STATEMENT
OF
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U.S. HOUSE OF REPRESENTATIVES

HEARING ON
"IMPROVING SAFETY AND TRANSPARENCY IN AMERICA'S FOOD AND DRUGS"

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Dear Chairman Pallone, Chairwoman Eshoo, Ranking Member Burgess, and Members of the Subcommittee, by way of introduction, my name is Fernando Muzzio and I am a Distinguished Professor of Chemical and Biochemical Engineering at Rutgers, The State University of New Jersey. I am also the Director of the NSF Center on Structured Organic Particulate Systems, an NSF Engineering Research Center dedicated to the design of pharmaceutical products and their manufacturing processes.

I greatly appreciate the opportunity to appear before you at the hearing on improving the safety and transparency of America's food and drugs, and to share my views on H.R. 4866, the National Centers of Excellence in Continuous Pharmaceutical Manufacturing Act of 2019. I strongly believe that this bill is critical to maintain the viability of drug product manufacturing in the United States.

Continuous Pharmaceutical Manufacturing – an Ongoing Transformation in the Pharmaceutical Manufacturing Paradigm

Continuous Manufacturing is an emerging technology that has been shown to greatly reduce both the time and the cost of developing and manufacturing new medicines, while enabling significant improvements in the quality of the final product and the reliability of the manufacturing process.

As defined in H.R. 4866,

> *The term 'continuous manufacturing'— ''(A) means a process where the input materials are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system; and ''(B) consists of an integrated process that consists of a series of two or more unit operations.*

In traditional batch manufacturing, the entire amount of raw materials to be transformed into products are loaded all at once into equipment, and then this large amount of material undergoes processing to transform it into a large number of finished product units (e.g., 1,000,000 tablets). In this manufacturing modality, there is limited opportunity to control the process and to ensure product quality. Moreover, this approach to manufacturing is slow, labor intensive, and very difficult to optimize.

In contrast, Continuous Manufacturing is a modality where the ingredients are fed continuously at controlled rates, and travel non-stop from one manufacturing step to the next, until the process is completed. Only a small amount of material is in residence in an equipment item at any time, and the process is operated at, or near, steady state in a condition of closed loop process control. The continuous state of control enables the continuous monitoring and assurance of product quality. This modality enables a high level of automation and optimization and can minimize quality failures, decrease manufacturing cost, and improve quality. While this description is given in terms of powders and tablets, continuous pharmaceutical manufacturing is also feasible

for products in fluid, suspension, and semi solid form, including injectable solutions, ophthalmic suspensions, creams, ointments, and a myriad other product forms.

Current State of Implementation of Continuous Manufacturing

As a result of its numerous demonstrated advantages, Continuous Manufacturing of both small molecules and biologics has become a priority for biopharmaceutical companies, its technology suppliers, the FDA, BARDA, and the United States Pharmacopeia, an organization dedicated to quality standards. Dozens of pharmaceutical manufacturers, equipment and instrumentation suppliers, and ingredient vendors are actively engaged in this major reinvention of their pharmaceutical manufacturing platform. Companies such as Johnson and Johnson, Vertex, Pfizer, Eli Lilly, Glaxo SmithKline, Merck, Sanofi Aventis, Bayer, and Novartis, have all made corporate goals of converting a large fraction of their total production volume to Continuous Manufacturing in the next few years. Other brand-based manufacturing companies are also following suit.

We must also consider that the biopharmaceutical market has already exceeded a trillion dollars in annual worldwide sales. Within the next decade, we are likely to witness a worldwide conversion to Continuous Manufacturing of a significant fraction of the brand-based sector, which would mean that just a few years from now, pharmaceutical products worth hundreds of billions per year, spanning many drug product forms, including tablets, capsules, vaccines and injectables, could be manufactured using the new continuous methods.

Countries that are able to implement these methods effectively will capture much of this activity. This represents a large opportunity for the United States. Selection of manufacturing venues for traditional batch manufacturing activities has been driven in substantial part by labor costs and perceived regulatory burdens[1]. As a result, the US has lost a significant fraction of its manufacturing activities, in particular in labor-intensive industries. Implementation of continuous manufacturing processes, on the other hand, are less labor intensive, but they require access to a significant amount of specific knowledge that is not generally available in the public domain, as well as a suitably trained workforce. It is therefore likely that Continuous Manufacturing activities will concentrate in countries and locations where this knowledge and highly trained workforce are available, because these activities cannot be carried out without access to such knowledge and training.

[1] Dr. Janet Woodcock's testimony in front of this subcommittee, October 30, 2019.

The Rutgers-led Engineering Research Center for Structured Organic Particulate Systems (C-SOPS), which was one of the origins of this technology revolution, is also one of the largest repositories of relevant knowledge. Funded by the NSF in 2006, C-SOPS formed a coalition of six universities (Rutgers, Purdue, NJIT, UPR, Hawaii, and Rowan) to create a long-term strategic plan seeking to transform pharmaceutical manufacturing. C-SOPS implemented one of the first working Continuous Manufacturing systems in 2008, and subsequently worked closely with more than 50 member companies to create a functioning ecosystem devoted to developing, demonstrating, and facilitating the implementation of Continuous Manufacturing systems for solid oral dosage products.

Critical to C-SOPS' success was the active participation of the FDA, which joined the center shortly after its inception and has provided critical input and additional funding for research and educational activities. After the NSF funding period for C-SOPS concluded in 2016, the FDA became C-SOPS main federal sponsor, providing support for research and educational activities that continue to this day, which in turn helped FDA to acquire and maintain clear intellectual leadership among worldwide regulatory agencies.

In the 14 years since C-SOPS was established, our academic-industrial-regulatory partnership has attracted research funding in excess of $100 million, published over 500 peer-reviewed papers, and enabled implementation of advanced manufacturing methods at numerous companies. Among many examples of successful interaction, C-SOPS undertook a significant partnership with Johnson and Johnson in 2010, which remains active to this day, and lead to the implementation of the first FDA-approved conversion from batch to Continuous Manufacturing for the HIV drug, Prezista.

Implementation of Continuous Manufacturing systems is accelerating. The FDA has already approved six finished dosage forms (FDF) to be manufactured by four companies (Vertex, Johnson and Johnson, Eli Lilly, and Pfizer) using integrated Continuous Manufacturing processes. Many other brand-based pharmaceutical companies are also actively engaged in exploring, developing, and implementing continuous manufacturing processes, not only for small molecule prescription products, but also for biologicals and over-the-counter products, and many more products are currently at various stages of submission.

It is important to highlight the enlightened and highly positive role the FDA has played in enabling this ongoing technology transformation. The FDA embraced Continuous Manufacturing early on, funding academic research and strongly encouraging industry to pursue its implementation. Moreover, FDA hired people from other industries with relevant expertise, invested in the education and training of its personnel, and created a separate vehicle to encourage companies to engage in a productive dialogue. In these and other actions, the FDA made the ongoing technology revolution possible, and set an example for regulators worldwide.

Potential Advantages of Continuous Manufacturing

Reducing Drug Prices

Continuous Manufacturing can help reduce the cost of both prescription and OTC drugs in multiple ways. Some of the impact is direct: Continuous Manufacturing processes have smaller footprint, achieve higher yields, and require less direct labor than their batch counterparts, so they are able to directly impact the cost of making pharmaceutical products. Some of the impact is indirect: because Continuous Manufacturing processes also enable the manufacture of products with superior quality, and because they enable real-time quality control, they reduce the cost of assuring product quality. While Continuous Manufacturing processes require up-front investments in both physical and human infrastructure, they can return this investment rapidly. Moreover, Continuous Manufacturing products and their required manufacturing processes can be developed faster than their batch-based counterparts. As a result, products developed and manufactured using Continuous Manufacturing technology can reach the market place faster, extending profitability periods for the companies making them. These factors could contribute to lower drug prices to the US consumer, if Continuous Manufacturing technologies could be adopted in the highly price-competitive generic and the over-the-counter sectors of the pharmaceutical industry.

Improving Product Quality

Continuous Manufacturing processes can enable superior product quality. Our collaborations with the FDA and with industry, and our partnership with organizations like the United States Pharmacopoeia, help to ensure this outcome. There are three main reasons for this. First, the near-steady nature of the process enables all portions of material to be processed under equivalent conditions at a constant state of control. Second, because only a small amount of material is processed at any given time, quality attributes of every portion of the process stream can be rigorously monitored to assure quality. Any defective product units can be tracked and scrapped, while retaining only quality-compliant product units. Third, and again because the system is nearly-steady and continuous, real time monitoring, active control and advanced optimization can be used to ensure that the process remains within operational specifications at all times. In addition, Continuous Manufacturing enables detailed and accurate computer modeling, assuring a much deeper scientific understanding. This improvement in quality can translate directly into health benefits, since defective product may fail to provide its therapeutic benefit, or in extreme cases, cause harm to patients.

Faster Product and Process Development

For solid dose products such as tablets and capsules, which comprise the great majority of drugs taken by patients, Continuous Manufacturing has been shown to greatly reduce both the time and cost of developing new medicines. A typical Continuous Manufacturing line for solid dose product reaches an operational state of control in a matter of minutes. Therefore, extensive studies examining alternative product formulations and multiple process conditions and can be performed in just a few days, using only a small amount of raw materials. Moreover, because such development studies are performed using the same equipment that will be subsequently used for manufacturing, no scale up studies of the process are needed, and process development is further accelerated. As mentioned, this ability to develop products and processes faster and with less waste can have a major impact on the profitability of both brand-based products (which are protected by patents with finite life) and generic products (where the first company to file an approvable application often accrues a larger share of profits). In my opinion, an even more important benefit is the ability of accelerating access to life-saving new medicines to patients that literally cannot wait, providing the strongest incentive for implementing technologies that enable rapid product and process development.

Faster Responses to Shortages and Emergencies

By enabling faster product and process development, Continuous Manufacturing can allow manufacturers to develop products quickly to respond to emergencies, to address shortages, and to bring break-through therapies to market. The current state of knowledge often enables a skilled practitioner to create a formulation and a process for a given product in just a few weeks. Under emergency conditions, such processes need not be optimum, just adequate, which further enables rapid development. As mentioned, such processes can be developed at the full manufacturing scale and using only a small amount of materials, which is often critical early in the life cycle of a product, or when quality issues are detected, because under such conditions suitable raw materials can be scarce. Moreover, the intrinsically higher reliability of continuous processes should make them safer and easier to approve by regulatory authorities, further enabling rapid response during emergencies.

Growing US-based Manufacturing and Related Employment

Due to its many advantages, Continuous Manufacturing is likely to become a dominant drug manufacturing mode in the future, spanning most drug product types. Its development and deployment is an opportunity to bring drug development and manufacturing operations back to the United States and grow output and domestic employment in one of the largest consumer goods producing industries of the US economy.

While, as mentioned, Continuous Manufacturing processes allow substantial automation and require less direct labor to be operated --which is a key reason why lower labor cost destinations

provide less of an incentive-- they do require highly skilled scientists and engineers to support their specification, implementation, and optimization and well-trained operating personnel to run these modern plants. These jobs typically command high salaries, further growing the US economy and its tax base.

The pharmaceutical industry's transition to manufacturing a large fraction of its output using knowledge-intensive continuous technologies will take place not only in the US, but in all advanced economies, and in many emerging economies with large populations that require access to low cost medications. Designing and implementing the technology platforms to enable this transformation will likely create tens of billions of dollars in economic activity. Importantly, a strategic initiative in continuous pharmaceutical manufacturing would trigger significant activity in many other industries up and down the supply chain, including (1) raw materials suppliers, which are already indicating an interest in developing ingredients in grades optimized for continuous processing; (2) equipment and instrumentation companies, many of which are actively commercializing specialized manufacturing equipment, sensors and process analyzers; (3) companies that commercialize closed-loop control systems, and many others. Moreover, effective implementation of continuous manufacturing for pharmaceuticals will also provide an opportunity for enhancing other industries that rely of powder processing, including cosmetics, food, consumer products, dietary supplements, etc. These industries utilize manufacturing processes that are very similar to those used by the pharmaceutical industry and in many cases the technology is directly portable. The US is at an ideal position to capture – or to lose – much of this activity.

Reshoring pharmaceutical development and manufacturing operations would also facilitate more effective regulation. When those activities are carried out within our country's borders, they are easier and less expensive to inspect, facilitating compliance and enforcement of regulations. On-shoring pharmaceutical manufacturing will also increase the security of the drug supply, reducing the current high level of dependence of US patients on foreign suppliers. Moreover, by increasing its knowledge base, the proposed centers will also help consolidate and preserve FDA's intellectual leadership in this area.

The Need for Centers of Excellence in Continuous Manufacturing

More than 14 years of experience at the Rutgers' C-SOPS has taught our team a key lesson: ***Continuous Manufacturing platforms are highly integrated systems that are best developed by highly integrative programs*** where all necessary technical skills interact and synergize efficiently to create and capture all the required knowledge, including: (1) understanding of the properties of raw and intermediate materials and their effect on process and product performance, (2) effective design, accurate performance characterization, and optimal integration and operation of equipment, (3) accurate modeling of system dynamics, (4) effective sensors and

data analytics, measuring meaningful material and process variables, and (5) effective control methodologies. This integration of relevant technical components was essential to the success of C-SOPS and its partner member companies (Janssen, Eli Lilly, Vertex, and Pfizer), which to-date developed and operate all of the solid dose Continuous Manufacturing processes approved by the FDA and by the EMA.

This level of complexity currently makes it difficult for smaller branded and generic pharmaceutical manufacturers to implement Continuous Manufacturing. Currently, such integrated development capabilities for solid dose products reside only at a few universities in the US and Europe, and at a small number of leading brand-based pharmaceutical companies that have gained this experience through many years of sustained collaborative efforts and substantial investments. Such companies have created in-house expertise pools to enable them to implement these technologies. However, smaller pharmaceutical companies, and the generic sector, as well as adjacent industries such as supplements and cosmetics manufacturers, do not have effective in-house access to such expertise.

Moreover, while we have been able to demonstrate effective implementation of Continuous Manufacturing methods for solid dose manufacturing of small molecule products, Continuous Manufacturing of medium size and large molecular entities, such as peptides or monoclonal antibodies, is at an earlier technology readiness level. However, although complete integration of all relevant unit operations in a state of closed loop control has yet to be achieved for these product families, significant development of component technologies is in progress.

In brief, until the knowledge required to integrate Continuous Manufacturing systems is made broadly available and accessible, full implementation of Continuous Manufacturing across the entire field of applications (small, medium, and large molecules, drug substances, and drug products), will remain a difficult task and adoption will remain a slow process in the US. Meanwhile, international companies in Europe and China are actively investing in Continuous Manufacturing platforms as one of their key strategies for growth, placing US leadership at risk.

The recent past provides perhaps the best perspective on how to overcome this situation. The Continuous Manufacturing initiative in its present form is the result of a collaboration between government, industry, and academia, which joined forces to create, implement, and demonstrate this technology. The combination of all of these stakeholders made the effort affordable, relevant, and practical. Each player had a critical role. Universities, initially supported by NSF, provided the scientific strength and the long-term research perspective required to create something new, and also provided critically needed training and education to industry and FDA employees. Industry provided the critical input needed to make sure the technology was developed in a relevant and practical matter. The engagement and support by FDA support made it feasible.

The best way forward is to re-energize the original US-based partnership of universities, industry, and government, with participation of all relevant expertise, and charter it with the mission to make the required knowledge accessible and easy to implement. Key mission elements of such Centers should include:

1. Supporting US companies and US regulatory agencies in implementing continuous manufacturing methods;
2. Organizing and conducting R&D activities needed to create new and more effective technology, capture and disseminate know-how, create IP, and maintain technological leadership in Continuous Manufacturing methods that will enable industry to develop and manufacture products faster, less expensively, and more reliably;
3. Creating and maintaining a vibrant technological ecosystem, providing the ideal environment for entrepreneurial activities, collaborative research and development, and continuing innovation; and
4. Facilitating the creation of a highly skilled workforce in Continuous Manufacturing, ranging from specialized design engineers to capable plant operators.

As described by H.R. 4866, centers of excellence in continuous pharmaceutical manufacturing will nucleate and organize industry efforts to develop, implement, approve, and operate continuous manufacturing technologies, growing the number of companies capable of using these technologies from the current group of about ten companies, to an estimated 100+ end users. The resulting infrastructure will attract significant private sector involvement, serving as leverage to magnify investment from all stake-holders to maximize the benefit to all contributors. Moreover, centers will facilitate and de-risk adoption so that adopters can deploy these technologies across their entire organizations (new products, established products, OTC products, consumer products, animal health products, etc.). This would lead to the design, acquisition, and implementation of hundreds of manufacturing lines, to be housed in dozens of facilities across the country. Incentives, proximity to know-how and access to highly trained personnel, and other means of keeping those facilities in the US would help to maximize the overall impact on our nation's economy. This will provide all participants with a role in addressing the country's needs, including:

- The need to reduce the cost of developing and manufacturing medicines,
- The need to improve product quality and manufacturing processes reliability,
- The need to respond rapidly and effectively to medical emergencies, shortages, new technologies, and rapidly evolving market conditions,
- The need to reduce dependence of US patients on foreign suppliers, especially for critical medicines such as antibiotics,
- The desire to create supply chains that are robust, flexible, and highly efficient

- The desire to grow the country's manufacturing infrastructure, create high paying jobs, and strengthen our country's economy.

Continuous Manufacturing technologies, if supported by long term funding and enabled in the right forum, like those envisioned in H.R. 4866, can deliver these benefits.