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Securing the supply of benzathine penicillin: a global perspective on risks and mitigation strategies to prevent future shortages

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Abstract

Benzathine benzylpenicillin is a globally indispensable medicine. As a long-lasting injectable penicillin, it serves as the primary treatment for syphilis, group A streptococcal infections, rheumatic fever and rheumatic heart disease. A competitive market and low profit margins, compounded by limited visibility of demand, have resulted in a decreased number of active pharmaceutical ingredient (API) manufacturers. By 2016, only three Chinese API manufacturers remained, continuing to supply to the global market today. Recurring global shortages, a consequence of supply and demand imbalances, indicate underlying market risks. Therefore, the need for mitigation strategies is imperative.

Keywords

benzathine penicillin; drug manufacture; medication shortages; rheumatic heart disease; syphilis

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The Global Significance of Benzathine Benzylpenicillin

Benzathine benzylpenicillin, colloquially known as benzathine penicillin G or BPG, is deemed an essential medicine for a considerable population globally. Injected intramuscularly,[1,2] this long-acting form of penicillin is the primary treatment for syphilis, group A streptococcal infections, acute rheumatic fever and rheumatic heart disease (RHD).[1] Each of these conditions represent significant public health challenges on a global scale. Annually, mother-to-child transmission of syphilis causes >350 000 adverse birth outcomes, two-thirds of which result in stillbirth or neonatal death.[3] BPG is the sole treatment recommended by the World Health Organization (WHO) to prevent this congenital infection.[2] Furthermore, since 1955, BPG has been the antibiotic of choice for prophylaxis against acute rheumatic fever caused by group A streptococcal infection.[4] Recurrent episodes of acute rheumatic fever can cause heart valve damage and the development of RHD. Such episodes and consequent RHD can be mitigated or halted with regular long-term administration of BPG. Presently, >39 million individuals live with RHD and approximately 320 000 deaths annually are attributed to RHD.[5]

Evaluating the Global Demand for BPG

Despite its crucial role, the existing market demand for BPG is projected to fulfil less than half of the actual requirement. Historically, BPG was employed to address a broad array of conditions, but the development of alternative antibiotics have narrowed its usage.[6] The WHO estimates that >6 million annual doses of 2.4 million units of BPG are required to treat adult syphilis. Of these, at least one million doses are needed for treating pregnant women to prevent congenital syphilis.[7] In contrast, a far larger amount, estimated at 200 million annual doses of 1.2 million units, is required to treat RHD. Both syphilis and RHD are disproportionally prevalent in low-resource settings, where underdiagnosis and limited disease surveillance are commonplace. Utilizing public-sector procurement data from 20 countries, the Clinton Health Access Initiative (CHAI) estimated the global market demand for BPG at 74–100 million doses (standardized to 1.2 million units) in 2016, representing less than half of what is required to treat these conditions.

The Downward Trend in BPG Manufacturing and Supply

The relatively small BPG demand compared with other similarly manufactured products, combined with a narrowing range of uses, competition and low profit margins, have produced a reduced number of manufacturers of the active pharmaceutical ingredient (API). By 2016, only three Chinese API manufacturers remained to supply the global market, a status they maintain today.[8]

In contrast, CHAI estimates that at least 30 companies were producing the finished pharmaceutical product (FPP) in 2016. Several companies produce quality assured product (approved by stringent regulatory authorities[9]) for regulated markets where BPG is considered a niche product and commands relatively high prices. The USA exemplifies this, where one supplier controls the entire market.[10] Yet most companies serve markets in low- and middle-income countries with weaker regulatory systems, where the bulk of the demand

originates. Prices for BPG in these markets are low, typically less than US$1 per dose. Factors such as price ceilings, competition and multiple small buyers of non-quality-assured product undermine economic incentives to supply quality-assured product that is costly to produce. As of July 2023, only one BPG product has received WHO prequalification and is included on the WHO list of prequalified products.[11]

Global and National Implications of BPG Shortages

Between 2014 and 2016, at least 39 countries reported BPG shortages,[8] resulting in patients receiving non-recommended therapies and leading to an increase in congenital syphilis cases.[12, 13] These shortages were triggered by concurrent and unrelated events that disrupted the API supply from two of the three active manufacturers. The global community, although aware of the presence and magnitude of BPG shortages in individual countries, rarely had a comprehensive view. Although production now aligns with demand, the root causes and underlying market risks of the global supply shortages persist. For the majority of markets, commercially producing BPG is not considered profitable, leading to prolonged order times and large minimum orders. Limited compliance with good manufacturing practices further increases the risk of production suspension by international regulatory authorities. This risk is amplified when production is restricted to only a few manufacturers, as is the case with API production. External factors also represent a threat to supply, as API manufacturing is concentrated in two regions of China where environmental regulations have disrupted production in the past.[14]

Country-level supply issues warrant attention. A 2019 WHO-led survey identified six countries still reporting shortages.[15] However, further investigation revealed that supply issues could potentially be resolved at the national level. For instance, South Africa's National Department of Health has been procuring BPG since 2016 on temporary (Section 21) authorization due to challenges with the registration of new suppliers. As of May 2023, due to a surge in demand from increasing syphilis rates, the USA is experiencing BPG shortages from a single source supplier that are expected to persist through mid-2024.[16] The WHO is currently soliciting information from member states regarding national-level availability of BPG for syphilis treatment.[17]

Proactive Measures to Prevent Future BPG Shortages

Global stewardship must be employed to identify market trends and optimize strategies, aiming to remedy existing national BPG shortages and mitigate risks of future global shortages. While proposed mitigation actions contribute to the response, they fail to offer a structural solution to prevent shortages. Activities to enhance market conditions for affordable, quality-assured product are also necessary, as outlined in Table 1.

Despite progress ensuring patient access to BPG in countries previously reporting shortages, buyers must remain aware of fluctuating market factors and the current producers' inflexibility in filling orders. The authors recommend the adoption of context-specific mitigation strategies. At the country level, there is a need to strengthen forecast and procurement processes, monitor stock levels and keep track of market authorization of

active suppliers. At the global level, it is essential to maintain and reinforce efforts to enhance market visibility, strengthen notification systems for shortages and monitor market risks. Finally, market conditions for the affordability of and incentives for producing quality-assured BPG require improvement.

Given that >40 million people globally depend on BPG every year to avoid premature death, it is critical that the strategic importance of this lifesaving medicine is recognized and receives more attention.

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Table 1.

Ensuring global access to benzathine benzylpenicillin: mitigation strategies and structural solutions to prevent BPG shortages

Mitigating strategies	Structural solutions
• Bolster country-level procurement and demand forecasting, utilizing robust disease surveillance data to quantify national demand, particularly for RHD and syphilis.[19, 20] • Monitor national stock levels and the quantity of active authorized suppliers to inform procurement decisions. Single-supplier nations are more susceptible to shortages. • Enhance global market transparency via disease surveillance and direct manufacturer engagement. • Strengthen mechanisms expediting shortage notifications and ensuring rapid, targeted response.[18] • Continually monitor market dynamics and maintain an up-to-date response plan for global shortages, encompassing advocacy initiatives and access to a backstop supply. Key stakeholders should initiate, regularly review and adjust this plan.	• Facilitate BPG quality assurance to foster confidence among public health partners and donors. Facilitate manufacturers access to institutional buyers subsidized by international donor agencies. The WHO's prequalification (PQ) program provides specialized technical assistance to manufacturers, accelerating attainment of unified standards of quality, safety and efficacy.[22] Availability of a quality-assured product may not stimulate new demand or buyers that opt for a switch from non-PQ products unless accompanied by wider market intervention. • Enhance capacity of BPG manufacturers to comply with international quality standards to mitigate production stoppages and poor-quality BPG manufacturing. Drawing from HIV/AIDS and vaccines markets, unified quality standards can be achieved when supported by a large payer or well-coordinated group of payers.[21] • Identify support from institutional funders to transition the market towards quality-assured product. Donor payers such as The Global Fund can aggregate demand for quality-assured products.[23] The newly released 2023 PEPFAR Country Operational Plan Technical Guidance now stipulates that ministries of health work with programs to ensure that the appropriate treatment for syphilis is readily available at the point of care.[24] Other funding mechanisms such as development banks could mandate procurement of quality-assured medicines, enabling access to affordable, quality-assured, donor-funded products. • Collaborate with global donors and implementing partners to support programs reliant on BPG, strengthening BPG supply, mitigating shortage risks and enhancing market visibility and conditions. Initiatives like the WHO initiative for elimination of mother-to-child-transmission of HIV, syphilis, or hepatitis B presents opportunities to integrate BPG with the procurement of donor-funded HIV treatments.[25, 26] RHD programs, requiring larger and long-term treatments, hold great potential for future market influence.[27]