

**Strengthening the Antimicrobial Supply Chain – an Issue of National Security**

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Shortages of pharmaceuticals can have a serious impact on public health. This is especially true for antimicrobials. In order to strengthen policies meant to prevent pharmaceutical shortages, in March 2020, the Economic Affairs Division of the Ministry of Health, Labour and Welfare (MHLW) Health Policy Bureau established the “Stakeholder Meeting on Stabilizing the Supply of Pharmaceuticals.” This Meeting published its findings in September 2020. Because Japan is highly dependent on overseas supply chains for its pharmaceuticals and related products, the Japanese Government announced that it would provide financial support for efforts to build a domestic infrastructure for pharmaceutical manufacturing during an extraordinary Cabinet Meeting in April 2020. The Government then further increased its financial support for this issue within a supplementary budget announced the following December. With the aim of further supporting efforts to policy momentum on this topic, on January 15, 2021, AMR Alliance Japan hosted “Stabilizing the Supply of Antimicrobials: An AMR Alliance Japan Forum.” The key points raised by speakers during that forum are summarized below.

1. **Ensuring the stable supply of antimicrobials is a matter of national security and crisis management for every country. It is therefore important to share information widely on preventative measures and costs related to antimicrobial and pharmaceutical supply issues.**
2. **Antimicrobial supply problems contribute to the spread of antimicrobial resistance (AMR).**
3. **For both existing and new antimicrobials, investments must be made in human resources, supply chains, and manufacturing facilities. Quality standards must be harmonized to ensure supply chain stability.**
4. **Supply chain issues cannot be solved without Government involvement. To facilitate efforts by the Government, it is important that more be done to communicate with the public about this issue and facilitate public understanding.**
5. **Antimicrobial supply problems are global issue for which international cooperation is essential. Attractive market conditions must be established to encourage developers of new antimicrobials.**

Further details are provided below.

1. **Ensuring the stable supply of antimicrobials is a matter of national security and crisis management for every country. It is therefore important to share information widely on preventative measures and costs related to antimicrobial and pharmaceutical supply issues.**
  - **Public health is an issue of national security and crisis management.** In 2019, disruptions in the supply of cefazolin, a key antimicrobial (hereinafter “Key Drug”), and shortages of alternative antimicrobials resulted in lower infectious disease treatment success rates, more adverse events, and increased mortality.
  - **To ensure the stable supply of Key Drugs starting with cefazolin, appropriate pharmaceutical pricing must be maintained.**  
 (“Key Drugs” include: penicillin G, ampicillin sodium/sulbactam, tazobactam/piperacillin, cefazolin, cefmetazole, ceftriaxone, cefepime, meropenem, levofloxacin, vancomycin, spectinomycin hydrochloride, metronidazole, colistin sodium methanesulfonate, faropenem sodium, aztreonam, amikacin sulfate, amoxicillin hydrate, cefditoren pivoxil, minocycline hydrochloride, azithromycin)
  - **To prevent antimicrobial supply problems, the findings published by the Stakeholder Meeting on Stabilizing the Supply of Pharmaceuticals recommend diversifying manufacturing sources and establishing a domestic manufacturing base for key materials. Information on the challenges of these measures, such as cost, should be shared widely.**
  - The Stakeholder Meeting on Stabilizing the Supply of Pharmaceuticals Working Group compiled a list of pharmaceuticals that are essential for treatment, are widely used, and that require special consideration to ensure stable provision (hereinafter referred to as “pharmaceuticals requiring ensured supply chain stability;” 551 substances proposed by 58 academic societies). These pharmaceuticals are organized into three categories: “pharmaceuticals requiring the highest priority in efforts to ensure stable supplies,” “pharmaceuticals that must be prioritized in efforts to ensure stable supplies,” and “pharmaceuticals requiring ensured supply chain stability.” Categorization decisions were made while considering the following factors: (1) the severity of the target disease; (2) the availability of alternative pharmaceuticals or treatments; (3) the number of people affected; and (4) the status of the manufacturing and supply chain of the pharmaceutical in question.
  
2. **Antimicrobial supply problems contribute to the spread of antimicrobial resistance (AMR).**

- Each year, at least 700,000 people worldwide are thought to die from antimicrobial resistant bacterial infections. It is estimated that 8,000 people die each year of AMR-related causes in Japan. According to Japan Nosocomial Infections Surveillance (JANIS), a national surveillance program organized by the MHLW, antimicrobial resistant organisms have been detected at almost every healthcare institution in Japan.
  - AMR spreads as microorganisms evolve following exposure to antimicrobials. There is shared recognition in the healthcare community that it is important to use antimicrobials that are appropriate for the target organism in a rational manner. In other words, from the perspective of combating AMR, **it is crucial to not just limit the use of antimicrobials, but ensure that antimicrobials are always being used appropriately.**
  - To discourage the spread of AMR, it is important to encourage the use of narrow-spectrum antimicrobials that target specific pathogens without killing bacteria that are not harmful to the body. Cefazolin is an excellent narrow-spectrum antimicrobial, but the suspension in the cefazolin supply has made it more difficult to use. At one healthcare institution, the cefazolin shortage resulted in a decrease in the susceptibility of *Enterobacteriaceae* to third-generation cephalosporins by approximately 20% and a rapid increase in antimicrobial-resistant organisms was observed.
  - Antimicrobial supply problems prevent healthcare providers from being able to select the best antimicrobial for their intended use. Over both the short and long term, this creates more antimicrobial-resistant organisms and lowers treatment success rates.
3. **For both existing and new antimicrobials, investments must be made in human resources, supply chains, and manufacturing facilities. Quality standards must be harmonized to ensure supply chain stability.**
- As antimicrobial manufacturing entails strict manufacturing and quality control standards, it is important to invest into capacity building, supply chain enhancements, and manufacturing facilities in order to make the manufacturing and stable supply of Key Drugs possible.
  - Issues related to the production of existing and new penicillin and cephem **antimicrobials** include the state of oligopolies in China that produce certain core raw materials including 6-aminopenicillanic acid and 7-aminocephalosporanic acid; the withdrawal of Japanese manufacturers from the market (particularly for non-core raw materials); and the fact that Japanese production of APIs is entirely handled now by only three pharmaceutical companies.

- The establishment of a domestic API production system would require at least **five years of work and 60 billion yen in investments**. Due to differences in personnel costs and scale issues, total costs of producing APIs domestically would likely be **three to five times the cost of importing and purchasing APIs from abroad**.
  - In order to combat AMR, ideally, **new antimicrobials would be introduced to the market continuously in order to respond to the spread of ever-evolving antimicrobial-resistant organisms**. **Measures related to antimicrobial pricing should be considered to make that possible**.
  - One challenge facing the stable supply of antimicrobials is that Japan's buying power for APIs and other materials is weak. **Bold measures to promote the harmonization of the Japanese Pharmacopoeia with the European Pharmacopoeia and the United States Pharmacopoeia** are necessary to strengthen Japan's buying power. **Efforts for harmonization with Europe and the United States must be advanced and the Japanese market must be made more attractive**. This will require a review of Japan's standards (regarding foreign substances, color, etc.) as well as efforts to review Japan's Drug Master File entry requirements, such as those requiring information on API manufacturing methods or language (for instance, English entries should be allowed).
4. **Supply chain issues cannot be solved without Government involvement. To facilitate efforts by the Government, it is important that more be done to communicate with the public about this issue and facilitate public understanding.**
- **Ensuring the stable supply of pharmaceuticals is primarily the responsibility of manufacturers and distributors. That said, some pharmaceuticals are crucial to the delivery of healthcare. Government involvement is necessary to ensure that patients always have access to these pharmaceuticals.** For pharmaceuticals requiring ensured supply chain stability, the Government should undertake the following sets of measures, in order: (1) measures to prevent supply problems; (2) measures to rapidly identify signs of supply instability and enable early action; and (3) measures for when supply problems actually occur.
  - Measures needed to prevent supply problems include those to **improve understanding of manufacturing processes, those to promote the continued supply of antimicrobials and the diversification of manufacturing sources** (the amount of support should be based on how the drug is categorized in line with the three categories mentioned in point 1), and **those to promote pharmaceutical pricing measures**. Measures that must be taken to rapidly identify signs of supply instability and enable early action include **risk assessment measures at each company** and **supply instability reporting**. Measures for when supply problems actually occur include **increased production and shipment adjustments** and the

implementation of systems for rapid review and approval as well as other schemes to further ensure stability.

- It is likely that it will be easier to justify needed increases to antimicrobial prices if the public understands their medical necessity.
  - It is thought that the public does not really care whether or not antimicrobials meet special quality standards, so these standards could probably be relaxed (specifically, it is thought that certain standards are making quality assurance difficult without actually leading to higher quality).
  - It is thought that the public will generally accept policy decisions on pharmaceuticals falling into the aforementioned three categories of pharmaceuticals requiring ensured supply chain stability. However, that is contingent on whether or not sufficient information is provided to the public and whether public understanding can be fostered. Even if a pharmaceutical is only used by a small number of patients, supply problems can develop into a serious scandal, so it is crucial that attention be paid to the situation of each relevant pharmaceutical. It is also necessary to consider measures for providing logistic support in the event a pharmaceutical supply problem occurs on a global scale.
5. Antimicrobial supply problems are global issue for which international cooperation is essential. Attractive market conditions must be established to encourage developers of new antimicrobials.
- Each year, nearly 6 million people globally (largely in low- and middle-income countries) die due to lack of access to antimicrobials. In 2017, an explosion at a factory in China led to an international shortage of piperacillin-tazobactam that lasted three months and cost the United Kingdom over 30 million pounds (approx. 4.27 billion yen). Instability in the antimicrobial supply chain impacts public health and is a cause of AMR.
  - The United Kingdom will hold presidency of the G7 in 2021 and AMR will be one of the priority items at the G7 Health Ministers' Meeting. The antimicrobial supply chain is a global issue, and the United Kingdom believes that this issue requires cooperation from every country. Further efforts are needed to diversify supply chains and eliminate over-reliance on China and India for antimicrobial manufacturing. These efforts must be based on an accurate understanding of the entirety of the supply chain, from the manufacturing of raw materials to delivery to patients. The United Kingdom is encouraging pharmaceutical companies to consider the re-introduction of older antimicrobials that are still effective to antimicrobial markets and to adopt environmentally-friendly manufacturing methods. The United Kingdom is also reconsidering the antimicrobial reimbursement system to support such efforts. Consideration is also being made to ways to encourage better information sharing between pharmaceutical makers and API suppliers.

- The United Kingdom and other G7 countries, including Japan, must remind themselves that new types of antimicrobials have not been introduced to the market in over thirty years. **Each country must work to develop attractive market conditions that better encourage antimicrobial research and development.**

This report does not represent the opinion of any specific speaker. It was compiled by the AMR Alliance Japan Secretariat (HPGI) based on discussions held at the forum.