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Division for Pharmaceutical Industry Promotion and Medical Information Management  
Health Policy Bureau, Ministry of Health, Labour and Welfare

Health and Global Policy Institute (HGPI)

### **Opinions Regarding the Proposed “Action Policy for Ensuring a Stable Supply of Antimicrobial Substances”**

Health and Global Policy Institute (HGPI) expresses its gratitude to the Government of Japan for designating antimicrobial substances (hereinafter, “antimicrobials”) as “specified critical materials” under the Economic Security Promotion Act. Ensuring a stable supply of items like antimicrobials, pharmaceuticals, and personal protective equipment (PPE) has presented a growing challenge in the field of healthcare in recent years. However, efforts to examine methods of ensuring stable supplies of antimicrobials have proceeded rapidly since the March 2020 establishment of the “Stakeholder Meeting on Stabilizing the Supply of Pharmaceuticals” by the Ministry of Health, Labour and Welfare (MHLW). With the objective of building sound, robust, and effective systems that will contribute to ensuring stable antimicrobial supplies, we offer the following three recommendations.

**Antimicrobials that have been designated as “specified critical materials” by the Government of Japan should be expanded from  $\beta$ -lactam antimicrobials to include all those designated as “pharmaceuticals requiring the highest priority in efforts to ensure stable supplies (category A),” and steps should be taken to consider further expanding that list to include the “32 Key Drugs” in the future.**

Four  $\beta$ -lactam antimicrobials are currently designated as specified critical materials (cefazolin, cefmetazole, ampicillin/sulbactam, and piperacillin/tazobactam), and action policies for securing stable supplies of these antimicrobials are likely to be formulated in the future. These were all categorized as “pharmaceuticals requiring the highest priority in efforts to ensure stable supplies (category A)” during the Stakeholder Meeting on Stabilizing the Supply of Pharmaceuticals hosted by the MHLW in March 2020. We believe the decision to select these pharmaceuticals was appropriate.

In addition to the four antimicrobials designated as specified critical materials, antimicrobials categorized as “pharmaceuticals requiring the highest priority in efforts to ensure stable supplies (category A)” at that meeting also included meropenem and vancomycin. According to recommendations compiled by the Japanese Society of Chemotherapy in November 2022, Japan is almost entirely dependent on foreign countries to supply the raw materials and active pharmaceutical ingredients (APIs) for meropenem, vancomycin, and the four specified critical materials. In addition, there are ongoing disruptions in the supply of meropenem as of December 2022 (the time of writing). In light of these circumstances, meropenem and vancomycin should also be designated as specified critical materials for a total of six antimicrobials.

Furthermore, in 2019 and 2022, a number of academic societies for various infectious diseases selected 32 Key Drugs (as of March 2022) as priority antimicrobials for which stable supplies will be essential. Many of these overlap with pharmaceuticals that are recommended as alternatives in the event of shortages. To prevent chains of supply shortages from occurring, active steps should be taken to expand the list of specified critical materials to include the “32 Key Drugs” in the future.

**Support for revitalizing the domestic antimicrobial production system should be reinforced by providing higher subsidy rates over multiple years.**

In FY2020, the MHLW started a one-year program aimed at stabilizing the domestic supply of antimicrobials and other pharmaceuticals by providing a 50% subsidy rate (in which the Government and businesses receiving the subsidy would split costs evenly). Establishing a domestic production system for antimicrobial APIs will require at least five years of work, 60 billion yen in investments, and - owing to differences in labor costs and scale compared to overseas manufacturing bases - measures (including the purchase of APIs) to cover three to five times the cost of imported APIs. There is no planned fiscal year for the completion of the MHLW's current action policy and receives a budget that is continuously allocated, but this initiative requires stronger support with a higher subsidy rate over multiple fiscal years. All of the antimicrobials designated as specified critical materials as of December 2022 are  $\beta$ -lactams, which require particularly strict production management. This means it will be extremely difficult to complete steps needed to revitalize domestic production of these substances, such as converting and operating manufacturing facilities in line with the concept of dual line manufacturing. In recent years, there has also been a drastic increase in the need for wastewater treatment and other environmental considerations. In addition, domestic manufacturers have withdrawn from the antimicrobial market one after another, placing Japan on the verge of a technological vacuum in antimicrobial production. With this point in mind, urgent steps should be taken to support the restructuring of the production system, including efforts to pass down technology.

**In light of the structural challenges of the antimicrobial market, steps should be taken during non-emergency periods to ensure market feasibility and profitability for antimicrobials by introducing pull incentives and similar measures.**

The action policy proposed by the MHLW assumes that, during periods of non-emergency, APIs derived from raw materials manufactured overseas ("imported APIs") will be used alongside APIs derived from raw materials manufactured domestically, and that all APIs produced in Japan will be sold. As previously discussed, the costs of producing APIs domestically are greater than purchasing APIs produced overseas, which makes it more difficult for antimicrobials using domestic APIs to stay feasible in the market during periods of non-emergency. At the same time, regardless of where an API is produced or its indications, current circumstances in the antimicrobial market make it difficult for companies to stay in business. While taking steps to address the antimicrobial market's structural issues, which are rooted in proper antimicrobial stewardship, and while providing continuous Government support for establishing a domestic infrastructure for producing antimicrobials and ensuring their stable supply, it is also desirable that new antimicrobials are introduced to the market in a continuous manner to ensure ever-evolving AMR bacteria can be treated. This will require complementary systems that energize the market, including those for drug pricing and pull incentives.

Antimicrobials are at the heart of measures to combat AMR and uphold the foundation of modern medicine around the world. They are provided to 9.8 million people who undergo chemotherapy each year for cancer treatment; to those receiving one of the 150,000 organ transplants conducted annually; and to over 400 million people who receive dialysis and kidney transplants each year. In addition, it has been projected that a 50% reduction in a certain strain's resistance rate will lower domestic hospitalization costs by 22.8 billion yen to 58.8 billion yen over a ten-year period.

Although it may appear paradoxical at a glance, a long-term view of the situation shows us that global cooperation in the supply of APIs and other critical materials will be a key factor in building a secure supply system of reliable antimicrobials. It will allow Japan to benefit from economies of scale, which is likely to create room for the Government of Japan and other parties to reconsider the ideal structure of the support system. In addition to domestic security, efforts to combat AMR and to ensure a stable supply of antimicrobials must be continued from various perspectives,

including for pandemic prevention, preparedness and response (PPR) and for contributing to global health.