
# Fortifying API Supply Chains 2025 and Beyond: Aligning Current Strengths with Future Opportunities for Better Patient Outcomes

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The US FDA has highlighted vulnerabilities in the supply of active pharmaceuticals (APIs) and key ingredients. According to the agency, 72% [1] of API manufacturers [Figure 1] serving the US market are located overseas. Consequently, when disruptions occur at these limited sites-whether due to geopolitical events, natural disasters, economic tariffs, or pandemic-related shutdowns, the patients bear the impact. Thousands of pharmaceutical formulation plants worldwide rely heavily on imports. For small molecule drug products, API costs represent the most significant expense. Policymakers in the world's largest pharmaceutical market, the US, and the largest generics producer, India, are increasingly concerned about dependency and its implications on patient care.

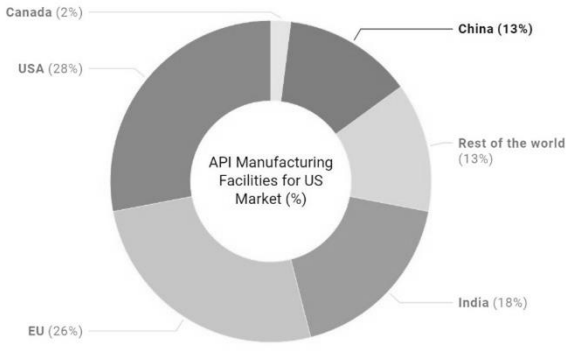


*Figure 1: US Marketed Products API Supply*

*Reference: US FDA Testimony Before the House Committee on Energy and Commerce, Subcommittee on Health*

An older World Bank exploratory study on APIs revealed that Western API manufacturers face an average wage index of 100, whereas, in Asia, it is as low as 8 to 10. Additionally, India and China benefit from lower electricity, coal, and water costs. These countries also have the advantage of being part of extensive networks of raw material and intermediary suppliers, reducing shipping and transaction costs. Furthermore, firms in India and China often rely on less expensive equipment, resulting in lower depreciation costs. [2]. Meanwhile, capacity utilization for API manufacturing sites in the US remains low. Over the past decade, Taiwan saw the highest percentage growth in new API manufacturing facilities globally, with a 326% increase and 189 new sites. India followed with a 254% growth and 3,676 new facilities, while Israel recorded a 131% increase with 142 new sites. China ranked fourth, achieving a 55% growth with 531 additional API manufacturing sites [3].

The FDA believes that advanced manufacturing technologies hold the potential to restore US competitiveness and reduce national security risks, even amid current challenges. New regulatory guidelines aim to support emerging technologies, such as flow chemistry and continuous manufacturing, acknowledging that traditional methods cannot match the cost efficiencies and productivity of established facilities. Historically, the US FDA's long-term strategies have proven effective in addressing industry challenges. While flow chemistry is widely appreciated in theory, its practical implementation and commercialization have

faced significant obstacles despite efforts from innovators and regulatory encouragement. It is well understood within the industry that flow chemistry may not provide a universal solution. However, continuous manufacturing based on mean residence time is often more practical and feasible for finished drug product formulators compared to similar applications in drug substance development. This discrepancy stems from various factors, including endpoint testing-based reaction pathways for drug substances, high costs of process characterization and stabilization, regulatory review complexities, challenges in managing the solid flow and reactor components at scale, applicability in slow reaction processes, and issues with low solubility compounds (emerging molecules) etc. [4]. Nevertheless, progress is being made, and organizations committed to innovation should take note of these advancements. A landmark achievement came in 2019 with the introduction of the first fully integrated end-to-end flow-chemistry/continuous manufacturing system for commercial production [5]. To further support domestic adoption, the US government has provided a $69-million grant [6].

From an Indian perspective, the country has enjoyed economic, political, and geopolitical stability for over a decade. Coupled with its democratic framework, expanding infrastructure, and policies such as production-linked incentive (PLI) schemes, India's bulk drug industry remains highly competitive. These factors place Indian bulk drug manufacturers, with their well-established processes, in a favourable position despite potential US tariff threats, which are largely viewed as short-term trade negotiation strategies. With plans for process innovation and technology adoption, Indian facilities are well-positioned to capitalize on emerging opportunities over the next five years. However, investing in strategies to mitigate regulatory compliance risks will be crucial to realizing this potential.

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# Methods for solving APIs Solubility & Stability Issues

APIs are often available in the forms of co-crystals, salts or polymorphs, hydrates, solvates, as well as amorphous forms in nature. The formation of salts, cocrystal, solvates are hydrates as well as the existence of polymorphs is rarely predictable. API manufacturing companies modify them to enhance the properties of a parent drug for finding or getting the best form of a drug with various innovative characterization methods.

APIs exist in several forms that vary significantly in their properties, leading to physical, chemical, mechanical and biopharmaceutical properties, they are organic chemicals used as ingredients in drug products. Organic chemicals are chemical compounds that contain carbon as part of their molecular structure and they can be either natural or synthetic.

Pharmaceutical ingredients solubilize, suspend thicken, dilute, emulsify, stabilize, preserve, colour, flavour and fashion medicinal agents into efficacious and appealing dosage forms. Each type of dosage form is a unique in its physical and pharmaceutical characteristics.

**Solubility of an API**

Solubility of an active pharmaceutical ingredient is critical for its bioavailability (BA), dosing precision, stability, and overall, its efficacy, forming eutectic mixtures between an active pharmaceutical ingredients and an excipient has been widely used to improve solubility of active pharmaceutical ingredient.

Active pharmaceutical ingredients solubility is necessary for the final drug to succeed in terms of therapeutic efficacy. In the case of solid and liquid oral formulations, good active pharmaceutical ingredients solubility is a prerequisite for sufficient absorption of the active pharmaceutical ingredient by the body. If an active pharmaceutical ingredient is insoluble, it cannot pass the gastrointestinal membrane and enter systemic circulation. Thus, their intended physiological effect will not be realized. Liquid formulations typically require the actions typically require the active pharmaceutical ingredient to be present in a dissolved form. Solubility is especially important for parenteral solutions which also need to be particle-free.

**Eutectic systems**

Eutectic systems are mixtures of components miscible in the liquid phase and either immiscible or partially miscible in the solid phase. The melting temperature of the eutectic system within a specific composition range can be lower than that of its pure constituents.

To increase the solubility, stability, and bioavailability of APIs, they have been combined with a second component (excipient) to form eutectic mixtures, such as the combination of lidocaine and camphor. These types of systems could exhibit a significant depression of the melting temperature and are regarded as a subgroup of deep eutectic solvents called therapeutic deep eutectic solvents.

Eutectic systems offer an alternate way to enhance the solubility of APIs. Eutectic systems are generated by physical mixing of two (solid) components in a ration that causes a melting point depression.
It is reported that presently over 40 percent of new drug candidates entering the drug development pipeline fail due to the non optimal biopharmaceutical properties like solubility, permeability.

These non-optimal biopharmaceutical properties of the molecules present many delivery issues to the formulators and need diverse approaches to overcome this issue.

Solubility and permeability of the molecule can be improved using various approaches which include pH modification, salt formatioin, co-solvency and surfactant assisted solubilization, nanocrystal line solid dispersion, cocrystals, polymeric micelle, canonization, liposomes, micromulsions and self-emulsifying drug delivery systems.

Many research papers have reported that mesoporus silica-based dosage forms offer the potential to improve the absorption of poorly soluble drugs after oral administration.

High throughput screening and target-oriented drug discovery offer results challenging issues in active pharmaceutical ingredients that are poorly water soluble and unable to commercialize product. Solubility and permeability are two important factors that correlate with in vitro and in vivo performance. Poor solubility is a growing issue in drug development in pharmaceutical sector. Which after leads to optimized medicinal products or increased development timelines.

Physical properties of API solid forms can have a significant influence on many physical properties, including melting point, solubility, stability, hygroscopicity, bulk density and mechanical properties. In fact, most screening and selection processes focus on improving physical properties to enhance the drug-handling characteristics, absorption, and delivery options.

An appropriate active pharmaceutical ingredient form has the properties to facilitate its production such as purification, isolation, handling, stability, storage, and shipping. It also supports and enhances the ability to develop a formulation and manufacture the required dosage form.

Key active pharmaceutical ingredients properties that influence medicinal product attributes and performance are: crystallinity; polymorphism; density; solubility; stability(chemical and physical stabilities); particle size distributing and crystal morphology and habit.

Globally active pharmaceutical ingredients manufacturing technologies are rapidly changing due to the advent of globalization, the growing significance of generic drug manufacturers, the rising awareness of environmental impact and the encouragement by the domestic regulatory to enhance process understanding and improve quality and efficiency while minimizing risk have led the pharmaceutical sector to reconsider the way pharmaceuticals are manufactured and the process development is approached.

This self-reflection has resulted in the promotion of continuous pharmaceutical analytical technology in order to significantly increase the efficiency and sustainability of manufacturing processes.

The stringency of current good manufacturing practice in active pharmaceutical ingredients manufacturing should enhance as the process proceeds from early active pharmaceutical ingredients steps to final steps of purification and packaging. Physical processing of active pharmaceutical ingredients, such as granulation, coating, or physical manipulation of particle size like milling and micronizing should be conducted in accordance with the specifications of pharmaceutical guidelines.
As quality of the product becomes more stringent to exist in international regulated markets, which automatically increases cost of production, but low –cost products with quality. When raw material cost increases it is very tough to pass on directly to these costs to customers.

In such a situation the active pharmaceutical ingredients manufacturers can mitigate this

challenge up to a limit by constantly inspecting their manufacturing system to see how they can increase the productivity and decrease effluents discharge, which will increase some level of profitability.

Across the globe most countries are regulating APIs manufacturing because the quality of active pharmaceutical ingredients in a drug always will have a direct effect on the safety, efficacy and stability of that drug. The drugs produced by bad quality and contaminated active pharmaceutical ingredients with negative health effects such as illness or deaths.

An active pharmaceutical ingredient with a appropriately defined form adequately serves the development and manufacturing of the selected dosage form. It will provide a bulk drug material with properties tailored to the needs of the dosage form such as enhanced density, flow, compressibility and other mechanical properties, solubility, dissolution rate, and content uniformity.

## Conclusion:

Active pharmaceutical ingredients play vital role in drug formulations. APIs form the most important part of new drug formulation even if generics or branded drugs. Solubility of APIs is critical for its bioavailability dosing precision, and stability. Forming eutectic mixtures between an API and excipient has been widely used to improve solubility of API.

Production of API is challenging as per the cGMP. As active pharmaceutical ingredients form the main ingredients of the new drug formulation and it contamination takes place at the time of production, it will affect the safety and efficacy of the new drug product and will lead to an adverse drug reaction.

Global active pharmaceutical ingredients markets of regulated and unregulated offer tremendous opportunities for Indian API players. Due to highly increasing healthcare expenses, all government regulatory bodies are sincerely trying to reduce healthcare costs by producing drugs from efficient production units in the country.

The cost reducing measures in healthcare sector by the highly regulated markets have pushed up the urgent demand for low cost generic drugs. The manufacturing of active pharmaceutical ingredients moves on to rise with more international pharmaceutical manufacturing companies are favourable looking towards India for quality wise low cost APIs to meet their demands.

**Source: Chronicle Pharmabiz 28th November 2024 (the author is a retired chemical Engineer)**