INTEGRATED SUMMARY:

BIOPHARMACEUTICALS

In the short term, policies to adopt advanced manufacturing technologies are more likely than innovation to enhance generic pharmaceutical supply chain resilience. Public engagement strategies will need to address the public's lack of industry trust and pricing concerns.

Type of critical technology assessment Commodity product for which loss of access would have high social and security impacts

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Program management Put side-by-side the results of performers with different disciplines, perspectives, and methods; workshop engaging leaders from academia, industry, and government to launch analytics

Methods Interviews, economics, descriptive statistics, expert elicitation, citizen elicitation for public awareness and early input

Data Expert interviews; IQVIA pharmaceutical market data; USP data on supplier locations and drug raw materials; FDA data on drugs that have had supply shortages; expert and citizen survey data

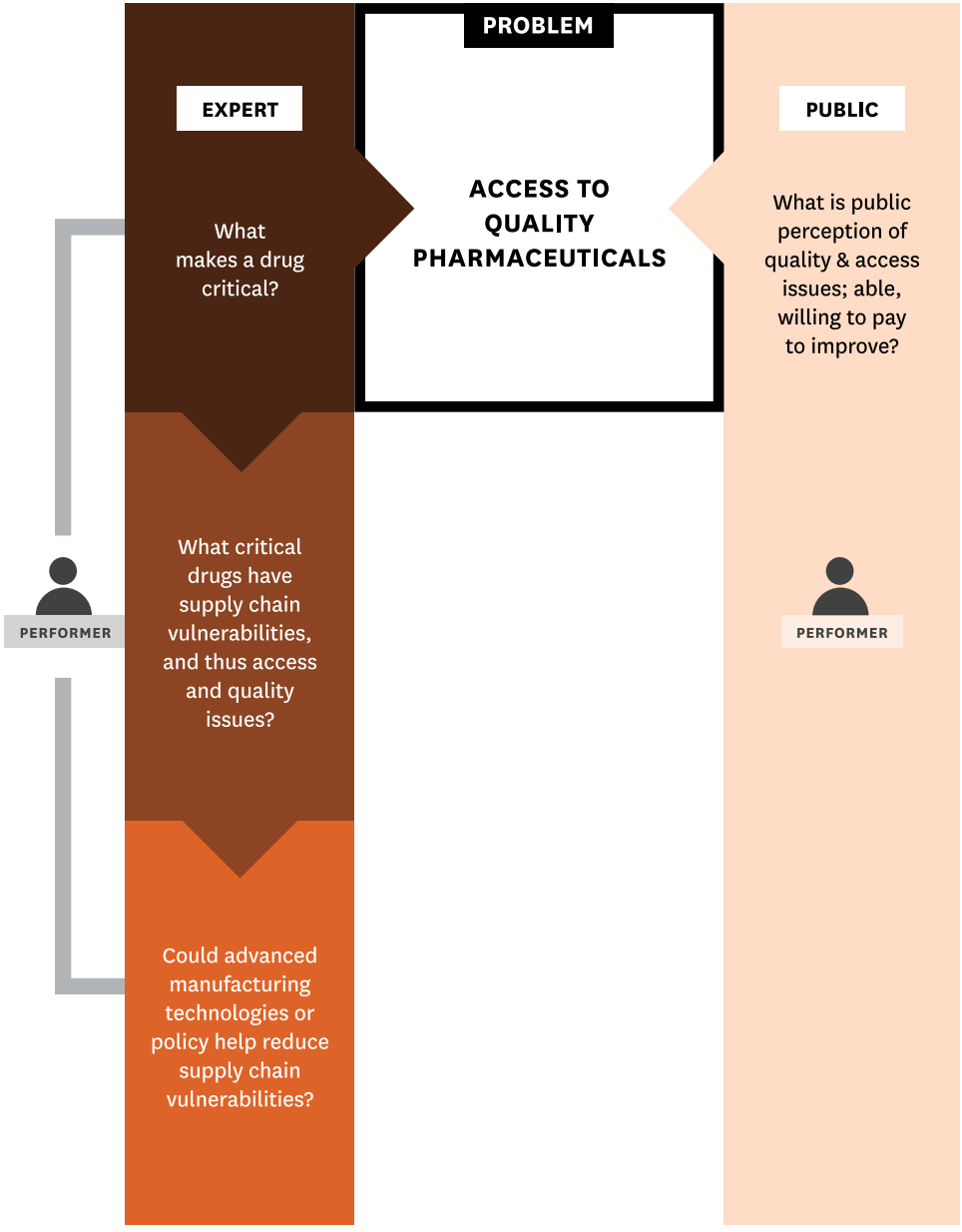
Criticality dimensions measured Social well-being (health, demographics of populations affected)

Challenges for future critical technology assessment Limited government and nonstakeholder analyst access to product-level supply chain data

Additional contributor: Emily Grayek

BIOPHARMACEUTICALS

Different disciplines, methods offer different perspectives on same problem



BIOPHARMACEUTICALS

FINDINGS: The United States is vulnerable to manufacturing supply chain resilience deficits, which result in shortages. Advanced manufacturing technologies (AMTs) such as continuous manufacturing, modular manufacturing, advanced batch processing, and digital twins offer advantages in ensuring product quality and reliability of the manufacturing process, yet the private sector does not adopt such technologies where they are needed most: generic off-patent drugs. This AMT adoption needs to be supported by financial incentives from the federal government.

We propose a framework for determining which drugs are critical, which supply chains are vulnerable, and which are best suited for AMT solutions. We identify priority use cases to test the benefits of AMT techniques to improve resilience and identify data and analytic needs necessary for future private sector efforts and federal policy.

RECOMMENDATION: To advance private sector efforts and federal policies, we suggest expanding surveillance efforts and developing an empirical evidence base to evaluate the benefits of AMT to improve resilience relative to other policies. We suggest that the development of empirical evidence should focus on what could improve individual and population health outcomes, ensure that citizens across all demographics benefit, and improve domestic manufacturing capacity.

FINDING: Public communication strategies for policies in this area are not developed or defined. Respondents to a general public survey had many, and often strong, feelings about policies' impact on generic drug prices and manufacturers' potential abuse of policies. The public is aware of, concerned about, and affected by access issues, but may not be aware of quality issues.

RECOMMENDATION: Policy implementation and communication in this area will need to address these concerns in order to achieve public acceptance. The mental models method applied by the public acceptance initiative in this demonstration area can identify similar gaps between expert and public understanding across the NNCTA's selected critical technologies.

Research Questions

Could the federal government leverage advanced manufacturing technologies (AMTs) to support greater generic drug supply chain resilience? What factors determine which drugs are critical for health outcomes? What products are "critical" and "vulnerable" from patient, provider, and public health perspectives and amenable to AMT intervention? What are the most effective strategies for communication with the public?

Motivation/Framing

Pharmaceuticals are the most used medical care in the United States, yet their supply chains are not resilient, resulting in quality deficits and shortages that pose risks for patients and the medical system. The risks of supply deficits are concentrated among generic (off-patent) drugs, which represent the majority of pharmaceutical prescriptions. AMTs such as continuous manufacturing, modular manufacturing, advanced batch processing, and digital twins have been suggested

as possible investments to improve resilience, but there is inadequate evidence to assess their applications, priority use cases, economic barriers and costs, and benefits relative to alternatives.

Our work supports both Executive Order 14081: Advancing Biotechnology & Biomanufacturing Innovation for a Sustainable, Safe, & Secure American Bioeconomy and the CHIPS and Science Act by identifying (i) essential medicines whose supply resilience could be addressed through advanced manufacturing technologies, (ii) barriers to AMT adoption, and (iii) interventions to overcome the barriers.

Methods and Sources of Data

Analysis of pharmaceutical supply chain resilience involved interviews with multidisciplinary academic and industry experts in pharmaceutical manufacturing, regulation, medicine, pharmacy, distribution, regulation, procurement, and reimbursement about potential private sector market failures in the supply of pharmaceuticals, qualitative assessment of available AMTs and their amenability to support resilience, and a quantitative assessment of pharmaceutical criticality and supply chain vulnerability among priority technology use cases.

Relevant AMTs were identified based on research literature, government reports, and 60+ hours of iterative discussions with multidisciplinary academic and industry experts, culminating in a workshop of stakeholders in March 2023 hosted by MIT. Analysis of the discussions suggested (i) definitions of "critical" pharmaceuticals and "vulnerable" supply; (ii) potential matches between highly critical, highly vulnerable drugs and available AMT (we term these "priority AMT drugs"); (iii) market-driven failures in the private sector's investment in resilient supply, and economic rationales for public sector investment to improve the supply resilience of priority drugs; (iv) policies that may improve pharmaceutical resilience; and (v) data gaps that reduce situational awareness of existing and potential supply vulnerabilities and of private and public sector investments in resilient supply, including AMT. We augmented concepts ii–v with a literature review and additional analyses.

Quantitative assessment of the supply chain of priority AMT drugs identified through the expert interviews was based on IQVIA data on the sale, use, and characteristics of pharmaceuticals in the United States in 2022; US Pharmacopeia (USP) data on the location of all finished dosage form generic drug suppliers in 2022; USP data on 329 excipients (inactive base ingredients) of all finished generic drugs; and FDA data on the 231 drugs that were in short supply in 2020–22. We generated descriptive statistics on priority AMT drugs to further characterize their demand and supply and inform decision making.

The public acceptance perspective on this area adapted the mental models approach, a flexible risk communication method that has been applied to a variety of technologies and policies. It has been used to study and inform individuals' decisions about their lives (e.g., how much more will I pay for an assured drug supply?) and about public policies (e.g., how much do I support industry subsidies?). It facilitates two-way communication between experts and stakeholders and can be used to understand what the public (i) already knows about a problem and (ii) needs to know in order to make informed decisions. It recognizes that the public includes diverse groups, with differing backgrounds, preferences, and information needs.

The mental models approach has four interdependent steps. The first asks what factors are most important to address the problem at hand, based on the research literature and expert interviews. In this case, two expert models were created. One addresses the impacts of the technology and potential supporting policies, the other addresses interactions with the public that affect its trust and acceptance of the technologies and policies (see figures 1 and 2 in the supporting documentation at nncta.org). These models were refined based on the findings from seven open-ended interviews with experts from industry, academia, and government (recruited at NNCTA's March workshop on technology solutions for generic pharmaceutical shortages). The interviewees suggested that the public would be more likely to care about implemented policies than specific technologies used by innovator companies.

The second step involves semi-structured interviews with members of the general public, paralleling those with the experts, so that their mental models can be compared to the expert model. This step may be skipped in situations, like the present one, where there has been little public discussion of an issue. In that case, the structured survey offers background information. The developed survey explains several policy options, identified in the expert interviews as having particular potential. This survey was administered to a diverse but not representative sample of 100 US participants 18 or older, recruited through the Prolific platform.

In the third step, development and deployment of those interviews inform the development of structured surveys suited to large sample administration, identifying critical topics and appropriate language. The fourth step is to develop and deploy communications to address gaps in understanding between experts and the public identified in the third step. As with all research elements, that information is extensively pretested for comprehensibility and balance. For more detailed information about the public acceptance study please see the supporting documentation.

Integrative Findings

Pharmaceutical supply chain vulnerability concentrates in generic drugs, which constitute most units sold but the minority of revenues, as they are low priced relative to brand (on-patent) pharmaceuticals. Vulnerability can result from demand shocks (e.g., pandemics, CBRN [chemical, biological, radiological, or nuclear] threats, new uses) or supply shocks (e.g., manufacturing quality problems, geopolitical risks, natural disasters), any of which may disrupt supplies and adversely affect patient care. In 2020–22, 231 pharmaceuticals were in short supply, primarily due to supply shocks. The absolute number of shortages remained stable in comparison to the 2 years pre pandemic.

There is significant enthusiasm by experts interviewed for this project for the application of AMT to resolve or mitigate challenges in pharmaceutical supply quality and resilience. Main use cases of AMTs are in prescription drugs that need better and more consistent quality, more flexible supply that can scale up, and reduced lead times between identified need and production at scale. Workshop experts suggested prioritizing focus on prescription drugs that are amenable to AMT-based improvements in manufacturing and that are high volume, with sustained demand, and include generic drugs with complex manufacturing requirements, such as sterile injectables, antibacterials/antivirals, and drugs with a narrow therapeutic index (NTI) which require greater precision in formulation. These drugs comprise central therapy in inpatient settings, for children, and for other vulnerable populations, and they account for a minority of drugs sold by count and use measures; of approximately 4,600 pharmaceuticals, sterile injectables constitute 22% (992), antibacterials 7% (294), and NTIs <1% (11).

Market forces, specifically price pressures that keep margins low, do not support private sector investment in AMTs for generics because private sector actors (pharmaceutical firms, hospitals, pharmacies, among others) do not internalize the benefits of such investments in their work processes to justify the costs incurred. Experts at the March workshop suggested that AMT investments in generic drugs cost an individual firm at minimum $3.5–$5 million and take approximately 3 years from conception to production at scale. The small number of firms that supply priority drugs would not invest in applying AMT to their production today. This compels a role for the federal government in correcting market failures through incentives to adopt AMT. To guide such investments, it is important to quantify their benefits and costs, weighed against alternative policies to support resilience, and to assess pharmaceuticals' vulnerability and their criticality to patient health and medical care, bearing in mind that criticality goes beyond that defined by the FDA's essential medicines list.

Manufacturing of these products is concentrated in selected firms and locations, but data are limited. Market concentration data are available for AMT drugs at the finished dosage form level, but not for upstream supply chains making intermediate and base ingredients. Finished dosage form drugs were mostly supplied by two or more suppliers,

although market share-based calculations suggest the dominance of one or two suppliers. Finished dosage form drugs in shortage were concentrated among sterile injectables (58%), low in price, and on average manufactured by two or fewer firms. The finished dosage form for most priority drugs (weighted by volume) is made in the United States (41%) and India (42%); the European Union (11%) and China (4%) account for smaller shares.

The FDA knows the location of active pharmaceutical ingredient (API) suppliers, but not their volume produced, sold, and linked to fill and finish drugs, and the agency has no insight into supply chains for key excipients and starting materials for APIs and excipients. We obtained data on 380 excipients linked to fill and finish drugs, but not the location of production. Experts interviewed suggest that many commonly used excipients have no substitutes or that substitution would require additional studies to support use. Experts suggested that concentration and opacity increase supply vulnerability to disruption. Conversely, improvements in supply resilience require increased transparency into the supply of and demand for pharmaceuticals.

Because private firms do not bear all of the social costs of supply chain failures, they have inadequate incentive to invest in resilience. Several pull and push mechanisms pursued by federal policies may be effective in generating private investment. But the intended and unintended consequences of these policies are unclear. For example, while private insurers are dominant payers of these pharmaceuticals, the public payers (Medicare and Medicaid) are responsible for a sizable share of priority AMT drug payment. This suggests the vulnerability of publicly insured populations to low-quality prescription drugs and vulnerable supply and the importance of federal efforts in identifying effective and cost-effective solutions to resilience challenges.

To shore up congressional support for government investment and industry support to match, better evidence is needed about AMT benefits, costs, risks, and uncertainties of public investment relative to alternative policies. For example, little is known about the effectiveness of government policies and private sector efforts in improving pharmaceutical supply chain resilience during the pandemic and other shocks, and empirical evidence of material impacts of supply vulnerabilities on patient health is limited. Improved data and additional efforts into situational awareness are needed to prospectively identify supply vulnerabilities and their amenability to policies to support improved resilience including but not limited to AMT.

PUBLIC ACCEPTANCE INSIGHTS

The survey results revealed that drug shortages are a widely experienced concern. All respondents to the physician and pharmacist surveys have dealt with them. Many noted that although shortages often have no consequences for patients, in some cases they lead to rationing or use of imperfect substitutes. Wrote one, "Many times, it doesn't matter. Other times, it can have important adverse consequences, including increasing the risk of death."

Survey respondents in both groups felt that manufacturers and the government were responsible for preventing the shortages they had experienced. "Ideally it would be the pharmaceutical companies themselves based on internal code of ethics. However, that seems largely unlikely in [the] pure capitalist society that we live in, so it is then left to the federal government to ensure that the health of the populace can be maintained...."

Among respondents to the general public survey, 42% had experienced, or knew someone who had, the shortage of a drug on the FDA or American Society of Health-System Pharmacists shortage list; another 10% reported shortages of other drugs. Most shortages were for ambulatory medications such as Adderall (17%) and insulin (5%). Many respondents gave detailed, and painful, descriptions of their struggles to find drugs, the health problems experienced when they failed to find them or used inferior substitutes, and stress even when they were successful. One respondent said "For me, one of my most prominent issues is lack of emotional stability. I am also Bipolar II and I was going through a manic episode at that time. Without my Adderall, I was even more unstable than usual."

Respondents to the general public survey believed that life-saving drugs should be the top priority for investments in improved supply chain resilience. That preference is generally aligned with the FDA's definition of essential medicines, which emphasizes acute emergencies, CBRN threats, and pandemic response. But there may be important differences in definitions. One respondent, for example, ascribed life-saving status to a drug that might be classified for a chronic condition: "A shortage that would be a big problem for me personally would be…acid reflux medication. I take prescription reflux pills and without them, I cannot eat." Many respondents reported dire consequences for other drug shortages that would not be used for acute emergencies (as seen in table 1 in the supporting documentation).

The imperfect match between the reference categories for experts and nonexperts regarding "generic drug shortages" could lead to miscommunication about problems and policies. For example, the public could have unrealistic expectations about the scope of policies, expecting that drug shortages for chronic drugs are also addressed. Communication about the reasons for generic drug shortages and the health impacts of common shortages could create a shared understanding of policy objectives between experts and the public.

Respondents to the general public survey had many, and often strong, feelings about policies' impact on drug costs and manufacturers' potential abuse of policies, such as reporting false information about supply chain resilience. Common policy recommendations were caps on drug prices or government incentives and subsidies to offset an increased price. Policymakers should account for these concerns when designing policies and communicating about implemented policies to the public.

Respondents to the general public survey were not always optimistic that policymakers were interested in hearing them (e.g., "ultimately I don't think it changes the minds of policymakers as they are often in a more advantaged place, and can be out of touch"). Physicians and pharmacists expressed similar sentiments (e.g., "The voice of the healthcare professional has been severely muted, not to mention the relationship between those in the corporate world and our politicians.").

Pharmaceutical leaders feel that public acceptance is critical for the success of policies aimed at increasing supply chain resilience for generic pharmaceuticals. They also believe the public is likely unaware of the implications of supply chain issues not just for access but also for drug quality. They perceive that the public is unlikely to care about the specific technologies involved, but will care deeply about how policies affect their health and economics. As one expert put it, "I'm not sure people want to know, oh, this drug was made with artificial intelligence or this drug was made with continuous manufacturing.... I think they want confidence that when they go to the pharmacy, what they need is going to be there and then that it's going to be safe and effective."

While pharmaceutical leaders recognize the need for communication about the drug shortage problem, its potential impacts on drug quality, and potential policies, it is unclear who will lead this communication. For example, one expert felt that "physicians, pharmacists, hospitals, government, educators,…the whole shabang" should be responsible for communication. While this recognizes that communication is important, it leaves a gap in leadership for this effort. A strategic communication initiative will be needed to engage the public about policies, incorporate their concerns in decision making, communicate about decision making, and monitor public opinion.

Options and Tradeoffs for the US Government

How best to balance short-term resilience needs with other objectives such as minimizing drug costs is the key unanswered question. Our work supports the building of a comprehensive and contemporaneous data infrastructure and a research agenda to provide an empirical evidence base to answer this question.

Beyond data, no matter what policy options are chosen to address drug shortages, effective communication will be required to (i) address the public's current understanding and lack of trust in the healthcare system and pharmaceutical industry and (ii) realize benefits, including those for health, national security, manufacturing productivity, and the economy. Communication about oversight and

monitoring will be important for policy acceptance, and addressing concerns about drug pricing and automation will be equally important. Communication strategies will need to be tested to make sure that adequate information is shared about the policymaking process and the public's concerns. Both experts and the public recognize that communication about the policymaking process is important, but from expert interviews it is unclear who will be responsible for this communication. A dedicated body should be tasked with communication when policies are developed and implemented, in this and other critical technology areas.

Vision for Future Analytic Work

We put forward a framework for identifying priority use cases in supporting adoption of AMT to enhance pharmaceutical supply resilience. Using available data, we identified a preliminary list of prescription drugs suited for AMT investments, characterized their supply vulnerability, identified benefits and costs of AMT investment to improve resilience, and determined how such a list could be refined with improved data infrastructure.

Moving forward, we plan to augment the existing data infrastructure to continue improving situational awareness and complete a series of empirical studies using modern causal inference methods to support future investments by the private and public sector to improve pharmaceutical quality and resilience. We plan to prioritize answering the following questions:

- Which pharmaceuticals create the largest negative impacts if their supply is disrupted?
- Who are the populations most impacted by nonresilient pharmaceutical supply chains? What are the patient health and payer impacts of current and past supply chain vulnerabilities?
- What are current and future climate-associated supply chain vulnerabilities and opportunities for investments in resilience?
- What are the benefits, costs, risks, and uncertainties entailed in supply chain resilience investments, including but not limited to those associated with AMT?
- What investments have US federal agencies made in pharmaceutical supply chain resilience and what has been their impact?
- How have other OECD countries addressed pharmaceutical supply chain resilience? Are there opportunities to improve resilience by leveraging existing capacities among trade partners?

Planned work will require additional complementary expertise to our current research team, including greater access to data related to base ingredients as well as international drug use and supply, and experts in trade and environmental economics, geospatial modeling, and ethics and equity.

COMMUNICATION AND PUBLIC ACCEPTANCE

Proactive reciprocal communication with the public could help shape policies and create the trusted channels that would secure and retain public acceptance. Absent that communication, opportunities might be missed (or worse). The next step in the process would be developing communications that elicit reactions to more fully developed policy proposals, drawing on analytical NNCTA research, focused on the specifics of those policies. That work would require additional iterations involving experts, representative samples of the public, and professionals, in consultation with policy and technology leaders cognizant of which policies are possible and interested in developing the most effective ones. In the case of the pharmaceuticals area, communication about policy development and outcomes could be tested for comprehension. In addition, communication addressing the public's top concerns (drug pricing and industry trust) could be tested for impacts on public acceptance of presented policies.

The mental models method demonstrated here integrates research knowledge (in the draft expert models), input from expert interviews, and survey research (with members of the public and front-line professionals). Although the application focuses on generic drug shortages, the issues revealed in this case study are present in some form in all emerging technologies and policies, of different prominence in each domain and perhaps with some additional concerns. The present methodology thus provides (i) a common analytical framework for addressing

public acceptance of the critical technologies that define a future US national technology strategy, and (ii) economies of scope, in terms of the models, empirical research procedures, analyses, and, eventually, communications that all technologies will need. Future work should apply these methods to other critical technologies, such as energy storage, focusing their analytical research and developing their communication strategies.

Given that there are limited resources to assess public acceptance across all critical technologies, the Network would benefit from assessing in which technologies and policies public input would be most important. Predictive models could be used to analyze what topics the public is most likely to engage with and where policymakers should have communication strategies. It will also be important to study what communication avenues the public is most likely to interact with; social media, for example, presents challenges in terms of misinformation but can be useful with effective communication strategies. Data analysis across platforms and surveys could help determine where the public is most likely to seek certain types of information.

Potential Broader Lessons for Critical Technology Assessment

Opaque and complex supply chains, geopolitical risks, and climate change will continue to stress access to needed pharmaceuticals. The private sector is underinvesting in solutions to improve supply resilience for critical products because such resilience has lower value to private firms than to the health system as a whole. Prioritization is needed both for effective and cost-effective investments by the private sector and for the development of government policies that improve supply chain resilience for pharmaceuticals. But the opacity of supply chains and improper framing of the problem have limited the capacity to identify priorities. Additional data and analytics will improve situational awareness and support private efforts and government responses to support supply resilience of critical products and thus improve individual health, public health, equity, national security, domestic capacity to manufacture and innovate, workforce development, and economic growth.

The CHIPS and Science Act requires "educating researchers on engaging with end users and the public…regarding United States societal, national, and geostrategic challenges." Fulfilling that requirement requires proactive reciprocal communication among technology developers, policymakers, and the public. Technology leaders are often poorly informed about the public, limiting their ability to realize the potential of the technologies and making them vulnerable to misinformation and disinformation. Critical technology assessment must provide analytically and behaviorally informed guidance for securing public acceptance, in terms of what technologies and policies are created and how they are communicated.