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Review

Re-Envisioning Pharmaceutical Manufacturing: Increasing Agility for Global Patient Access

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ABSTRACT

The traditional paradigm for pharmaceutical manufacturing is focused primarily upon centralized facilities that enable mass production and distribution. While this system reliably maintains high product quality and reproducibility, its rigidity imposes limitations upon new manufacturing innovations that could improve efficiency and support supply chain resiliency. Agile manufacturing methodologies, which leverage flexibility through portability and decentralization, allow manufacturers to respond to patient needs on demand and present a potential solution to enable timely access to critical medicines. Agile approaches are particularly applicable to the production of small-batch, personalized therapies, which must be customized for each individual patient close to the point-of-care. However, despite significant progress in the advancement of agile-enabling technologies across several different industries, there are substantial global regulatory challenges that encumber the adoption of agile manufacturing techniques in the pharmaceutical industry. This review provides an overview of regulatory barriers as well as emerging opportunities to facilitate the use of agile manufacturing for the production of pharmaceutical products. Future-oriented approaches for incorporating agile methodologies within the global regulatory framework are also proposed. Collaboration between regulators and manufacturers to cohesively navigate the regulatory waters is ultimately needed to best serve patients in the rapidly-changing healthcare environment.
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Introduction to Agile Manufacturing

While the pharmaceutical industry is well-known for applying innovative approaches in research and development to routinely provide patients with access to lifesaving drugs and biologics, the industry has faced notable challenges in using cutting-edge technologies to modernize manufacturing processes and to adapt quickly to an evolving technological landscape. From a manufacturing perspective, utilizing innovation to drive continual improvement is encumbered by hesitation or reluctance to change the current standards of manufacturing and production processes employed by the majority of global pharmaceutical companies. Additionally, significant

Abbreviations Used: Abbreviated New Drug Application (ANDA); Active Pharmaceutical Ingredients (API); Additive Manufacturing of Medical Products (AMMP); Advanced Therapy Medicinal Products (ATMP); Artificial Intelligence (AI); Biologically-derived Medicines On Demand (BioMOD); Center for Biologics Evaluation and Research (CBER); Chemistry, manufacturing and controls (CMC); Chimeric Antigen Receptor (CAR); Code of Federal Regulations (CFR); Contract Manufacturing Organizations (CMO); Critical Quality Attribute (CQA); Defense Advanced Research Projects Agency (DARPA); Electronic common technical document (eCTD); European Federation of Pharmaceutical Industries and Associations (EFPIA); European Medicines Agency (EMA); European Union (EU); Food and Drug Administration (FDA); Good Manufacturing Practice (GMP); Hospital Exemption (HE); Integrated Scalable Cyto-Technology (InSCyT); Information Technology (IT); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); Internet of Things (IoT); Investigational New Drug (IND); Industrial Vision Systems (IVS); Mammography Quality Standards Act (MQSA); Manufacturing Execution System (MES); Medical Device Regulation (MDR); Medicines and Healthcare products Regulatory Agency (MHRA); Mutual Recognition Agreements (MRA); New Drug Application (NDA); Near-Infrared (NIR); Near Infrared Spectroscopy (NIRS); National Institute of Standards and Technology (NIST); Pharmaceuticals and Medical Devices Agency (PMDA); Pharmaceutical Inspection Co-operation Scheme (PIC/S); Portable, Continuous, Miniature, and Modular (PCMM); Positron Emission Tomography (PET); Portable on Demand (POD); Real Time Release Testing (RTRt); SKU (Stock Keeping Unit); Toyota Production System (TPS); Vapor phase hydrogen peroxide (VPHP); World Health Organization (WHO)

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challenges exist with the inflexible and often heterogeneous global regulatory requirements that shape manufacturing and product quality expectations.

Specifically, the traditional, centralized manufacturing paradigm is a fixed model system that produces high-quality, reproducible pharmaceutical products in mass quantity, but includes substantial systematic rigidity, which may hinder innovation, speed, efficiency, and resiliency in a volatile market. In this way, current practices could contribute to delays in patient accessibility to medicines and drug shortages due to supply chain disruptions. Patient accessibility, herein, refers to patient access to medicines from a logistical framework by examining the physical proximity of patients to therapies for localized or point-of-care manufacturing considerations. The evolution of personalized or precision medicine requires a transition from mass production of a few products at a single site to low-volume and high-mix product manufacturing in multiple dispersed locations.

As a proposed potential remedy to allow for greater flexibility, agile manufacturing approaches encompass manufacturing and organizational methodologies that enhance business flexibility by allowing organizations to respond to variation of process inputs in real-time, enhancing industry's ability to better serve individual -patient needs. Portability further adds to agility, providing flexibility to deliver medicines specific to a given patient at the most appropriate location. However, in order to meet the evolving demands of industry stakeholders, a supportive and agile regulatory framework must develop alongside emerging manufacturing technologies to support flexible production. Production at the point-of-care can only occur with a combination of manufacturing and regulatory innovation, to further enhance patient access to medicines, thereby allowing patients to obtain medicines close to the site of manufacture, where appropriate.

In this review, we will provide an industry perspective on the use of agile manufacturing approaches and technologies to move toward adoption of point-of-care manufacturing to support on-demand patient access to medicine. We will also examine opportunities for leveraging existing regulations and originating new regulatory perspectives to meet the needs of the changing manufacturing landscape.

Challenges With the Traditional Pharmaceutical Manufacturing Paradigm

Traditional, centralized biopharmaceutical manufacturing chains are highly complex with a worldwide network for different raw materials, equipment and technology providers, and manufacturing sites. Conventional approaches are static, relatively immobile and unable to adapt to current health-care needs brought about by the advancements towards personalized medicine. The centralized manufacturing approach has been the dominant method for large scale production strategies since the Industrial Revolution of the late 18th century, which saw the advent of modern factory systems, assembly line production, and mechanized tools.[1] Notable advantages of centralization include low cost of mass production, limited use of resources, and increased uniformity and consistency of product.[2] While these attributes continue to be highly relevant and valuable qualities of current manufacturing and production systems, modernization of manufacturing and distribution processes can help to accelerate patient accessibility, address current gaps contributing to drug shortages, decrease time to market for emerging therapies, and minimize barriers for production of complex, precision therapies that rely upon personalization and flexibility in production.[3,4] As a result of evolving business, consumer, product, and environmental complexities, it has become imperative for manufacturers and regulators to consider a wider variety of manufacturing strategies to cover both high-volume, standardized therapies as well as comparatively more-complex smaller scale therapies.[5] As shown in Fig. 1, centralized manufacturing approaches used to support mass production of pharmaceutical products on a global scale require a gradual scale-up of production throughout a product's lifecycle, whereas smaller, identical, modular facilities may better support regional production as well as patient customization.

While new modalities, particularly autologous cell-based therapeutics, require the most business flexibility, agility is ultimately needed for all modalities. Across product types and therapeutic areas, manufacturers face increased cost and timeline-related pressures to bring new medicines to patients, adapt to local manufacturing requirements, and manage manufacturing equipment and processes throughout the entire supplier chain. Despite the evolving need for agility, the traditional manufacturing model remains of high value and importance to industry, as centralized, mass production of therapies remains a practical option for many products. While alternative approaches are desired for many new or complex modalities, not all products or companies will require decentralization or adaptation of agile approaches. However, the option for manufacturers to pursue agile approaches where appropriate (e.g. personalized, point-of-care therapies) should be made accessible from a regulatory perspective.

New Modalities and Increasing Complexities

The biopharmaceutical industry has achieved notable progress over the past 5 years evolving from producing primarily small molecule drug products to include complex protein therapeutics with recent acceleration in bispecific, multispecific, cell and gene therapies.[6] These new modalities are extremely complex and there is little historical precedence in generating these highly targeted therapies. Cell-based therapies, such as Chimeric Antigen Receptor (CAR) T cells, require a highly-personalized and adaptable production scheme, as every batch is created on-demand on an individual basis for each patient.[7] Similarly, regenerative medicines utilizing human cellular and tissue components also require small-batch handling and production from multiple localized manufacturers, which may be single-investigator or physician-based sites.[8] As personalized medicines continue to evolve and grow, it will be beneficial to harness agile approaches to manufacturing to shift away from the current manufacturing landscape consisting of few large-scale facilities to localized, small facilities that are equipped for point-of-care production. The diversity in new modalities with distinct manufacturing needs requires agility and adaptability throughout the product lifecycle. In addition to manufacturing and clinical challenges these new modalities bring in a unique set of regulatory challenges.[3,9-12]

As personalized medicines continue to evolve and expand, decentralized manufacturing approaches will likely become increasingly attractive, as smaller regional facilities can better accommodate the need for patient-specific customization. Manufacturers may seek to adopt patient centric drug development approaches, which identify the critical needs for patient comfort and compliance, incorporating the patient feedback from the early stages of drug development. Bedside manufacturing is a particularly compelling extension of patient-centric development, in which single-batch therapies are produced at the point of care to support patient access, therapeutic customization, and optimal safety and efficacy tailored to each patient's unique disposition.[13,14]

In addition to the promise of personalized medicine and bedside manufacturing, delivery of traditional medicinal products to patients can benefit greatly from technologies that offer enhanced agility, including portable manufacturing. Drivers include the ability to move complex manufacturing equipment that is not widely available across global networks, "right-sizing" manufacturing of low volume products to reduce environmental impact and enhancing speed of product to patients. For example, many precision oncology therapies target

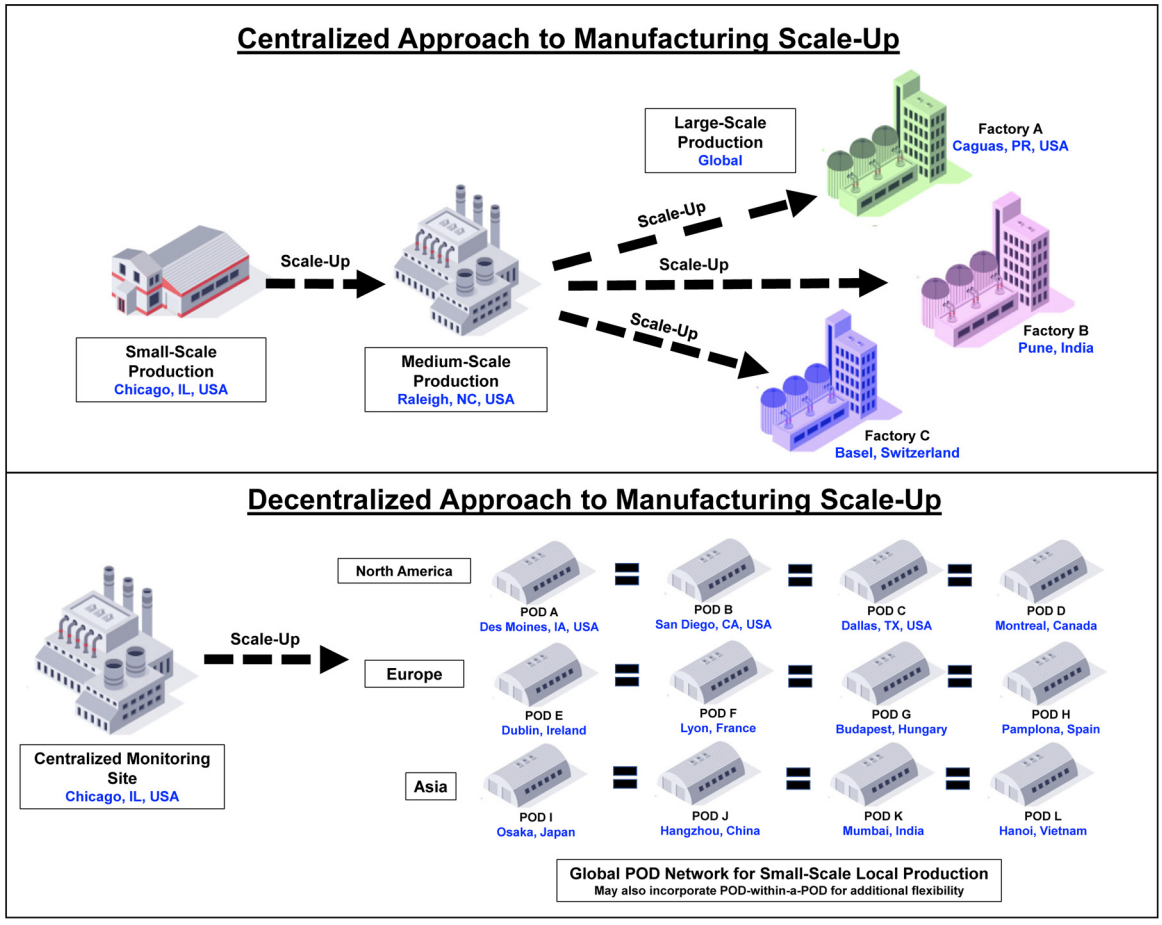

Figure 1. Centralized and Decentralized Manufacturing Paradigms.**Figure 1.** Centralized manufacturing approaches typically require gradual scale-up from small and medium scale production facilities to multiple, similarly-designed, but not identical, factories in different regions for large scale global production. Conversely, using a decentralized approach may enable local production at several identical small-scale manufacturing sites. Each Portable on Demand (POD) facility is monitored by a centralized facility that ensures process control and product quality.

specific gene mutations that are prevalent in a subset of patients, and thus need to be produced and distributed on a smaller scale than conventional biologics.[13,15] Agile technologies can be valuable in emergency situations, for bringing new treatments to market, or for swift response to increasing volume demands.

Regulatory Challenges Relating to Implementation of Agile-Enabling Technology

Despite the advancement of many technological elements that are needed to facilitate restructuring of centralized pharmaceutical manufacturing sites towards decentralized models that support greater customization and accessibility, significant regulatory uncertainties inhibit the industry's ability to embrace and invest in agile production applications for pharmaceutical products. The pharmaceutical industry is highly regulated, and shaped by extensive, globally-heterogenous regulations and legislation that may differ drastically between regions. While all regions must be considered prior to broad implementation of paradigm changes, the scope of discussion in this review is limited to a few major markets.

From a manufacturer's perspective, many of the regulatory barriers associated with innovation-enabling manufacturing technologies are the same across modalities and therapeutic areas. Key challenges include: the inability for industry to invest in agility-enabling innovation without substantial endorsement from regulators; the rigidity of long-established regulatory frameworks, and inefficiencies surrounding the current method of data exchange between industry and health authorities.

Perhaps most notably, implementation of new technologies and processes requires considerable investment from the pharmaceutical industry. Manufacturers are unwilling to invest in agile-enabling manufacturing technology to a meaningful extent until there is a high possibility of regulatory acceptance and flexibility. However, regulators are challenged to grant the desired level of flexibility and acceptance of agile manufacturing technologies until they are provided with concrete examples that confirm feasibility, including continued safety, efficacy and product quality. Restructuring of traditional facilities in favor of portable solutions that leverage novel technologies across multiple sites will require a supportive and flexible regulatory framework to be successful and to legitimize the degree of investment needed.

Agile manufacturing can encompass enhanced portability and mobility to enable decentralization and localized production. Manufacturers may seek to convert to using moveable, modular manufacturing facilities to support their production needs. It follows that movement of these modular systems should have substantially lowered risk than traditional approach of transferring a process to a different facility that may have different manufacturing equipment or scales. However, current regulations do not delineate between these approaches for moving manufacturing locations. Applying old regulations to new technology presents significant limitations that effectively preclude the benefits of portable production sites.

For example, the US Code of Federal Regulations (CFR) (21 CFR § 207.1, 21 CFR § 607.3, and 21 CFR § 807.3) defines an establishment as "a place of business under one management at one general physical location".[16-18] Changes to the registered location are considered significant requiring up to 3 months of stability data, comparative dissolution, and in some instances a bioequivalence study as per SUPAC-IR/SUPAC –MR guidelines.[19,20] Similarly, in the European Union (EU), a street address is expected to be provided in the Site Master File and any changes to this document require submission and subsequent review and approval of the variation prior to implementation.[21] The traditional regulatory paradigm not only mandates a fixed street address, but can also require full validation, months of stability data, and bioequivalence study data to be collected before the review process begins across multiple jurisdictions.

The global review and approval process itself is highly labor intensive. The processes by which data are collated and organized into regulatory dossiers present key inefficiencies and significantly impact timelines. It is a challenge to seamlessly compare manufacturing and quality data between sites, which grow increasingly complex as more sites are added and product modalities become more heterogenous. Additionally, as manufacturers add sites, they accumulate magnitudes of data, which typically is manually compiled, summarized, and organized for formal electronic common technical document (eCTD) submission to regulatory agencies.[22] Following filing, regulators will carry out inspections of new sites, thereby continuing a cycle of increased administrative burden and paperwork. In an agile model, there could be improved communication and transparency between manufacturers and regulators worldwide. A more advanced method of submission management and review would support the evolution from a manual system of data analysis to a system that encourages greater flexibility and additive learning. Data exchange, requests for information, and regulatory approvals could be made easier, quicker, more collaborative and concurrent across regions.

Agility for Pandemic and Emergency Response

In addition to increasing business efficiency and flexibility, agile approaches and accompanying supportive regulations are also needed for adaptation in emergency scenarios, wherein fluidity is a crucial driver of innovation in challenging circumstances. Specifically, the emergence of the global public health emergency due to the COVID-19 pandemic that started in early 2020 could serve as a pivot point to drive changes and updates to existing processes, as pharmaceutical manufacturers have faced additional pressure to adapt to a fast-paced, unpredictable landscape. Throughout the pandemic, ongoing drug shortages have highlighted key limitations in current manufacturing and supply chain paradigms. The pandemic has also required health authorities to perform assessments concurrently in real-time as data is generated to support authorizations. Addressing hyper-accelerated development timelines for innovative therapies coupled with worldwide demands for billions of doses requires unprecedented collaborative efforts between industry and regulatory agencies on a global scale.

The landscape of regional manufacturing is also changing quickly with an exponential increase in the number and geographic distribution of manufacturing sites and individual regulatory approvals, particularly in the post-approval space. The partnerships forged between companies and regulators throughout the pandemic can be leveraged as opportunities to transform manufacturing and distribution systems to improve efficiency and patient access to therapeutics, as outlined in the following discussion.

Advancements in Agile Manufacturing

Foundations of Agile Manufacturing

While agile manufacturing is currently an emerging ideology in the pharmaceutical industry, real-world use of decentralized, flexible manufacturing and distribution techniques is widespread across several industries. Companies in the information technology, consumer goods, shipping and logistics, and communications sectors, including several large multi-national companies, have seen increased productivity and organization, and subsequent economic benefits, following implementation of agile methodology. Though the biopharmaceutical industry has been slower to adapt technological advancements and digitization, there are many valuable lessons that can be applied from adaptation of agile manufacturing concepts from other industries.

Agile manufacturing has diverse conceptual roots ranging from Walter Shewhart's Plan-Do-Study-Act cycle of quality and process control, developed at Bell Telephone Research Laboratories in the 1930s, to the Toyota Production System (TPS) established in the mid-20th century.[23-26] Throughout the 1980s, the TPS was increasingly utilized as the framework for lean manufacturing principles at companies such as Canon, Fuji-Xerox, and Honda, which focused on minimizing waste and optimizing productivity, thereby stepping away from less-efficient mass production methods.[24] Researchers and industry experts at the Iacocca Institute of Lehigh University noticed a shift in manufacturing principles and techniques utilized in Japan, which led to the publication of a report on agile manufacturing in 1991 that highlighted its potential utility in the US.[27]

In addition to its applications to manufacturing, the term "agile" encompasses a multifaceted paradigm and project management system that can be applied to flexible workflow processes at every stage of the product development lifecycle.[28]

Examples Outside the Pharmaceutical Industry

While there are a myriad of industry-specific, potential reasons for a given company to adapt agile methodology, the present discussion will focus on utilization and adaptation of agile technologies across three functional areas of business improvement across industries: supply chain decentralization; digital innovations in computing technology and automation; and enhanced customization in product development.

Highly-centralized supply chains are operated and controlled by limited sources of decision-making authority. For example, in a centralized model, a single supplier will typically coordinate inventory sourcing decisions on behalf of itself as well as its buyers.[29] Supply chain decentralization can afford businesses comprised of many subsidiaries and/or locations greater autonomy for sourcing goods based on region or site-specific needs. Amazon is a prominent example of a business that has implemented a highly decentralized supply chain through its dynamic e-commerce model, consisting of an extensive outsourcing network and multiple fulfillment methodologies.[30]

Across industries, the ongoing COVID-19 pandemic has increased awareness and need for flexibility. For example, for many professionals, work environments have transformed from in-person settings to entirely virtual atmospheres supported by digital communications providers such as Zoom. Because decentralization relies on connectivity, digital innovations are integral for optimizing business flexibility. Transformations in computing technology, information technology (IT) infrastructure, and automation enable agile methodology by fostering interconnectivity between worksites and optimizing workflow efficiency.

Even though specific facilities within an organization may be self-sufficient and decentralized, sites can maintain sufficient connectivity and alignment with the larger organization. Dell Inc., which develops and produces computers and computing accessories, has relied on a "Configure to Order" model for building PCs since its inception in 1984.[31] To transform its facilities to accommodate disparate consumer needs, Dell simplified its manufacturing processes by leveraging IT solutions that allow for enhanced communication between internal facilities and external manufacturing networks, which permits need-based reconfiguration of facilities.[31,32] Similarly, IBM, another multinational computer technology company, utilizes their hardware and software solutions to engineer sophisticated IT-based factory floors, enabled by Internet of Things (IoT) and cloud-based technologies to connect machines and processes to a unified hub within their manufacturing facilities.[33] Enhanced automation and cloud-based systems allow agile facilities more flexibility by granting more precise monitoring and control over their production lines.[34]

Among the most discrete advantages of agile methodologies is the ability to leverage manufacturing flexibility to enhance customization of both the production site and the end-product. For example, 3M, an international company that produces a variety of consumer products and industrial materials, utilizes agile techniques for production of their Scotch-Brite line of abrasive products intended for home use to industrial applications.[26] Similar to Dell, 3M is able to make both highly standardized products for off-the-shelf utilization and custom products that can be individualized based upon business needs.

Nokia, a technology and telecommunications company, is collaborating with other industry leaders to develop a "Factory in a Box" solution to enable supply chain decentralization, site and machine connectivity via IoT technologies, and customization of facilities and end-products in a way that ties together all of the above agile advantages in a cohesive, portable factory format.[35] To create the factories, cargo shipping containers are transformed into small-scale, portable manufacturing sites with IoT-accessibility to join machines onto a unified network for synchronization of machinery and remote monitoring. Similar advancements in modular manufacturing have been made within the pharmaceutical industry. For example, pharmaceutical manufacturers are adapting their own unique renditions of elements of this "Factory-in-a-Box" type of methodology through the establishment of portable on-demand facilities in trailers and self-contained cleanrooms, as discussed later.

Examples of Mobile Healthcare Services and Solutions

While not directly related to pharmaceutical manufacturing, other regulated healthcare service entities have recognized the need for portable decentralized patient care solutions that facilitate easy patient access to medical procedures. Existing mobile healthcare facilities set a preliminary precedent for health authority regulation of decentralized, portable manufacturing facilities. For example, in the United States, the Food and Drug Administration (FDA) oversees the safety and quality of the US blood supply by setting standards for blood collection and blood products under 21 CFR Part 606. Accordingly, mobile blood banks, which are often stationed in a vehicle that can be parked on-site as needed, are regulated by Center for Biologics Evaluation and Research (CBER)and inspected by FDA every 2 years, with increased frequency for facilities with a history of violations.[36] If deviations from standard operating procedures defined under 21 CFR Part 606 occur, this must be reported to FDA by the licensed blood manufacturer, even if blood collection and blood product manufacturing were outsourced to a third party, such as an unlicensed registered blood collection site or a transfusion center.[37] The license-holder retains responsibility for blood product quality across facilities, which may be highly decentralized. Similarly, the European Union Blood Safety Directive, 2002/98/EC, establishes blood safety regulations for blood collection and quality system expectations for blood products obtained in EU member states, including mobile collection sites.[38] The European Commission subsequently authored a Memorandum of Understanding clarifying that single, mobile sites would not require inspection if they are managed under the quality system of the primary collection establishment.[39]

In addition to mobile blood collection, mobile mammograms are a prevalent mobile health solution that is regulated in the United States by the FDA.[40] The Mammography Quality Standards Act (MQSA) was introduced in 1999 under 21 CFR Part 900 and applies to both stationary and mobile units.[41] The MQSA holds mobile mammogram units to the same standards as stationary units and requires each mobile unit to undergo a post-move verification analysis each time the facility is relocated before imaging data can be obtained from patients. Sites are inspected annually, and for mobile units, post-move verification data and a travel log from each facility are examined. If multiple mobile units are managed by a single mammography provider, all must be deployed for inspection at the host facility at the time of inspection. In the EU, mobile mammography is a relatively widespread practice across member states.[42,43] However, there is no centralized regulatory guidance currently in place and individual countries regulate mammography standards, including mobile mammography sites.

Decentralized manufacturing or on-site compounding also takes place commonly at many medical centers with in-house radiopharmacy capabilities for positron emission tomography (PET) imaging drugs that enable visualization of malignancies and other pathologies. While PET systems are not necessarily mobile, they present an interesting example of the necessity of point-of-care manufacturing, as the reagents typically have short half-lives and must be prepared shortly before administration. In the US, PET imaging agents are regulated analogously to other drugs: manufacturers are required to file Investigational New Drug (IND) applications for first-in-human investigational studies and for marketing of compounding kits, a New Drug Application (NDA) is required for new products and an Abbreviated New Drug Application (ANDA) is needed for generic products.[44] Conversely, in the EU, there is no well-defined unified process for regulating radiopharmaceuticals. Instead, national procedures at the country-level exist, leading to wide variability across Europe. In select countries such as Austria, Belgium, the Netherlands, and Sweden, marketing authorization is not needed for PET imaging agents, as these are considered aspects of compounding as a part of standard practice of pharmacy. In contrast, France and Hungary require marketing authorization for use of radiopharmaceuticals.[45]

The examples above provide about US and EU regulatory perspectives on regulation of mobile facilities and/or point-of-care manufacturing. Namely, for mobile blood collection establishments, a centralized license holder maintains primary responsibility for all portable facilities deployed in respect to inspection and management of deviations in both the US and EU. Similarly, in the US, mobile mammography equipment must undergo post-move verification testing each time it is moved and this data, along with a travel log, must be available at the time of FDA inspection. These same principles and concepts could be extended to the biopharmaceutical industry encouraging flexibility in support of agile manufacturing concepts for both new and existing product types.

Pharmaceutical Industry Examples

As discussed previously, decentralization of manufacturing through the use of multiple manufacturing sites, including mobile manufacturing units, is of increasing interest within the pharmaceutical industry as a means to enhance flexibility.[5] Case studies and market research from pharmaceutical companies suggests that

single-source production or raw material supply creates significant risk to public health by increasing the potential for drug supply shortages.[46] While a complete reinvention of the manufacturing systems across the pharmaceutical industry may not be a feasible or desirable solution for all products and all companies, supplementing current processes with agile manufacturing systems, such as additive and/or distributed manufacturing, where appropriate, may prove advantageous. For modalities requiring increased personalization and flexibility, agile manufacturing approaches could be essential for patient access and commercial success. As companies seek additional options to stay nimble, industry may shift from a traditional open-based manufacturing network towards a more closed-based system relying on isolated modules within the same facility or modules that can be co-located or even transported. When technologies enabling both portability and agility intersect and synergize, point-of-care manufacturing can be eventually fully-realized for production of personalized, patient-specific therapeutics at the bedside.

Within the pharmaceutical industry, agile manufacturing can encompass a variety of cutting-edge technologies that confer flexibility, including, but not limited to: PODs, digitalization, continuous manufacturing, additive manufacturing (3D printing). Herein, several select, prominent examples and emerging solutions are explored further.

Modular Manufacturing Facilities

In contrast to traditional pharmaceutical manufacturing facilities that are typically constructed with fixed configurations of machinery and equipment to drive a predetermined system of operations, a modular manufacturing facility is comprised of flexible, reconfigurable modules that can be swapped in and out depending on production needs and scale. The modules can break down the production process into parts, with specialized, interchangeable pieces of equipment dedicated to each function. Modular facilities may feature an empty warehouse as a backbone, which is then filled with interchangeable functional, box-like modules to carry out production activities.[47] This high degree of flexibility is especially desirably for manufacturers that require specialized equipment, for example when producing multiple product modalities.

Modular facilities are in use at several companies including Cytiva, formerly GE Healthcare, which uses its modular, single-use FlexFactory platform for production of viral vectors and elements of cell and gene therapies.[48] Additionally, Biogen utilized a modular approach for the development of aducanumab, a monoclonal antibody in development for treatment of Alzheimer's disease. Aducanumab was fermented and manufactured in several separate but identical modules to provide flexibility during scale-up.[49]

Production on-demand (POD) Modular Manufacturing

POD or "Portable on Demand", a type of mobile modular manufacturing unit, are one potential solution that companies are adopting to facilitate agile, on-demand pharmaceutical manufacturing.[5] PODs are a type of modular manufacturing unit which include added portability as an asset. POD-based facilities are engineered and produced by several different companies, including G-CON BIO, which produces prefabricated, self-contained Good Manufacturing Practice (GMP) certified cleanrooms and offers a variety of customizable products with options for variable scalability.[50] G-CON BIO has established ongoing collaborations between companies such as Pfizer, Merck & Co., Inc., Kenilworth, NJ, USA, GenCure, and Lonza.[51-54]

As a specific example, Pfizer, in collaboration with G-CON and GEA Process Engineering, pioneered the Portable, Continuous, Miniature, and Modular (PCMM) development model in 2013. As part of its PCMM model, Pfizer established a POD-based PCMM facility in Groton, Connecticut for continuous production of oral solid dosage formulations. The facility has continued to add and install new PODs with additional functionality, such as in February 2019 when the facility onboarded a new POD to incorporate tablet coating process steps.[51] This new facility seamlessly connects with existing PODs but retains the capability to be repurposed for future redeployment. To date, the PCCM facility has been used to expedite the launch of an oncology product and is currently in use for three of Pfizer's pipeline products in clinical development.[55]

Similarly, at Merck & Co., Inc., Kenilworth, NJ, USA, G-CON-engineered PODs lay the framework for the Research Laboratories' GMP FLEx Center, located at Merck's Rahway, NJ campus.[52] The FLEx Center's equipment is compatible with oral solid dosage formulations and can be reconfigured as needed, depending on project needs. The center is intended to aid in product scale-up and scale-down for products in clinical development, with a particular focus on small-scale production to support treatment of unique patient populations.[56]

Other examples of PODs currently in development include the iCON turnkey facility for monoclonal antibody, autologous cell therapy, and CAR-T cell production. iCON's facilities are portable, prefabricated, and buildable in less than 12 months.[57] The iCON platform was established in collaboration with Integrated Product Services (IPS), an engineering and manufacturing technology firm, and G-CON.[58] Just - Evotec Biologics provides another modular option for agile production of biologics through their J-POD manufacturing services, which utilize autonomous GMP cleanrooms to carry out batch and continuous bioprocessing operations.[59] Just – Evotec Biologics is collaborating with G-CON to build the first J-POD commercial bioprocessing manufacturing site in the United States, which is currently under construction in Redmond, Washington.[60] Evotec is also establishing the first J-POD production site in Europe, with development ongoing in France, which is expected to be completed in late 2021.[61]

Another company, Germfree, has designed bioGO branded modular cleanroom facilities, which are mobile bioproduction trailers that offer controlled GMP environments for small-scale manufacturing and compounding.[62] Germfree's products include a BSL-2+ laboratory deployed in a semi-trailer truck, with capability for continuous high-power equipment usage, including freezers and laminar flow cabinets, for up to 3 days.[63] Germfree also aided global efforts towards the development of novel COVID-19 therapeutics by rapidly deploying a biocontainment cleanroom to support the manufacturing of an experimental antibody-based therapy, as requested by an undisclosed pharmaceutical company located in Indiana.[64]

To enable even smaller scale portable, modular manufacturing, the Massachusetts-based biotech start-up, Sunflower Therapeutics, is developing prototypes for modular, benchtop bioreactor systems for production of biologics on-demand.[65] Sunflower Therapeutics' pilot-scale model, the Dahlia system, is capable of automated, continuous manufacturing of drug products, including in-unit formulation and clearance of host cell proteins and impurities.[66]

Additive Manufacturing - 3D Printing

3D printing is an emerging technology with potential for personalized medicine. Currently 3D printing is limited to solid dosage forms, transdermal patches and vaginal delivery systems.[67] In 2016, SPRITAM® became the first 3D printed drug to attain FDA approval. SPRITAM® is developed by Aprecia Pharmaceuticals and is based on the ZIPDOSE technology which allows for high dose loads up to 1000 mg, fast dissolution due to rapid disintegration upon liquid contact, and enhanced taste-masking technology.

In 2020, FabRx, a start-up company based in the United Kingdom, launched the M3DIMAKER 3D printer to enable personalized medicines. Equipped with biometric login for secure use by healthcare professionals, M3DIMAKER has the option of three printing nozzles

for either clinical manufacturing or a personalized dose for a patient. M3DIMAKER is fitted with a camera to monitor in-line quality of the final 3D printed product. For the first time, 3D printed tablets are being used in a clinical setting for maple syrup urine disease, a rare metabolic disorder, to supplement isoleucine in pediatric patients.[68]

Mobile Fill and Finish Facilities

Traditional fill finish facilities have an enormous footprint with standardized systems in place for analytics and fill and finish processes often based on a container type (vial, syringe, etc.). Flexible aseptic robotic fill finish facilities are key to agile manufacturing by requiring a smaller footprint than a traditional manufacturing setup. One such example is the VanRX robotic aseptic filling Workcells, which have the capability to fill vials, syringes, including dual chamber syringes, and cartridges.[69] Vapor phase hydrogen peroxide (VPHP) decontamination is built-in to ensure quick change over between fill formats and stock keeping unit (SKU) changes, such as vial, syringe, or cartridge.

Similarly, Syntegon Technology's modular manufacturing units, provide another example of mobile fill and finish solutions and include an automatic bag opener, automatic tub opener, de-and renesting of SKUs, filling, capping, closing of SKUs, external washing, lyophilization unit and a hydrogen peroxide transfer chamber. Syntegon's platforms can be installed and validated for a fill finish operation for multiple SKUs. These platforms offer filling and isolator integrated as a single unit, integrated air management and biodecontamination to switch between fill formats.[70]

Terumo BCT's Finia® platform is another example of first-of -its-kind modular manufacturing for cell and gene therapies.[71] Finia® is a fully automated bench top temperature controlled closed system for final formulation and user defined aliquots for patients.

Another example of modular pharmaceutical processing is the VarioSys®, which is a combination of two systems – an isolator and machine modules which provide options for clinical, commercial, personalized or small batch manufacturing.[72-74] The VarioSys® features adaptable modules that are slotted in the isolator for various packaging materials (including vials, ampoules, syringes, cartridges, IV bags etc) and processing ability. VarioSys® can fill liquid and lyophilized drug products. By changing the combination of the modules along with the isolator, one has the ability to perform multiple fill finish options in a defined space, unlike traditional fill finish units which are set for a particular type of product and container only.

Thus, mobile fill finish facilities are an important instrument for supporting modular manufacturing. These systems ensure drug product quality while accelerating final product manufacturing and supporting options for both small-batch and bedside manufacturing as well as large batches for commercial manufacturing.

Automated Visual Inspection

Mobile fill finish facilities can be enhanced with automated visual inspection units equipped with advanced optics coupled with artificial intelligence (AI) to capture particles in the final drug product. These automated inspection systems can be integrated to provide real time analysis for at-line decisions to accelerate lot release.

Visual inspection is one of the standard assessments before a drug product lot is released to ensure the final drug product is practically free of particles. Traditionally it is performed manually by certified visual inspectors. In a manual visual inspection, each vial is inspected either one by one or several syringes or cartridges at a time. Visual inspection can be especially challenging for certain drug products to differentiate true particles from artifacts, like air bubbles. Recently, automated visual inspection systems have been adapted as a substitute for human eye. Use of multiple camera angles, alongside the ability to take pictures and videos of the drug product in motion, provides additional data points which can be re-inspected if needed. For example, Industrial Vision Systems (IVS) launched the IVS-COMMAND-Ai-in-line inspection. The IVS system relies on artificial intelligence algorithms to navigate subtle changes in visual inspection trends. Syntegon Technology installed the first validated visual inspection system in an automated inspection system. Amgen uses this system to distinguish between air bubbles and foreign particles at the rubber stopper in syringes.[75]

Portable and Remote Access Analytics

As part of the drug production process, manufacturers require instruments enabling quick, accurate drug product or raw material in-process analysis on the production floor. Portable and remote analytics are foundational for agile manufacturing facilities by enabling real-time decisions. Remote analysis enabled with digital data functionality provides continuous access to data globally thus increasing efficiency for biopharmaceutical manufacturing.

An example of a portable analytics tool is Thermo Scientific's handheld Raman spectroscopy TruScan™ RM analyzer and microPHAZIR RX, based on Near-Infrared (NIR) Spectroscopy for a qualitative and quantitative analysis of raw materials and drug product.[76,77] Both analyzers meet GMP and 21 CFR Part 11 requirements. Applications include dosage form identification, solvent distillation, blend analysis, end point determination, and active pharmaceutical ingredient (API) quantification to ensure drug product quality. The TruScan™ RM analyzer is designed to be chemical /drop resistant, weighing less than 2 pounds for extended use in a manufacturing facility.

Recent publications have highlighted the use of benchtop NMR analysis as a nondestructive tool to analyze both solid and liquid drug products. Benchtop NMR, which has a small footprint and is nondestructive, has been used to analyze contents of tablets,[78] aggregation in monoclonal antibody liquid product,[79,80] and adjuvant fill levels for vaccines.[81] These systems have the potential to aid in biophysical characterization, lot release testing, and stability assessment of the drug product at the fill finish facility.

Near infrared spectroscopy (NIRS) has also been used in academic and industry settings to support real time release testing (RTRt) for solid oral dosage forms. RTRt approaches allow for dissolution profiling via *in vitro* modeling, which incorporates real-time data inputs of critical material attributes and critical process parameters to enable batch release.[82] NIRS can enable real-time data collection, verification of dissolution modeling approaches, and continuous process monitoring through rapid and reliable quantification of chemical and physical attributes of in-process samples.

Modular manufacturing is only as robust as the digital data capacity and integration platform of the facility, which grant real-time data insights. An example of mobile and remote analysis is Lonza's unified data management system where scientists and engineers have real-time access to analytics information across all projects globally which has drastically reduced troubleshooting time and production costs.[49] Similarly, Eli Lilly uses real time sensor data enabled by the cloud to ensure visibility and control for the manufacturing of insulin pens before they are sent to contract manufacturing organizations (CMOs).[49] Real-time access to data reduces downtime on production floors for root cause analysis. To further enhance monitoring of in-process controls, Rockwell Automation offers a PharmaSuite Manufacturing Execution System (MES), a plantwide production management software that enables end-to-end tracking to of discrete and batch production processes, currently in use by Pfizer and Ferring Pharmaceuticals.[83]

Traditional and new analytical technologies may contribute to ensuring that product quality and release specifications are met in a timely manner for agile manufacturing. With new modalities, such as complex biologics, unique testing toolboxes are still evolving. Considerations to ensure analytics can be adapted on an agile

manufacturing setting include footprint for instrumentation; ease of recalibration; and cloud connectivity.

Emerging Technological Developments

Many of the technologies and processes that currently support pharmaceutical manufacturing were initially discovered and piloted in small-scale academic laboratories before their adaptation to large-scale clinical and commercial production in industry. For this reason, manufacturers can look to up-and-coming scientific advancements made in basic research to obtain a preliminary assessment of the potential future of technologies. Currently, in the early discovery stage, there is a demonstrable trend towards increasingly smaller-scale, bench-top systems, which may help to bridge the gap between medium-to-small scale POD production to enable truly personalized, micro-scale production for individual patients.

A prominent example of a benchtop manufacturing unit is the Integrated Scalable Cyto-Technology or InSCyT system, developed by MIT researchers with the purpose of making small-batch medicines for precision medicines.[84] The InSCyT system uses *Pitchia pastoris* yeast as an expression system to enable manufacturing capability for a variety of different protein biologics in an autonomous bench-top bioreactor with in-process purification steps. To date, it has been used to produce small batches of human growth hormone, interferon alfa-2b, and granulocyte colony-stimulating factor with comparable quality to commercially-available products. The InSCyT system is currently being utilized by the biotech start-up, Sunflower Therapeutics, as previously discussed.

For small molecule production, a different team of MIT researchers has developed a refrigerator-sized, portable continuous manufacturing system that can produce small-scale quantities of small molecule API.[85] The system has been used in a pilot testing program funded by the Defense Advanced Research Projects Agency (DARPA) to synthesize liquid formulations of diphenhydramine, lidocaine, fluoxetine, and diazepam and is optimized to be operated by a single user, which can be contrasted with current batch manufacturing methods which often require large teams to manage. These research efforts ultimately led to the creation of a start-up company, On Demand Pharmaceuticals, which aims to increase access to affordable medicines by decentralizing manufacturing efforts through the use of miniature, modular drug production facilities.[86]

Similar to MIT's InSCyT system, University of Maryland Baltimore County researchers at the Center for Advanced Sensor Technology (CAST) have developed the BioMOD (Biologically-derived Medicines On Demand) system, which is an automated, portable device that uses Chinese hamster ovary cells and a continuous purification process for small-scale GMP manufacturing of protein biologics, including granulocyte colony-stimulating factor, erythropoietin, and glucose binding protein.[87,88] Notably, the BioMOD system is a small manufacturing unit the size of a briefcase, which represents a considerable scale-down even in comparison to today's POD facilities.

Another small-scale production system, the Cocoon Platform, is rapidly becoming adapted by industry leaders, such as Lonza.[89] The platform features a customizable, automated, closed-system for small-scale production of a variety of cellular immunotherapies for point-of-care use in clinical settings.[90] Lonza has ongoing collaborations with research institutions including Stanford University School of Medicine, Fred Hutchinson Cancer Research Center, and the Parker Institute for Cancer Immunotherapy. The manufacturing processes utilized for each autologous immune cell therapy have been previously established at each respective institution and are currently undergoing tech transfer to the Cocoon Platform.[91]

While the technological aspects of agile manufacturing, as previously discussed, are pivotal for driving forward agile approaches in the pharmaceutical industry, the regulatory implications associated with said technologies are perhaps the most important consideration for real-world implementation. Without assurance of support and guidance from global regulators, these innovative technologies, despite their functionality or efficiency, will not have practical utility for expanding patient access to therapies.

Regulatory Initiatives and Opportunities

Across regions, regulators have recognized the need for change and in many cases have provided avenues for increased dialogue with manufacturers on new technology through the publication of guidance documents, establishment of regulatory initiatives, and issuance of forward-looking vision statements. However, it is important to note that despite the recognition that decentralization and associated technologies have received as potential remedies to current problems, regulatory risk remains a perceived roadblock for new technology as a definitive answer on acceptability is only attained upon implementation and demonstration for a specific product. As a result, there is little precedent on a globally accepted regulatory paradigm for distributed manufacturing itself.

Advanced manufacturing encompasses many different types of agile-enabling, novel manufacturing processes and methodologies, including, but not limited to: additive manufacturing, continuous manufacturing, machine learning, automation, digitization, artificial intelligence, and adaptive process controls. On a global scale, regulators have been largely supportive of the development of new technologies, with several regulators publishing guidance documents and future-leaning strategic documents focusing on these areas of innovation.

In the United States, the FDA has released a variety of guidance documents and vision statements in addition to establishing working partnerships and research initiatives that convey the Agency's overall commitment to developing a regulatory framework that is supportive of scientific innovations. Primarily, FDA's efforts to-date have focused on additive manufacturing approaches for medical devices,[92] AI-based software for medical devices, and continuous manufacturing of pharmaceutical products.[93,94] To help further understanding of the process control risks and mitigations, FDA established an in-house Additive Manufacturing of Medical Products (AMMP) core research facility, which assesses and develops standards for devices and drugs produced via additive manufacturing methodologies. To help FDA regulators establish a keen understanding of the potential risks and control steps associated with continuous pharmaceutical manufacturing, FDA acquired the ConsiGma 1 oral solid dosage development unit, a modular continuous manufacturing platform developed by GEA Process Engineering.[95] FDA released a draft guidance on key concepts, control strategies, and process validation steps for continuous manufacturing in February 2019.[93]

In early 2021, the FDA established a new memorandum of understanding to support advanced manufacturing and supply chain innovations and announced a partnership with the National Institute of Standards and Technology (NIST).[96] Also in early 2021, FDA suggested that a guidance document will be issued for CMC considerations pertaining to manufacturing of CAR-T cell therapies.[97]

In the EU, the European Medicines Agency (EMA) shares FDA's perspectives on the necessity for manufacturers to pursue advanced manufacturing technologies to keep up with changing supply chains and complex new modalities. EMA released the "EMA Regulatory Science to 2025" strategic reflection statement to provide perspectives on future developments in regulatory strategy.[98] Among the goals outlined in the statement is the adoption of novel manufacturing technologies and development of supportive, modernized regulations. Similarly, in the EMA Pharmaceutical Strategy for Europe, "bedside manufacturing" is named as a potential future development, in

particular for advanced, highly-personalized therapies, such as cell and gene therapy products.[99]

To operationalize EMA's strategic goals towards advanced manufacturing techniques, a revised guidance document was published in January 2021, which goes into effect in June 2021, to provide advice for assessing quality aspects of medicinal products containing genetically modified cells.[100] For personalized therapies, the EU uses a variety of point-of-care regulation pathways that help to support advanced therapy medicinal products (ATMP) that rely on patient specificity, including hospital exemption, named patient use, and compassionate use.[101] In particular, the hospital exemption (HE) regulation allows prescribing medical institutions to manufacture ATMPs at the point-of-care, outside of the clinical trial setting.[101,102] The HE regulation is, in theory, a critical pathway to help enable decentralized, bedside production of complex therapies. However, there are few examples of HE's real-world usage due to financial limitations and lack of experience with requisite regulations and manufacturing techniques.[101]

From a medical device perspective, there is no specific guidance or regulation in the EU for additive manufacturing. Formerly, medical products produced through 3D printing would be regulated under the Medical Devices Directive 92/42/EEC.[103] However, the new EU Medical Device Regulation (MDR) issued in 2017 (2017/745) does not include specific recommendations for the regulation of 3D printed medical devices. 3D printed devices that are custom-made by in-house medical facilities would not need to follow guidelines for obtaining the CE mark.[104]

In the UK, a UK-focused Industry/Regulatory collaboration, known as the Advanced Therapies Manufacturing Taskforce, which includes members representing the UK's regulatory agency, Medicines and Healthcare products Regulatory Agency (MHRA), published the Advanced Therapies Manufacturing Action Plan (MMIP) in 2015.[105,106] The plan outlines a strategy for developing a supportive regulatory and manufacturing infrastructure for development and production of cell and gene therapies through investment in technologies and an experienced labor force. The plan also promotes decentralization by proposing a unified quality management system which could oversee multiple satellite sites, in contrast to the centralized model currently in place.

Outside of the US and Europe, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) is supporting advancements in continuous manufacturing through the establishment of an Innovative Manufacturing Technology Working Group, founded in July 2016. The group, made of up PMDA regulators from a variety of functions, including the Office of Cellular and Tissue-based Products, the Office of Manufacturing/Quality and Compliance, and the Office of Research Promotion, published their perspective on continuous manufacturing in 2018.[107,108]

Additionally, ICH is in the process of creating a draft guidance for continuous manufacturing, ICH Q13, which aims to support agility by establishing standards to harmonize continuous manufacturing regulations on a global scale and is planned to reach step 2 in June 2021.[109]

Local Manufacturing

In addition to supporting advanced manufacturing efforts globally, public health entities and regulators have expressed increasing interest in local production of pharmaceutical products. The World Health Organization (WHO) published a white paper in 2011 launching an initiative to create more local manufacturing facilities in low-access and remote areas to improve availability of medicines.[110] Non-profit organizations, such as the Medicines for All Institute, which supplies lamivudine for treatment of HIV patients and Civica Rx, which distributes heparin and other injectables products, have recognized the impact of supply chain concerns on at-risk communities and in response, have partnered with pharmaceutical manufacturers to provide added supply chain security for select life-saving therapeutics.[111-113]

In the US, the US Government Accountability Office published a report in June 2020 to support local production of medicinal products which suggested that there was considerably less FDA oversight of products produced overseas in foreign manufacturing sites.[114] In response to the report, the Senate Finance committee requested the FDA to consider incentivizing manufacturers to produce APIs and finished products in the US. FDA cited the need for advanced manufacturing systems that could aid quality assurance and product consistency. While not explicitly stated in the report, modular and/or decentralized facilities could be used as a potential solution to stimulate and support domestic production measures.

Remote Assessments and Virtual Inspections

Current regulations require all operating sites to undergo routine regulatory inspection. Remote facility assessments and virtual inspections can help enable agile manufacturing methodologies and decentralized production strategies by granting regulators and manufacturers additional flexibility. For manufacturers pursuing decentralized approaches, which could conceivably include dozens or even hundreds of modular and/or mobile facilities, remote monitoring and virtual inspections can be conducted more expediently, with no compromise to GMP compliance, and without requiring regulators to travel.

The COVID-19 pandemic has disrupted regulators' abilities to conduct routine, in-person inspections of manufacturing sites. Instead, regulators and manufacturers have had to adopt remote assessment solutions to ensure the safety and quality of medicinal products despite lockdowns and travel restriction measures enacted in most regions. In Europe, EMA has been conducting virtual inspections throughout the COVID-19 pandemic.[115] In a white paper outlining alternative GMP inspection techniques for use in emergency situations, the European Federation of Pharmaceutical Industries and Associations (EFPIA) recommended retaining many of these virtual procedures for use beyond the current pandemic. Among the virtual inspection implementations considered by EFPIA for continued investment are remote desktop reviews, a process outlined in greater detail by the Pharmaceutical Inspection Co-operation Scheme (PIC/S).[116] PIC/S encourages remote desktop reviews particularly for overseas inspections for facilities that have already been inspected in-person by local regulatory authorities. The remote review process utilizes a combination of previously acquired regulatory inspection data collected by foreign regulatory bodies, along with new information requested from the site via written correspondence.

In the US, FDA released a new guidance in April 2021 describing their use of remote interactive evaluations to aid in its assessment of manufacturing facilities.[117] In the guidance, FDA describes using a combination of remote desktop review techniques as well as real-time teleconferencing solutions, such as livestreaming of manufacturing operations, to monitor and certify GMP compliance from a distance.

Regulatory Collaboration

One of the key regulatory challenges that manufacturers currently must contend with is the fact that there is a lack of global harmonization amongst regulatory agencies, resulting in challenges when managing regulatory CMC submissions and manufacturing supply chains. These regional regulatory differences thus add further complexity to product development and production strategies and contribute to delays in patient access to approved therapeutics. This issue has been

further emphasized by the COVID-19 public health emergency, which has distinctly demonstrated the need for fostering synergy between agencies and has provided unprecedented opportunities for collaboration due to the urgency with which vaccines and therapeutics must be developed and distributed.

Mutual Recognition Agreements (MRA) increase regulator efficiency to oversee GMP practices and standards worldwide. In this way, information-sharing and regulatory collaboration can reduce the number of inspections that must be carried out. For example, the EU has MRAs in place with Australia, Canada, Israel, Japan, New Zealand, Switzerland, and the United States.[118]

From a manufacturing and quality assurance perspective, information sharing and work sharing amongst regulators can minimize the inspectional and administrative burden associated with large numbers of facilities. Parallel and web-based review opportunities across global health authorities can be utilized for agile manufacturing enabling technologies. Current harmonization and parallel review efforts include Project Orbis and the ACCESS consortium, all of which focus on uniting regulatory health authorities to promote regulatory collaboration and alignment on regulatory requirements and reviews.[119,120] Project Orbis, led by the US FDA's Oncology Center of Excellence, promotes parallel review between international regulatory partners of select oncology product marketing applications and post-approval supplements with the highest probability of providing significant benefit to patients.[119] Project Orbis' participating countries include Australia, Singapore, Brazil, Switzerland, the United States, and the United Kingdom.[121] Similarly, the ACCESS consortium supports virtual work-sharing and collaboration between regulatory authorities from Australia, Canada, Singapore, Switzerland, and the United Kingdom, as a means to increase the quality and efficiency of review and risk assessment for regulatory applications.[120] The ACCESS consortium exists as a consensus-building solution to continually increasing workloads and limited resource availability.

Future Perspectives

When considering agile manufacturing and the regulatory pathways needed to drive these manufacturing approaches forward, there are two outlooks. The first is near-term, which asks: "how can we work within existing regulations to accommodate agile and portable manufacturing today?" The second outlook is long-term, which considers: "how can we modernize the regulatory framework to enable agile and portable manufacturing?" Here, we will consider both near-term and long-term outlooks and propose potential changes needed to support each phase.

Near-Term Considerations

In the near-term, there are standard pathways of regulatory flexibility that can be pursued on a case-by-case basis. Portable manufacturing such as replication or relocation of a manufacturing unit is likely to be considered a manufacturing site change by current regulations. These regulations tend to presume the manufacturing process may be impacted by numerous changes to the equipment and facility that have the potential to impact final product quality. Risk assessments and risk-based reviews can be a powerful tool to identify what is expected to change when a facility is moved and identify where risk is reduced due to consistency and agile manufacturing compared to a typical manufacturing site change. Additionally, risk assessment enables succinct communication to regulators of points where risk remains (e.g. different operators of equipment at different locations), and what plans can be put in place to mitigate or control residual risk. However, risk assessments must be accompanied by globally consistent risk-based regulatory reviews to provide a consistent benefit.

Importantly, as industry seeks harmonization of global approaches to agile manufacturing, it would be of great use to standardize risk assessment approaches. Common risk assessment approaches would enable clearer communication with reviewers,

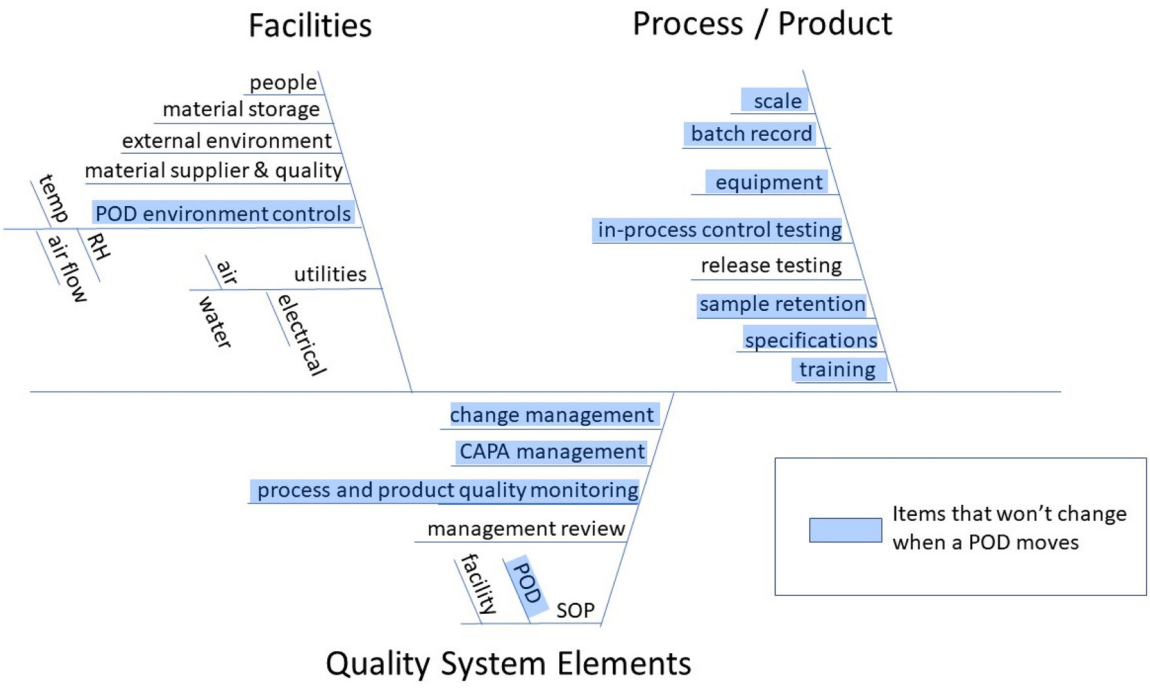

Figure 2. Proposed Paradigm for Site Change Risk Assessment for Mobile Facilities.**Figure 2**. Example application of fishbone diagram to identify key aspects for consideration when deploying a mobile fill finish facility. Factors that are not anticipated to vary upon POD relocation are highlighted in blue; Factors that are not highlighted may be variable upon redeployment and will require proper process control, risk assessment, and mitigation for mobile sites.

	Risk (Based upon Probability x Impact)									
CQA for Sterile Filling	People	Material Storage	External Environment (warehouse)	Material Supplier	Utilities: Water	Utilities: Air	Utilities: Electrical Connection	Release Testing Site	Management Review	Facility SOP
Characteristics (Description)	moderate	low	low	moderate	low	low	low	moderate	low	low
pH	moderate	low	low	low	low	low	low	moderate	low	low
Sterility	moderate	low	low	moderate	low	moderate	low	moderate	low	low
Potency	moderate	low	low	low	low	low	low	moderate	low	low
Dose Uniformity	moderate	low	low	low	low	low	low	moderate	low	low
Identity	moderate	low	low	low	low	low	low	moderate	low	low
Average Deliverable Volume	moderate	low	low	low	low	low	low	moderate	low	low

Figure 3. Probability-Based Risk Assessment for a Mobile Fill Finish Operation.**Figure 3**. An example of a probability-based risk assessment is shown above, outlining potential risks associated with a change in location for a mobile fill-finish operation. Low risks to product quality and process uniformity are shown in green, whereas moderate risks are depicted in yellow. There are no high risks identified, but several moderate risks are described. An initial risk assessment, similar to this above example, helps to better focus risk mitigations or controls.

greater consistency in approvals, and could lead to risk-and-science-based approvals, rather than a checkbox approach based on assuming all location changes are inherently high risk.

An example of a standardized, step-wise approach is provided below, in this case for the relocation of a POD used for sterile filling operations:

- Step 1: Identification of aspects that may be different between sites (Fig. 2)
- Step 2: Risk assessment as to whether these aspects that are different have low, medium, or high potential to impact product quality. (Fig. 3)
- Step 3: Risk mitigation / control strategy (Table 1)

As viewed in the example fishbone diagram below (Fig. 2), manufacturing aspects that may have an impact to the final product quality can be identified through consideration of the facilities, the manufacturing process and product, and quality system elements. Aspects from each category that may have impact upon final product quality are identified. Following that, the specific scenario is considered. Because several of these aspects, such as POD environmental controls or equipment used in the process will not change when a POD is relocated, these aspects are not considered for further risk mitigation activities. The POD itself serves as a mitigation to risks that are traditionally observed when relocating manufacturing processes; only aspects that have potential to impact the product quality remain for further evaluation .

Following identification of Facility, Process/Product, and Quality System Element aspects that may impact product quality, further risk assessment is required. Tables such as illustrated in Fig. 3 below, aid in discussion with regulators. The Critical Quality Attribute (CQA) for the sterile process filling in a POD are listed, and then considered for each aspect that could potentially impact quality due to relocation of the POD. The risk category is determined by consideration of the probability that this aspect will change, in addition to the impact to the CQA if it does change. The completed risk assessment allows for visibility into areas that need mitigation in the control strategy.

Following this example, the people conducting the operations, the material supplier, the general air supplied to the sterile filling POD, and the release testing site all may be different when changing locations, which may impact product quality. To reduce potential identified risks, mitigation or controls may then be applied, as further exemplified in Table 1.

At the end, the final risk assessment is conducted to verify that mitigations have reduced the risk sufficiently and to identify any potential need for continued monitoring of the manufacturing process or equipment performance.

As a manufacturing unit is moved, and data is generated at each location, a performance history can be built. The additive nature of this data may lead to a predictive model or may simply support reduced activities for future location changes based on demonstrated reduction in risk, and appropriate modifications to the risk assessment above.

Unique approaches for validating processes at decentralized manufacturing sites should be shared and confirmed with health authorities. The rigor of the validation at the first site versus the subsequent sites might be different. These approaches may be justified by a risk assessment, such as the example proposed in Fig. 3 and Table 1, and additive data. Health authorities could consider a similar approach for inspections where an initial site has more inspectional depth than subsequent sites.

Table 1
Potential risks and risk mitigation actions associated with site location change.

Potential Risk	Risk Mitigation
People (Site culture difference)	• Training at each site conducted by same individuals • Training at second site conducted by individuals from first site • Ongoing monitoring of deviations to track potential differences
Material Supplier	• Maintain same supplier across locations • Establish specification and testing to ensure consistency in purity/stability of materials received
Utility Air	• Air quality monitoring • Filtration at the POD interface
Release Testing Site	• Specify sample handling/storage conditions

Long-Term Considerations

When considering the long-term perspective and modernization of the regulatory framework, it is useful to first identify the barriers in regulations that can hinder full implementation of agile manufacturing, and then to consider how they might be modified to facilitate agile manufacturing. One such barrier regards how a manufacturing site is defined and registered. The definitions and registration requirements vary across country and regions, but generally they all assume a single physical location. One question to ask is, "Can a manufacturing site be registered independent of a location?" Current regulations, guidances and practices are not written with portable manufacturing in mind.

We posit that it is possible a mobile manufacturing unit, contains the critical aspects that maintain quality, and therefore may be considered the manufacturing site itself. If the consistency of controls from location to location is sufficient, the risk may be considered the same, albeit in a different physical location. Such a change might be considered an administrative change, and not a manufacturing site change.

GMP oversight presents an additional global regulatory challenge. GMP status is traditionally established after inspection, and the certification or licensing that is granted is based upon the physical site. For portable manufacturing, there is a need to establish a pathway to GMP certification that does not include full re-inspection upon every relocation, and a way to tie certification to the portable unit, rather than a physical location. If a manufacturing site may be registered independent of a location as suggested above, it would follow that GMP status, once established, could also be recognized independent of location, although relocation over different regulatory jurisdictions could add further complexity.

The static view of tech transfer risks reflected in current regulations need to be changed substantially to support manufacturing modernization. Current regulations related to moving sites presume that a process will change substantially, even though many companies may have identical equipment across facilities. Changing the definition of a site for mobile manufacturing could eliminate the need for "tech transfer" and the current underlying assumptions related to a "site change".

However, it is important to consider that not all mobile manufacturing operations will have the same level of risk, which could be evaluated by regulators on a case-by-case basis. In the best-case scenario, the associated risk of moving the mobile unit would be no greater than standard disassembly and reassembling associated with equipment cleaning. Such activities today are managed by site procedures and subject to evaluation by regulators upon inspection. Regulators should move away from a strict label of "site change" and assess what is different from a risk perspective and how that risk could impact product output. The fixed paradigm should be in the assessment of risk, rather than in a rigid categorization of the activity and associated regulatory requirements. Additionally, regulators should also consider that under a robust quality management system adaptation of risk management and process control approaches will evolve with additive learning.

Beyond changing the "site transfer" label, the future may include multiple identical sites that are primarily operated and monitored by a centralized control center, similar to how a modern homeowner can use consumer IoT technology to remotely control household appliances and utilities through the web. Risk-based assessment of mobile manufacturing may necessitate different reporting requirements. Virtual inspections may help ease the administrative burden on facilities and streamline regulatory compliance and may also be a useful tool for leveraging for multiple mobile facilities.

While the pharmaceutical industry continually produces vast amounts of quality data throughout a given product's lifecycle, the ways in which it collects, stores, and submits data to regulatory agencies presents many key inefficiencies which burden and delay both regulators and manufacturers. Various technologies have been proposed to help aid in the submission and review of quality data. One such example is a structured content management approach, in which summary data is organized into reusable content blocks, which has been demonstrated to assist with data accuracy and reduction in authoring time.[22] A more future-focused perspective might also present a cloud-based data exchange platform, which enables autonomous submission of data from the sponsor to the regulator on an accessible shared platform. The vision of the cloud-based exchange platform can be used to seamlessly integrate data across dozens or even hundreds of localized manufacturing sites, and enable a learning-based model whereby the acquisition of additional information can be instantly used to improve the knowledge base for manufacturing and quality data. In turn, this growing body of data can be made accessible to global regulators and thus can improve transparency and enable continual improvement. For example, each incremental change could in principle trigger a notification supplying the regulator with the context and assuring that risk management is appropriate.

Creation of innovative web or cloud-based solutions to reduce regulatory review times and to transform sponsor/health authority global data exchange is the objective of a new non-profit organization, Accumulus Synergy, which was formed in 2020 by leading biopharmaceutical companies.[122] This non-profit organization is focused on creating a first of its kind cloud-based exchange platform transforming the filing and review process improving interactions and transparency between industry and health authorities globally. Currently, submission content and data are "locked" or "trapped" in an intractable PDF image creating inefficient information exchange, due to repetitive and manual processing of sponsor data, content and visuals within a filed dossier. Accumulus Synergy aims to leverage a web or cloud-based exchange platform to facilitate concurrent filing builds and parallel health authority reviews to reduce the cost of industry innovation, improve patient access through speed, facilitate more efficient data usage capabilities and exchange, and improve efficiency and transparency in the regulatory process. Currently, two use cases; 1) Parallel Review Shared-Space and 2) CMC Data-Driven Stability Submissions are in process to assess and validate the cloud-based exchange platform core capabilities.

Conclusions

Science, and specifically genetics, have opened the gateway to treat a myriad of previously untreatable diseases and industry advancements have been vast in new therapeutic modalities including precision and personalized medicines. However, in order to fully realize the potential in these therapies research and development innovation must be matched with cutting-edge advancements in manufacturing technologies enabling the pharmaceutical industry to be more nimble, agile and flexible. There exist many opportunities within current regulatory frameworks and perspectives to advance agile manufacturing concepts for real-world use in a commercial and/or industry setting. The present time could be the most optimal moment for enabling agile manufacturing techniques and supportive technologies. Right now, there is a confluence of factors, including the desire for regulators to adopt modern manufacturing technology; the recognized need by industry and regulators to simplify post approval changes; and an unprecedented global pandemic, all of which highlight the urgent need for supply chain flexibility. As the pharmaceutical industry is only in its infancy relative to emerging agile technologies, lessons learned can be applied from the mature models within other industries. Pharmaceutical manufacturers and regulators must capitalize on this window of opportunity to progress

harmonization, advance science, and bring medicines to patients globally. This imperative goes beyond what industry wants, as it is what patients worldwide require. Now is the time to advance and innovate to enable the best possible patient care in a rapidly changing healthcare environment. Patients around the world are depending upon the pharmaceutical industry to proactively optimize manufacturing capabilities with the patient needs in mind.

Conflicts of Interest

MA, MJA, NSC, and TRC are employees of Amgen Inc. CFL is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD). CMVM is an employee of Organon. All authors contributed to the writing of the report, approved the final version of the manuscript, and agreed to submit the manuscript for publication.

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