on old products),
- changes in the rules for reimbursement or price setting
- diversify the supply chain and reduce dependency on one region, or,
- better demand forecasting.

WHO will prepare a shortlist of measures, representing a balanced diversity of products for human and veterinary use (e.g. iv/oral, community/hospital, niche/high volume of use). Possible measures to be taken at the European level will be listed separately. Based on the decision framework, a detailed analysis of the feasibility and implementability of the shortlisted measures that can be implemented by France will be provided. Antibiotics that are no longer available on the French/European market should be included in the analysis/shortlist.

After performing the feasibility and implementability analysis, WHO will develop an action plan to define the roles and responsibilities of relevant institutions and the steps that are necessary to implement the measures.

The product of this activity will be a shortlist of measures and related action plan to mitigate shortages and lack of availability of off-patent antibiotics and will be summarized in one chapter of the decision framework report.

Activity 2.3: French Working Group (FWG) meeting to validate the shortlisted measures and the action plan

The **French Working Group (FWG)** will meet back-to-back for one day in a conference (described under Activity 2.3). The meeting of the FWG will focus on the shortlisted measures and the related action plan, their likely impact and feasibility, how to make the final selection of the pilot measures and the related monitoring of their implementation. The input and buy-in of the FWG will be essential to ensure that the selected measures will be implemented within the framework of the project. WHO will manage and organise the meeting. In principle, participants will include the FWG members and other stakeholders if needed.

The product of this activity is input and buy-in to the shortlisted measures that may inform final decision-making of French Authorities. This will be summarized in one chapter of the decision framework report.

Activity 2.4: Conference to present the selected measures

WHO, in collaboration with the MSS and other relevant Ministries/agencies and stakeholders, will organise a conference to present the Action and the shortlisted measures to a broader public. The purpose of the conference is also to raise awareness and share the preliminary results of the Action with relevant stakeholders and government representatives of other countries.

WHO will organize and carry out a one-day conference in English/French with translation with approximately 100 participants. The venue will be decided in consultation with the MSS. WHO will bear the costs for room, catering, coffee break etc. WHO will cover the travel costs for certain international speakers, but not for national participants.

WHO in collaboration with the MSS and the Action Team will develop the concept, the programme, invite speakers and participants, prepare relevant presentations, write relevant background documentation in French and English, prepare other communication material. WHO will compile the material of the conference and provided it to the SC. WHO and MSS will prepare a press release.

The main purpose of the conference is to present the preliminary outcomes of the Action and present the shortlisted possible measures to gather feedback from participants. The conference will also allow to gather input from a broader group of stakeholders, including from other European and non-European countries and institutions, and to create synergies with other ongoing projects that address shortages and lack of availability of antibiotics.

The product of this activity is awareness raising and knowledge and buy in to the shortlisted measures that improve final decision-making. The main conclusions gathered during the conference will be summarised in one chapter of the decision framework report.

Outcome 3: The French Authorities and stakeholders are enabled to implement and to monitor and evaluate the implementation and impact of the measures

Output 3: French authorities are provided with implementation and monitoring plans and are accompanied in carrying out and evaluating the measures.

The output will be the final selection of measures, and the monitoring and evaluation (M&E) report that will include the M&E framework developed for the selected measures. The latter will enable the authorities to take actions to implement, monitor and evaluate the implementation and the impact of the selected measures. In close collaboration with MSS and concerned stakeholders, WHO will monitor and evaluate how measures are implemented. Three technical reports will also be provided with the results of the M&E process.

WHO will provide continued assistance throughout the Action to facilitate the implementation, M&E of the selected measures.

Activity 3.1: Final selection of the pilot measures

Based on the shortlisted measures, the French authorities will select those they are planning to implement, according to standard government selection procedures. At this stage, WHO will interact with MSS and relevant Ministries/agencies to ensure they have a good understanding of the measures and related action plans and possibly to provide input to internal briefings or policy notes. WHO also may support the authorities to:

- Assess whether there is consensus of the key players to implement the selected pilot measure;
- Facilitate buy-in from stakeholders that would be the implementers of the selected pilot measure;
- Inquire whether implementation needs Parliament approval or changes in legislation; and
- Estimate how long will the implementation take as well as other relevant aspects.

The product of this activity will be the finally selected pilot measures.

Activity 3.2: Elaboration of a monitoring and evaluation framework for the selected measures

WHO will develop a M&E framework in consultation with the MSS and relevant ministries/agencies. The M&E framework will be developed either for the shortlisted measures or for the pilot measures only, depending on the French authorities' needs. The respective M&E framework will include:

- a description of the measures,
- the required actions to implement selected measures, including a timeframe and clear responsibilities for different stakeholders
- quantitative/qualitative indicators, and
- baseline value and targets to monitor as well as
- other appropriate elements depending on specific nature of the respective measures,
- roles and responsibilities of actors involved in the M&E process.

The product of this activity will be the M&E report that will include the M&E framework developed for the shortlisted/selected measures.

Activity 3.3: Analysing and evaluating the implementation and impact of the selected measures

Using the M&E framework, WHO will provide three reports. The final dates for delivering the reports will be set depending on the National authorities' progress in implementing the selected measures (possibly at months 21, 28 and 36). The reports will include an overall review of the progress and achievements of the implementation of the Action. In addition, reports will also provide (at months 24 and 36) an analysis of the level of implementation of the selected measures and possibly of their impact. All reports will include feedback and recommendations to help identifying appropriate corrective actions to facilitate the implementation of the measures and to support ministries and concerned stakeholders in France on the best analytical approaches and data collection.

To carry out this activity, WHO will organize all necessary meetings in France with different actors, stakeholders and implementers in the human and veterinary sectors to provide possible assistance in implementing, analysing and gathering relevant data on the implementation of the different selected measures. This will include assessments of specific challenges encountered during the implementation phase and possible countermeasures.

The product of this activity will be three M&E reports.

Activity 3.4: Final French Working Group (FWG) meeting

At the beginning of final phase of the project (i.e possibly 6 months after the implementation of the measures), the final **French Working Group (FWG)** meeting will review the status of the implementation of the pilot measures and their impact. It will review the results of the M&E process for each measure and the proposed quantitative and qualitative performance implementation and impact indicators for the pilot measures, including the follow-up plan (baseline / target values / timelines) to

make sure that relevant stakeholders who need to be involved are in agreement and participate where needed. WHO will manage and organise the meeting.

The product of this activity will be feedback on the M&E frameworks and buy-in of relevant stakeholders.

Activity 3.5: Final conference

WHO in collaboration with the MSS (in coordination with relevant ministries/agencies) and relevant authorities and stakeholders will organise a final conference to present the outcomes of the Action and the pilot measures to a broader public. The purpose of the conference is to raise awareness and share the results of the Action with relevant stakeholders and government representatives of other countries. This will allow to garner the experience and best practice of this Action taking place in France and share it with other countries as well as on European level.

It will be a one-day conference in English/French with translation with approximately 150 participants. The venue will be decided in consultation with the MSS. WHO will bear the costs for room, catering, coffee break etc. WHO will not provide for travel costs for national participants and speakers.

WHO in collaboration with the MSS (in coordination with the Action Team) will develop the concept, the programme, invite speakers and participants, prepare relevant presentations, write relevant background documentation in French and English, prepare other communication material and write a report on the conference in French and English. WHO and MSS will prepare a press release.

The product of this activity will be awareness raising, dissemination of results of the Action. The main conclusions gathered during the conference will be summarised in one chapter of the third M&E report.

3. LOCATION AND DURATION

3.1 Location

Any physical meeting, presentation and/or conference with the national authorities will take place in France (Paris) unless decided otherwise by the Steering Committee.

3.2 Indicative Timeline for the Activities

The operational implementation period of this Action is expected to last 36 months, but will not last for more than 38 months from the official start date of the Action. The schedule of the activities and outputs is set out as indicated in the following table (indicative timeline) assuming continued support and commitment by the MSS and relevant ministries/agencies and assuming no delays in establishing meetings with stakeholders and working groups and in getting access to relevant policy, legal and regulatory documentation.

Table 1: Indicative Timeline (by month from start of the Action)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	24	36
Inception phase	*	*	*																			
Output 1				*	*	*	*	*	*	*	*	*										
Output 2													*	*	*	*	*	*	*	*		
Output 3																					*	*

4. ORGANISATIONAL SET-UP

The WHO team is responsible for coordinating and administering the Action, as well as consulting with the DG REFORM and the MSS (in coordination with relevant Ministries/agencies).

France will set up an **Action Team** comprising of representatives of Minister for Solidarity and Health, Ministry of Agriculture and Food, Ministry for the Ecological and Inclusive Transition, Ministry of Higher Education, Research and Innovation, Ministry of Economy and Finance, ANMV and ANSM, which have been identified by France as relevant. The Action Team may also include members of the French Working Group (FWG – see below) and DG REFORM and will be in charge of liaising on a regular basis with WHO. The Action Team will be the technical working group involved in the project.

A **Steering Committee** will be established for the Action that will be managed by WHO. The Steering Committee will comprise of representatives of WHO, DG REFORM and relevant French Ministries/agencies. The Steering Committee will oversee all planned activities, ensure effective coordination and engagement (Action annual review). The Steering Committee will guide and monitor strategic and technical aspects of the Action and review outputs, publications and communications.

The **French Working Group (FWG)** will be consulted at different stages of the project to review and validate the selection of pilot measures. Members of the FWG will include relevant ministries/agencies representatives and key stakeholders at a political and technical level designated by the MSS (in coordination with the Action Team). The SG will meet once per year with all partners (around 45 representatives) at MSS. WHO will manage and organise meetings of the FWG. France will provide a list of stakeholders and **National Working Committees (NWC)** and will invite WHO to relevant meetings with NWCs, for example meetings of Comité stratégique de filière des Industries et Technologies de Santé Antibiorésistance (CSF, One Health); Working groups 2019-2022 roadmap on pharmaceuticals shortages (Human Health), Ecoantibio steering committee, RFSA. The organisation of these groups falls outside of the scope of this Action.