National Network for Critical Technology Assessment

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BIOPHARMACEUTICAL TECHNOLOGY AREA SUMMARY

Policy shifts are needed to improve pharmaceutical supply chain quality & resiliency; these include, but are not limited to, investments in the adoption of existing advanced technology.

Summary: The U.S. is vulnerable to pharmaceutical supply quality and resiliency deficits, including shortages in critical medicines. Existing, advanced manufacturing technologies (AMT) offer advantages to quality and reliability among pharmaceuticals, yet the private sector faces barriers adopting such technology where it is needed most: 'generic' off-patent pharmaceuticals for which the risks of supply deficits concentrate and where potential negative impacts on individual and population health are greatest. Government insurers are also important payers for these products. This suggests AMT adoption to improve resiliency needs to be supported by the federal government. To aid government efforts we propose a framework for prioritizing which pharmaceuticals are critical, supply chains vulnerable, and best suited for technology solutions. We identify priority use cases to test the benefits of AMT techniques to improve resiliency and identify data infrastructure needs necessary for further refinement of priority lists.

To support future private sector investments and public policies, we suggest additional investments in data infrastructure to improve prospective surveillance efforts and the development of an empirical evidence base to evaluate the benefits of AMT investments relative to other policy levers and prioritize AMT investments. We suggest a focus on the potential for future investments to improve individual, population health outcomes and equity, without increasing medical spending.

Introduction: What technology could improve supply chain resiliency in pharmaceuticals?

Background: Pharmaceuticals are the most used medical care in the U.S., yet supply chains are not resilient, resulting in quality deficits and shortages that increasingly pose risks for patients and the medical system. Previous research suggests the risks of supply deficits concentrate among 'generic' off-patent pharmaceuticals, which are competitively supplied, low priced and non-orally formulated. Existing innovations in AMT have been suggested as priority investments to support improvements in supply resiliency, yet there is little evidence to assess their current applications, priority use cases, economic barriers and costs, and marginal benefits relative to alternative policies.

Methods and Sources of Data: Analysis of pharmaceutical supply chain resiliency involved structured interviews with pharmaceutical firms, experts in material chemistry and the use of AMTs applied to pharmaceuticals, and policymakers. We performed a qualitative assessment of available AMTs and their amenability to support high priority resiliency efforts in generic pharmaceuticals, their potential benefits and costs and barriers to their adoption. We then conducted a quantitative assessment of pharmaceutical supply chain vulnerability, using gold standard data and targeted to priority use cases amenable to AMT solutions to provide robust, contemporaneous estimates of their criticality and vulnerability.

Available AMT types, advantages, uses, costs, amenability to improve supply chain quality and resiliency among critical and vulnerable pharmaceuticals, and barriers to their adoption were identified based on a review of published reports, iterative discussions with experts, culminating in a workshop of stakeholders in March 2023 hosted by MIT.

Quantitative assessment of the supply chain of pharmaceuticals vulnerable to quality deficits and supply chain interruptions and priority use cases amenable to the application of AMT based on expert elicitation was conducted using national data on pharmaceutical sales, use, and supply characteristics 2017-2022 (IQVIA NSP & NPA). These data were augmented with US FDA data on the 295 pharmaceuticals that were in short supply in 2020-22, US Pharmacopeia (USP) data on the location of all finished off-patent generic pharmaceutical suppliers in 2022 and USP data on 329 excipients (inactive base ingredients) of all finished off-patent generic pharmaceuticals. We generated descriptive statistics..

Results: (See White paper, Data Appendix and Supporting Documents)

- Pharmaceutical supply chains vulnerability concentrates in 'generic' off patent pharmaceuticals.

- Vulnerability entails demand shocks (pandemics, CBRN, new uses) and supply shocks (manufacturing quality disruptions, geopolitical risks, natural disasters). Shortages can result from exogenous demand or supply, or endogenous supply shocks and may adversely affect patient care.
- There is significant enthusiasm for the adoption of existing AMT to resolve or mitigate challenges in pharmaceutical supply quality and resiliency. Main use cases of AMTs are in pharmaceuticals that need more consistent quality, more flexible supply that can scale up, and reduced lead times between identified need and production at scale.
- Current market forces, specifically the price pressures that keep margins low, do not support private sector investment in AMT where it is most needed, meaning with generics. This underinvestment stems from private sector actors (e,g. pharmaceutical firms, hospitals, pharmacies) not internalizing the benefits of AMT investments in their own work processes.
- AMT investments into generic pharmaceuticals would cost an individual firm $3.5-5M per line and take approximately 3 years from conception to production at scale. The number of lines would need to be greater than currently because AMT works better with fewer pharmaceuticals per line. and, more lines may be needed, adding to the cost. Firms currently supplying priority pharmaceuticals would not invest given significant competition and low per product revenue. Private firms would need public support to induce investment. Several pull and push mechanisms pursued by the public policies were identified that may be effective in generating private investment into improved pharmaceutical supply chain resiliency.
- Pharmaceuticals amenable to the application of ‘low hanging fruit’ AMT based improvements in manufacturing should be high volume, with sustained demand, and include off-patent “generic” pharmaceuticals with complex manufacturing requirements such as sterile injectables, antibacterial/antivirals, and those with a narrow therapeutic index (NTI) which require greater precision in formulation.
- The role of the federal government in correcting market failures suggests the importance of quantifying the benefits and costs of such investments, weighed against alternative policies to support supply resiliency. These include an assessment of pharmaceuticals’ criticality to patient health and medical care provision and their vulnerability. Criticality goes beyond that defined by the FDA’s essential medicine list.
- There is a paucity of evidence to support a systematic assessment of AMT priorities and investment recommendations. There are more gaps central to making systematic assessments and recommendations. Empirical evidence regarding the material impact of current supply vulnerabilities on patient health is limited.
- Ongoing investments in situational awareness are needed to assess pharmaceutical supply chain vulnerabilities and their amenability to policies to support improved quality and resiliency.
- Empirical results on vulnerable pharmaceuticals using gold standard data revealed the following:
    - Generic pharmaceuticals constitute most units sold, but the minority of sales, and are low priced relative to brand pharmaceuticals.
    - ‘Priority’ pharmaceuticals amenable to AMT constitute the minority of pharmaceuticals sold by count and use measures. There are approximately 4600 pharmaceuticals, Generic sterile injectables (GSIs) constitute 22% (992), antibacterial 7% (294) and NTIs <1% (11).
    - The prices, and by extension margins, of priority pharmaceuticals are low, emphasizing the unwillingness of manufacturers to invest in AMT from which they will not benefit.
    - There are high percentages of concentrated supply for some priority pharmaceuticals (GSIs & antibiotics) (volume calculated HHI>5000). Suppliers of priority pharmaceuticals were highly overlapped into a small number of firms (e.g., Teva, Viatris)
    - There were 231 pharmaceuticals in short supply between 2020 and 2022. The absolute number of shortages remained stable in comparison to the two years pre-pandemic. These pharmaceuticals are generic, most are supplied by 2+ suppliers (volume weighted), are commonly used (high volume), are concentrated in GSIs (58%) and have low prices.

- The finished dosage form formulation for most priority pharmaceuticals is made in the US (41%) and South Asia, India (42%); the EU (11%) and China (4%) account for smaller shares (estimates are volume weighted).
- Data are limited for upstream supply chains making intermediate and base ingredients. FDA knows location of API suppliers, but not the volume they sell to specific fill and finish manufacturers. FDA has no insight into the supply chains involving key excipients and key starting materials for API and excipients. We had data on 380 excipients, linked to fill and finish pharmaceuticals, but not the location of production. Magnesium Stearate is the most used excipient. Commonly used excipients have no substitutes or substitution would require additional studies to support use.
- Government insurers (Medicare & Medicaid) are important payers of 'priority' pharmaceuticals, suggesting the vulnerability of publicly insured populations to low quality and vulnerable pharmaceuticals. This underscores the important role of government to identify effective and cost-effective solutions to resiliency challenges.

Options and Trade-offs: How best to balance short-term quality and resiliency needs with long-term objectives is the key unanswered question.

EARLY WINS: How best to balance short-term quality and resiliency needs with long-term objectives is the key unanswered question. Our work supports the building of a comprehensive and contemporaneous data infrastructure and a research agenda that aims to provide an empirical evidence base to answer this question. Our work has put forward a framework for identifying priority use cases in supporting adoption of AMT. Using available data, we identified a preliminary list of potential pharmaceuticals suited for AMT investments and identified how such list could be refined with improved data infrastructure. Moving forward, we plan to augment the existing data infrastructure to enhance situational awareness and complete a series of empirical studies using modern empirical causal inference methods to support future investments by the private and public sector to improve pharmaceutical quality and resiliency.