Report on ISPE work to support establishment of the European Union Health Emergency Preparedness and Response Authority (HERA)

May 2023

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Executive Summary

ISPE worked with McKinsey and Company in 2022 to deliver two projects/workstreams to the European Health and Digital Executive Agency (HaDEA), an Agency of the European Commission. These projects are a 'Preparatory Action' which will serve the setting-up of the future European Health Emergency Preparedness and Response Authority (HERA). The workstreams were stockpiling of antimicrobial resistance medical countermeasures, and flexible manufacturing and innovation countermeasures. ISPE's work is summarized below.

Stockpiling Workstream: The following messages were obtained from two virtual workshops, and some follow up one-to-one discussions with ISPE team members:

- Demand and capacity for antibiotic products are hard to estimate.
- Stockpiling of drug product and drug substance is expensive and needs skilled management.
- Pharmaceutical supply chains are global and are likely to remain so. Introduction of more regional-based manufacturing of either drug substance/active pharmaceutical ingredient (API) or drug product will likely still require access to globally sourced materials, excipients, reagents, or equipment.
- Transparency of the supply chain related to demand is important, however, achievement of pan-European Union supply chain data will be hard to establish.
- Learnings from the COVID 19 pandemic should be introduced as normal practice.
- Global regulatory flexibility and more harmonization would be a great help to manufacturers and would provide increased assurance of supply.
- DG HERA should consult other regions and member states, particularly France.

Flexible Manufacturing Workstream: High level messages and recommendations below were obtained from a survey of ISPE members and other industry professionals and provided to McKinsey:

- Increasing capacity by 50% takes more than 12 months in most cases. Even to increase capacity by 20% would still take greater than 6 months in most cases.
- Increasing capacity by 20%, however, is relatively fast for liquids and solid dose production, with 40% of sites being able to scale up within 6 months.
- Transfer of technology between sites for all modalities would take greater than 6 months for a high proportion of cases with a proportion taking greater than 12 months.
- Regulatory was perceived as the highest factor as a bottleneck to technology transfer in modalities and drug product types. Reduction in regulatory burden also was noted in the free text as a major factor to create more flexible manufacturing capacity in the EU.
- Descriptive recommendations on how to increase flexible manufacturing capacity included changes to drug substance sourcing and consideration of flexibilities in manufacturing approaches during the development phase.

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Introduction

In 2022 ISPE worked with McKinsey and Company to provide technical and Chemistry, Manufacturing, and Controls (CMC) information on two workstreams to inform the newly, created European Commission Directorate-General, Health Emergency Preparedness and Response Authority (DG HERA). The workstreams were:

- Stockpiling of antimicrobial resistance medical countermeasures
- Flexible manufacturing and innovation countermeasures

This report summarizes the actions, discussions and recommendations made by ISPE to the projects.

The information provided herein is reflective of the composite feedback from individuals from multiple companies included in the workshops and surveys and does not necessarily represent the positions of all individual members of the ISPE project team or their companies.

Background

EU DG HERA was launched as a new European Commission Directorate-General in September 2021 with a mission to prevent, detect, and rapidly respond to health emergencies. As part of the preparation for this new Authority, the European Health and Digital Executive Agency (HaDEA) made a call for tenders in 2021 for a number of projects, among which were the following:

- A study assessing scientific, engineering, regulatory and economic considerations of f**lexible manufacturing** and innovation capacity medical countermeasures,
- A study on bringing antimicrobial resistance (AMR) countermeasures to the market,
- A feasibility study on **stockpiling** of medical countermeasures in the area of AMR,
- A feasibility study, design and prototype development for a mapping platform on COVID 19 therapeutics in the European Union (EU).

McKinsey & Company, having extensive knowledge and databases related to these projects, submitted a proposal that was accepted by HaDEA. McKinsey's proposal included several partners chosen to complement McKinsey's expertise (e.g., technical, regulatory, legal and academic). ISPE was engaged by McKinsey to provide technical and regulatory expertise and advice on chemistry, manufacturing and control (CMC) aspects of manufacture and supply. ISPE had already worked on a similar project to identify the regulatory, technical, and workforce elements favorable to creating a more robust and sustainable US domestic pharmaceutical

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manufacturing base for active pharmaceutical ingredients (APIs). A report was published in December 2020.[1]

Process

The two workstreams had different timescales, with an AMR Countermeasures Stockpiling report being due from McKinsey and Company initially in September 2022 and a Flexible Manufacturing report due from McKinsey by the end of 2022.

An ISPE Steering Committee for this project was appointed with representation from the ISPE Regulatory Steering Council (RSC) and ISPE International Board of Directors. ISPE's role was to challenge the thinking by providing input, expertise, and questions to ensure a diversity of perspective. Recommendations from ISPE were optional, and to be used at McKinsey's discretion. The experienced team of ISPE experts was able to align on recommendations which are outlined in this report.

The ISPE Steering Committee assembled a core project team of multidisciplinary, multicompany subject matter experts (SMEs) to provide technical input and challenge to the AMR Stockpiling work-stream and supplemented that core team with some additional members for the Flexible Manufacturing workstream.

ISPE Multidisciplinary Project Team

Stockpiling and Flexible Manufacturing Workstream

- George Beres, Roche
- Jean Francois Duliere, ISPE Advisor
- Ylva Ek, Robur Life Science Advisory AB
- Diane Hustead, Merck
- Manfred Maeder, Novartis
- Alice Redmond, Commissioning Agents
- Christopher Schmidt, Merck Darmstadt
- Tim Watson, Gilead (Pfizer at time of project)
- Georg Singewald, Roche
- Hannes Woerner, Sandoz
- Thomas Zimmer, ISPE

Additional Team Members for Flexible Manufacturing Workstream

- Can Aktar, CRB
- Michael O'Brien, NGT Biopharma Consultants

The two workstreams had different operating approaches. The Stockpiling workstream held two virtual workshops with some follow up one-to-one discussions, whereas the Flexible Manufacturing workstream obtained feedback from a survey of industry professionals.

Stockpiling of Antimicrobial Resistance Medical Countermeasures

The objective of the workstream was to develop a feasibility assessment on stockpiling of countermeasures in the area of antimicrobial resistance. In more detail, the feasibility and role of stockpiling would be assessed in addressing shortages of certain antimicrobials and APIs in the realm of AMR. A wide range of elements, would be covered including options for stockpiling, needs and availability in the EU, as well as international mechanisms, appropriate funding mechanisms and operational deployment issues.

[1] Increasing Domestic Resiliency in the Supply of Essential Active Pharmaceutical Ingredients. December 2020. ISPE. https://ispe.org/initiatives/regulatory/daf-act-initiative-support-domestic-manufacturing-active.

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ISPE's contribution to the AMR stockpiling workstream was to provide SMEs for two workshops held virtually in May and July 2022. For each workshop, McKinsey and Company provided background material and potential topics for discussion.

In both workshops Chatham House rules were applied whereby when a meeting, or part thereof, is held under the Chatham House Rule, participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed. Topics discussed as well as insights and statements provided could be utilized for the work of McKinsey and DG HERA without naming the individual source. All ideas and perspectives shared would be independently evaluated and, where relevant, integrated into overall assessment by the McKinsey team.

Inputs to Antimicrobial Resistance Stockpiling Workshops

AMR is well accepted as a public health problem accounting for an estimated greater than 1.2 million deaths globally. Stockpiling is recognized as one part of a broader set of potential interventions. It is essentially a short-term intervention to guarantee ready access to a critical quantity of medical countermeasures in case of uncommon demand spikes or disruptions of regular supply chains. Spikes in demand could be due to the fundamental properties of the pathogen (e.g., its capabilities for spreading and causing disease). EU member states and their supply chains for specific antibiotics are vulnerable to disruptions (e.g., because of major ex-EU sourcing, geographical colocation of production sites and/or consolidated supplier landscape).

It was recognized that there are many ways of managing and paying for stockpiles and it was anticipated that the workshops would highlight preferred options and challenges.

Antimicrobial Resistance Workshop #1

The objectives of the first workshop were to:

1. Identify critical vulnerabilities in the supply chain for the EU antibiotics market.
2. Improve understanding of current level of resilience in the supply chain for the EU antibiotics market.
3. Identify key industry actions and trends in response to recent supply chain challenges and policy.

Outputs from Antimicrobial Resistance Workshop #1

1. Identify critical vulnerabilities in the supply chain for the EU antibiotics market:

    1.1. Demand: Total demand in the EU and for most individual member states for most antibiotic drug products, which are generic may be hard to estimate. From a manufacturer's position, the more stable demand is over time, the more efficient it is to supply.

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1.2. Capacity: Total capacity for any drug product both at EU and global levels is very hard to estimate. Most capacity for manufacture of antibiotic drug products is outside the EU. Additionally, the point was made that there could be capacity in the EU that is currently mothballed.

A single manufacturer knows its own capacity and what flexibilities there could be. This manufacturer is unlikely to know or be interested in the capacity of competitors and hence the total capacity of the pharmaceutical industry for a single drug product is very hard to estimate. In terms of supply chain, each manufacturer sources its required materials, however, it is highly likely that some materials and most likely drug substances or APIs have a common source outside the EU. Manufacturing sites outside the EU are very likely to source many regions globally, not just the EU.

1.3. The option of using redundancy, for example, for manufacturing sites, input materials and excipients to assure a robust supply chain appears attractive. However, it is extremely expensive for a manufacturer in terms of resource and money from many perspectives, e.g., cost of developing and registering multiple site, material and excipient options, in addition to validating and maintaining a site which may not be used.

1.4. Supply chains are global, and one region cannot solve the challenges of supply. Reference was made at the workshop to work performed by an ISPE team in 2020 for the US Department of the Air Force Acquisition COVID-19 Task Force (DAF ACT) to advise regulatory, technical, and workforce elements favorable to creating a more robust and sustainable domestic pharmaceutical manufacturing base for Active Pharmaceutical Ingredients. An important section in that report is:

"Given the global nature of the pharmaceutical industry, creating a considerably more robust API ecosystem would require significant international cooperation. No country could bring every element of API manufacturing within its borders, since the raw materials, solvents, intermediates and reagents, etc. used to produce just one API are typically sourced from markets around the world. Regardless of where companies build API manufacturing facilities, they supply these products to global markets—serving just one market would not make business sense or meet ethical responsibilities to serve patients. Every major pharmaceutical supply chain is built to serve the world, not one country or region."[11 above]

A similar situation applies to drug product manufacture.

1.5. Small, unexpected events could have a big impact. An example could be the cargo ship, Ever Given blocking the Suez Canal in March 2021 for six days. This blockage caused significant disruption to supply chains for several months.

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1.6. Transparency: In addition to the large uncertainties in knowledge of demand and capacity for each drug product, there is also not available knowledge of how much product is in the supply chain and where this product is located. France has established a system for essential medicines managed by the French health agency, Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM). More discussion of this procedure, established in cooperation with the French pharmaceutical industry association (Les Entreprises du Médicament [LEEM]) occurred at the second workshop and with an ISPE expert and is discussed below.

Knowledge of how much product is in the supply chain and where this product is located is not available.

2. Improve understanding of current level of resilience in the supply chain for the EU anti-biotics market.

   To achieve and maintain a high level of resilience in the supply chain for the EU antibiotics market there are many challenges, which were discussed in the workshop and are summarized below.

   2.1. Challenges of facilities and sourcing/supply chain change.

      2.1.1. Sterile products: Many antibiotic products are sterile injectable products, facilities for manufacture of which are more costly to construct, validate and operate than facilities for manufacture of oral products. Changes to these facilities and manufacturing processes are more difficult to validate and obtain regulatory approval with long time periods (many months and often years). These time periods may be different between the EU and other regions, and between member states for some older drug products.

      Historically, sterile injectable products have been those products most likely to result in a drug shortage situation. The survey conducted as part of the Flexible Manufacturing workstream confirmed this finding (see Appendix).

      2.1.2. Dedicated facilities: Many antibiotic products are beta-lactam compounds, and these require dedicated facilities which almost allows cannot be used for manufacture of other drug products.

      2.1.3. Timescales: Whether a drug product is oral or injectable, change to a manufacturing facility or process takes many months and often years with the additional challenge that timescales for post approval regulatory changes are different between regions, which requires manufacturers to have great complexity of managing “old” and “new” process concurrently or to wait for the last approval before implementing a change. Some data relating to timescales to increase capacity are given as output from the survey conducted as part of the Flexible Manufacturing workstream and are provided in the Appendix.

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2.1.4. Regulations: Global harmonization of quality regulations both for approval of drug products and for post approval changes would help significantly in assuring constant supply of all products including antibiotic products. Lack of harmonization for supply chains which extend globally (most antibiotic products are manufactured outside the EU in manufacturing sites that source many regions) results in:

2.1.4.1. Complexity in managing product or API manufactured by a common process but having different approved control strategies.

2.1.4.2. Potential drug shortages in some regions

Not discussed in detail at the workshop, the following is further explanation of the problem. Despite regulatory harmonization activity having been very active since 1990 with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) there is evidence that implementation of quality guidelines is variable resulting in the same drug product and API having approved control strategies different between regions. In addition, post approval change regulations are different between regions globally, often require different data for submission, and have the same issue as at first approval of having further divergence in control strategies approved between regions. Managing these differences in control strategies as well as timescales discussed above for the same process at a manufacturing site gives complexity and cost to a global supply chain. As a relevant example of divergence of implementation of ICH guidelines, ICH Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management[2] was adopted by ICH in November 2019, however, it is not yet fully implemented in the EU nor in most other ICH regions. ICH Q12 is intended to provide "a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. A harmonized approach regarding technical and regulatory considerations for lifecycle management will benefit patients, industry, and regulatory authorities by promoting innovation and continual improvement in the pharmaceutical sector, strengthening quality assurance, and improving supply of medicinal products."

Variable implementation of quality guidelines results in the same drug product and API having approved control strategies different between regions.

2.1.5. Costs and relationship to price: Although the price of drug products is outside the scope of ISPE focus, the point was made that price paid and continuity of orders can impact the amount spent on maintaining and upgrading facilities. Great care is

[2] International Council on Harmonisation (ICH), Harmonised Guideline, Technical and Regulatory Considerations For Pharmaceutical Product Lifecycle Management (Q12), Final Version. November 2020, https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf.

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needed by a manufacturer to manage costs when "one vial of ampicillin injection costs less than a packet of chewing gum."

2.1.6. Repatriation of old manufacturing processes: Transfer of many antibiotics, particularly drug substance, into EU will not be possible due to technical, regulatory and business constraints. Re-inventing/modernization and re-establishment of processes in EU countries would take several years and require very large investments. No commercial player would be willing to make such changes today on their own for products that are economically challenging and with no clear perspective on future market.

2.2. Need for global regulatory harmonization and prioritization: The challenges for industry have been introduced above with respect to regulations applying to global supply chains. There also is increasing attention from regulators to assure continuity of supply to their region with many regions requiring notification of a drug shortage and in some cases advanced warning of a potential drug shortage. Additional requirements are emerging of the need for companies to have drug shortage prevention plans (e.g., France) or risk management plans (e.g., US) provided to health authorities and/or available at inspections. Each region has developed or is developing its own list of "essential" medicines and these lists and reporting requirements are different with long lists of "essential" medicines. Implementation of these reporting requirements has the potential to use important resource for reporting rather than manufacturing and supplying drug product with the unintended consequence of potential drug shortages. In addition to the obvious industry position of regulatory harmonization of requirements and terminology (e.g., of "drug shortage"), there is a need for prioritization of activities associated with regulatory requirements to ensure optimum use of critical resources.

Drug shortages can be an unintended consequence of using resources for reporting rather than manufacturing and supplying drug product.

3. Identify key industry actions & trends in response to recent supply chain challenges and policy.

3.1. Learnings from COVID 19 pandemic.

There are many learnings from the pandemic, and some of these are summarized as:

3.1.1. There were shortages of many components such as glass containers, vial closures, viral filters.

3.1.2. Complex, low temperature supply chains were introduced quickly.

3.1.3. Companies shared stocks of materials and facilities.

3.1.4. Companies took more risk such as advanced purchase of equipment and materials for COVID vaccines and therapeutic products when approval was not assured.

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3.1.5. A lot of good dialogue occurred between industry and regulators and between regulators.

3.1.6. Regulatory flexibilities introduced.

3.2. Consider learning from other regions.

The team gave feedback that DG HERA should consult other regions such as the US BARDA program, which has investigated stockpiling options for the US as well as repatriation of manufacture to the US. Funds are available to support activities important to the US.

An offer was made after the second workshop for the DG HERA program to consult a UK Department of Health, Head of Supply Chain Delivery based on a discussion with this individual by ISPE. This individual has great experience of managing stockpiles for various groups.

3.3. Challenges of stockpile management.

There are many challenges and questions relating to establishment of an EU stockpile of critical antibiotics such as

3.3.1. Location or virtual: where should stockpiles be located and how much space should be purchased/rented? Number of locations?

3.3.2. Management: who manages – manufacturer, distributor, third party, DG HERA?

3.3.3. Sustainability: managing shelf life, turnover and wastage.

3.3.4. Labelling: should packs in a stockpile be labelled, which language?

3.3.5. Costs: who pays? It is unlikely a manufacturer or distributor will carry the cost of a substantial stockpile above their normal inventory level.

3.3.6. Where in the supply chain to stockpile: obvious points are at API, bulk product, unlabelled packaged product or labelled packed product?

3.3.7. Learning from member state experiences: DG HERA should discuss experiences of member states, particularly France, with management of stockpiles or other activities to assure a reliable supply chain for AMR products.

As part of stockpile management, the ISPE team mentioned the use of blockchain technology and electronic labelling to assist with management of virtual stockpiles. These technologies are practical.

These points and others were discussed in more detail in the second workshop.

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Antimicrobial Resistance Workshop #2

The objectives of the second workshop were:

3. What is the most effective, efficient, and feasible setup for a potential stockpile for the EU market(s)?
4. What are key implementation challenges and considerations for the most suitable options?

Outputs from Antimicrobial Resistance Workshop #2

3. What is the most effective, efficient, and feasible setup for a potential stockpile for the EU market(s)?

   3.1. Stockpiling of APIs was discussed, and the following points were made:

      3.1.1. Given the specific nature of each API such as number of potential suppliers, process and lead time of manufacture, stability, handling issues, and challenges and timescales to deliver drug product it was recommended that a specific strategy is required for each relevant API.

      3.1.2. A decision tree of delivery requirements and risks was suggested.

   3.2. Many of the points relating to management of stockpiles from an industry perspective discussed at the first workshop were re-iterated such as:

      3.2.1. Stockpiles are expensive.

      3.2.2. Not easy to predict requirements.

      3.2.3. Lots of wastage.

      3.2.4. Difficult to manage flow-through (sustainability).

      3.2.5. How much space – good distribution practice (GDP) controlled?

      3.2.6. Less than 6-month remaining shelf life is unacceptable.

   In emergency situations shelf life of a drug product could be considered for extension based on data available from a manufacturer. Manufacturers often restrict shelf life to three years; however, data could be available to support a longer shelf life.

   As part of the preparation for the second workshop, the ISPE team introduced GIRP, the European Healthcare Distribution Association, which is the umbrella organization of full-service healthcare distributors in Europe. GIRP had recently produced a reflection paper on stockpiling of drug product from a distributor's perspective[3], a copy of which was provided to McKinsey and Company. In this short paper, GIRP discuss some of the options for stockpiling with a particular focus on the cost considerations.

[3]Reflection on medicines stockpiling and increased buffer stock at pharmaceutical full-line wholesaler/full-service healthcare distributor level. European Healthcare Distribution Association. https://www.girp.eu/sites/default/files/2022-06/Reflections%20on%20medicines%20stockpiling.pdf.

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4. What are key implementation challenges and considerations for the most suitable options?

4.1. There was discussion of models of managing drug supply in France and Netherlands. Both countries have introduced monetary penalties (fines) for noncompliance with reporting of required drug shortage information. From an industry perspective it was indicated that there are challenges.

4.1.1. For France, challenges are the quantity of information to be submitted (weekly data information – see below) and confidentiality of data submitted to regulators through a platform.

The French model appears not to be a problem for large companies. A summary of the French model was presented:

4.1.2. Drug Shortage Prevention Plans must be submitted on a yearly basis between 1-31 December.

4.1.3. Stockpiling for France is mandatory:

4.1.3.1. Two months for “essential” products

4.1.3.2. Four months for “essential” products facing shortages in the last two years

4.1.4. Data must be submitted on a weekly basis:

4.1.4.1. Product

4.1.4.2. Forecast sales

4.1.4.3. Sales

4.1.4.4. Forecast production of drug product

Safety stockpiling required for France could be outside of France elsewhere in Europe (EU). Lists of “essential” medicines requiring stockpiling are provided on the ANSM web site. Each company must identify if their products are Médicaments d'Intérêt Thérapeutique Majeur, MITM (essential medicines) based on risk assessment, market share, innovator or generic.

A checklist is available to inspectors to assure compliance.

A template of DSPP for companies to use is available on the ANSM website. There is also some information available on EMA website.

There is more transparency in France with this model with:

4.1.4.5. ANSM meeting every quarter LEEM where they consider the problem of shortages.

4.1.4.6. Every month ANSM meets with all stakeholders to discuss drug shortages and a report is published. Stakeholders are industry, health care professionals, patients’ organizations, and some other institutions such as the National Academy of Pharmacy.

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The situation and requirements in each member state is evolves over time.

Again, the ISPE team stressed the need for more regulatory flexibility in more normal situations as was applied during the Covid pandemic and more global regulatory harmonization to support global supply and assure availability of product to patients.

It was pointed out that regulators do have access via application dossiers and drug substance drug master files (DMFs) to supply chain information. Could this information be used more to the benefit of regulators?

Antimicrobial Resistance Recommendations from ISPE

After the workshops ISPE made two series of recommendations for consideration by DG HERA. One related to packed drug product and the other to management strategies.

- Packed Drug Product

  There are three quick win and two slightly longer-term possibilities that could be considered for finished goods.

  - Quick wins:
    - Batch depletion and batch ordering. Inventory can become obsolete at both manufacturer and wholesaler locations due to customers insisting on same batch deliveries. This results in multiple batches being depleted at the same time, and often each batch ends up with relatively low volumes that then do not meet customer volume requirements (and are written off). Can batch ordering be coordinated across the EU?
    - Available shelf life. Most purchasing customers (especially hospitals) insist on minimum shelf life (typically anywhere between 6 and 12 months). Again, this means perfectly serviceable inventory becomes unsellable and is written off. Could there be more flexibility regarding shelf-life requirements at customers sites for precious antibiotic stocks?
    - Commercial forecast to production demand planning. This is a highly granular process today, with manufacturers taking various local data and building the forecast up. The problem manufacturers often have is that individual market demand is not large enough to reach minimum production run capacity. In these situations, the manufacturer can produce product already knowing they will write off a portion of the inventory, or they can choose not to make. If the molecule has competition (generic for example), it can be better to not produce on the assumption that somebody else can provide the market. This assumption is not always the case. There is a lot here that can be done with a regional wholesaler in partnership with the EU to smooth out demand triggers with key manufacturers.

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