CONTINUUS Pharmaceuticals Response to Section 232 National Security Investigation

Background/Introduction:

CONTINUUS Pharmaceuticals is leveraging the most advanced technology platform, Integrated Continuous Manufacturing (ICM), to produce drugs faster, at reduced costs, and with better quality. ICM was initially developed through an $84M joint research endeavor between Novartis and MIT. It combines industry-leading know-how on process integration with IP-protected unit operations. With ICM, we were able to demonstrate significant advantages compared with existing batch manufacturing:

- Reduction in lead time from 200 days to 2 days (e.g., elimination of starts and stops)
- Reduction in projected COGS by ~30-50% (e.g., full automation → less personnel)
- Decreased footprint by >90% (e.g., smaller equipment that operate on a 24/7 basis)
- Decreased environmental impact (e.g., reduced solvent usage)
- Improved quality (e.g., better process control through second-to-second in-line monitoring)

ICM lines can easily be reconfigured to make different active pharmaceutical ingredients (APIs) and drug products (e.g., tablets, injectables). Using ICM to produce clinical phase drugs offers additional benefits:

- Reduced FDA review time (FDA published data showing that regulatory applications with continuous manufacturing could reduce review time by up to eight months*)
- Accelerated drug development by eliminating scale-up across clinical phases and commercial manufacturing (drug developers would just have to produce for a longer period of time)
- Access to chemistries/steps not safe or practical in batch (with ICM, certain reaction parameters are substantially reduced, such as surface area/volume)

It is within this context and our collective experience that we have provided our comments below.

Comments:

Overview: Pharmaceutical manufacturing is not a level playing field. Foreign governments have, for decades, intervened (e.g., subsidies) on behalf of their companies, allowing them to gain an overwhelming advantage over American companies. Significantly lower wages in these countries further exacerbated this gross imbalance. The US healthcare system (e.g., hospitals/health systems, pharmaceutical companies, insurance companies) have been complicit, happily accepting the lowest cost medicines, despite questionable quality practices in these geographies (mainly India and China).

The end result is that the United States is extremely vulnerable to and dependent on foreign countries for the production of the medicines it consumes. The critical nature of pharmaceuticals – Americans rely on them for their well-being and survival – justify drastic and unconventional interventions by the United States Government. Herein we provide our collective thoughts on the posed questions and how to start to dig ourselves out of this hole that can collapse on us at any moment.

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(i) the current and projected demand for pharmaceuticals and pharmaceutical ingredients in the United States;

There should be a distinction between drug substance (i.e., the Active Pharmaceutical Ingredient, or API) and drug product (e.g., tablets, capsules, injectables – the formulations that patients consume), and their respective issues. Furthermore, it is extremely important to include in the discussion the key starting materials used to produce the APIs, as they are critical and predominantly produced abroad.

Regarding the demand for all of these items (key starting materials, APIs, and drug products), this is more a function of the general population and health status, which we do not see changing significantly in the coming years. As the US population increases, and citizens get older, demand should increase for all three (they are all connected: key starting materials make the API, which is the key ingredient in drug products that patients consume). Major issues relate more to the supply, as will be discussed below.

(ii) the extent to which domestic production of pharmaceuticals and pharmaceutical ingredients can meet domestic demand;

Domestic production is inadequate in all cases.

The key starting ingredients, which are by definition essential to produce APIs are predominantly produced in China. We believe this is a problem, and will be at the core of any long-term solution.

For APIs, approximately 80% of APIs consumed in the US are produced abroad. However, it is important to note that many of these foreign-sourced APIs are readily available and at very low prices (i.e., in most cases shortages do not exist). The real issue with APIs (especially generic APIs) is our foreign dependence, especially on countries such as India, where there are often quality/compliance issues and China, where there are political/national security issues (in addition to quality/compliance issues). Shortages of APIs can and do become a problem when quality problems (e.g., plant shutdowns) or major health crises (e.g., Covid pandemic) occur. These problems highlight a foreign dependence problem for the United States, not a capacity problem.

For generic drug products, conversely, there are shortages that result from a lack of capacity in the United States and across the globe. Much of this is a result of prioritization of high value products (i.e., branded drug products that are much more expensive) over the lower value generic products (which make up the preponderance of the drug products on the FDA shortage list).

(iii) the role of foreign supply chains, particularly of major exporters, in meeting United States demand for pharmaceuticals and pharmaceutical ingredients;

Currently, foreign supply chains are critical in meeting the United States demand for pharmaceuticals and pharmaceutical ingredients. Simply put, we depend on foreign manufacturers for the necessary drugs Americans consume daily.

(iv) the concentration of United States imports of pharmaceuticals and pharmaceutical ingredients from a small number of suppliers and the associated risks;

This is an issue that is exacerbated by the geographic concentration of these companies (e.g., China and India).

The lack of redundant producers for many critical key starting ingredients and APIs can result in shortages when a company stops producing that compound (e.g., for business decisions, quality infractions). However, that there is a limited number of suppliers may be a difficult problem to solve for key starting materials and APIs, as these are generally low value, and companies need scale to be profitable.

For drug product, this is more a function of capacity and resource allocation based on the economics of the different drug products (i.e., generic vs. branded).

(v) the impact of foreign government subsidies and predatory trade practices on United States pharmaceuticals industry competitiveness;

We believe that the major issue here are the low costs of APIs and generic drugs (drug products), which make it virtually impossible for domestic producers to compete with foreign companies. A combination of subsidies and significantly lower wages contribute to this unlevel playing field. Furthermore, in some cases, companies sell APIs and generic drug products at a loss (i.e., price lower than manufacturing costs) just to maintain their presence on formularies.

(vi) the economic impact of artificially suppressed prices of pharmaceuticals and pharmaceutical ingredients due to foreign unfair trade practices and state-sponsored overproduction;

As above, these practices make it impossible for domestic manufacturers to compete.

(vii) the potential for export restrictions by foreign nations, including the ability of foreign nations to weaponize their control over pharmaceuticals supplies;

The impact of these scenarios will be devastating – our over-reliance on foreign nations and lack of domestic redundancy make the United States extremely vulnerable to such potential scenarios.

(viii) the feasibility of increasing domestic capacity for pharmaceuticals and pharmaceutical ingredients to reduce import reliance;

Currently, we do not have the infrastructure/capacity at a meaningful scale.

(ix) the impact of current trade policies on domestic production of pharmaceuticals and pharmaceutical ingredients, and whether additional measures, including tariffs or quotas, are necessary to protect national security; and

It is our opinion that tariffs, quotas, and trade policies can help increase incentives to produce branded pharmaceuticals in the United States. These large pharmaceutical companies have sufficient funds to build out facilities in the US.

However, the problem with the production of key starting materials, APIs, and generic drugs (which make up the majority of our drug shortages) will remain. The low prices of these items will preclude their production in the United States.

(x) any other relevant factors.

Our vulnerability to foreign suppliers of pharmaceutical products (key starting materials, APIs, and drug products, especially generics) is a result of decades of offshoring the production of these critical items for economic reasons – it was and is cheaper to produce in the aforementioned countries. There was a "race to the bottom" that rewarded the lowest cost providers. Consequently, there is no economically advantageous solution that can help extract us from this predicament. Any new infrastructure/capacity that will be built in the United Sates would have to compete with already depreciated facilities in India and China that have optimized their operations over decades of production. This is a fact.

We believe that any solution to this problem will need to consider the following:

- Drugs/drug classes, and their respective APIs/key starting materials to be reshored will need to be on a deliberate and well-thought-out basis. It would be unrealistic to reshore the manufacturing of all drugs; rather, we need to focus on select critical drugs that require domestic redundancy.
- Reimbursement/formulary schemes will need to be adjusted to prioritize these reshored drugs. Government intervention in the form of price-lowering subsidies may be necessary. Although this is contrary to our free market ideals, the hard truth is that government assistance/action is required, and this would not be a unilateral intervention – other countries have been doing the same thing for many years.
- The buildout of the infrastructure/facilities to produce the selected drugs/drug classes (and their respective APIs/key starting materials) will need to be heavily government subsidized. Investors will not fund such activities, as the returns will be very low. This is absolutely critical, and consistent with how other countries have established their respective capabilities/capacity.
- The buildout of the infrastructure/facilities will need to be staged (allowing for initial proof of concepts to lead the way to larger investments), with the acceptance that this will be a solution that will take decades. Although results should be demanded/expected in the short term (i.e., the proof of concept), actual meaningful capacity will not be established until much later. That drug production is heavily regulated will inevitably contribute to the pace of expected progress.
- The buildout of the infrastructure/facilities, to enable domestic producers to be competitive with existing manufacturers, will require advanced manufacturing that is automated and

complies with existing regulations (e.g., environmental). It makes no sense to invest in outdated manufacturing facilities employed in places like India and China.

- Competing technologies should be evaluated on a pragmatic basis – their economics and general applicability to the key objectives of any effort. For example, certain novel technologies, while exciting and innovative, have limited practical applicability (i.e., they provide an economically viable solution in only selected cases), and need to be utilized when it makes sense. Using advanced systems when the economics are unfavorable would not be recommended. For example, in many cases simple synthetic chemistry is much faster and cheaper than newer methods, such as synthetic biology.
- The US FDA will need to be involved. Providing incentives for domestic manufacturers (e.g., accelerated review times) and more rigorously scrutinizing foreign manufacturers would help level the playing field. Furthermore, accelerated paths for commercial certification for domestic facilities will fast-track these efforts.
- The buildout of advanced manufacturing facilities will have the added benefit of enhancing new drug development in the United States. More specifically, advanced manufacturing can: 1) accelerate process development (e.g., eliminate scale-up delays as drugs move across the different clinical phases of drug testing), 2) facilitate/accelerate regulatory approval times (e.g., leverage the Emerging Technologies Team at the FDA and other programs that can expedite the review process), and 3) provide access to chemistries/pathways aligned with continuous manufacturing (compared with batch manufacturing).