Department of Health Care Access and Information

CalRx

Report to the Legislature

Senate Bill 852 (Pan 2020) Health Care:

Prescription Drugs (2019 – 2020)

Health and Safety Code Section 127694(a)

Department of Health Care Access and Information

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"A healthier California where all receive equitable, affordable, and quality health care."

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About HCAI

The Department of Health Care Access and Information (HCAI), formerly the Office of Statewide Health Planning and Development, was created in 1978 to provide the state with an enhanced understanding of the structure and function of its healthcare delivery systems. Since that time, HCAI's role has expanded to include delivery of services that promote equitable access to health care for all Californians.

HCAI is a leader in collecting data and disseminating information about California's healthcare infrastructure, promoting an equitably distributed healthcare workforce, and publishing valuable information about healthcare outcomes. HCAI also monitors the construction, renovation, and seismic safety of hospitals and skilled nursing facilities and provides loan insurance to facilitate the capital needs of California's nonprofit healthcare facilities. HCAI works to improve affordability of health care costs including through spending growth targets and affordable generic drugs. These programmatic functions are advised by several boards and commissions.

HCAI serves as the building department for hospitals and skilled nursing facilities in California. Its primary goal is to promote patient safety by ensuring that each facility remains functional during a natural disaster.

HCAI collects, analyzes, and disseminates information about hospitals, skilled nursing facilities, clinics, and home health agencies licensed within California. Examples of facility information include financial reports and claims data, service utilization data, patient data and quality of care information.

To promote a diverse and culturally competent workforce, HCAI analyzes California's healthcare infrastructure and workforce needs. HCAI provides direct grant funding to medical schools, nursing programs, and other healthcare training institutions. HCAI also offers scholarships and loan repayments to students and health professionals who agree to provide patient care in medically underserved areas. Scholarship and loan repayments are offered for allied health, nursing, behavioral health, physicians, dental, and other medical professions.

The California Health Facility Construction Loan Insurance Program (known as the Cal-Mortgage Program) offers loan insurance to nonprofit and public health facilities to develop and expand healthcare services throughout California.

The Office of Health Care Affordability (OHCA) has three primary responsibilities: to slow health care spending growth, to foster high-value health system performance, and to evaluate market consolidation that may impact consumer affordability. OHCA accomplishes these objectives by collecting, analyzing, and releasing data describing total healthcare expenses. OHCA also enforces spending growth targets that are established by the Health Care Affordability Board. While curbing spending growth, OHCA promotes high-value health system performance by measuring quality, equity,

adoption of alternative payment models, investment in primary care and behavioral health, and workforce stability.

OHCA also implements the CalRx program, which the state established in response to the continuing rise of prescription drug prices. HCAI leads the CalRx program as it launches two initiatives to both produce its own insulin and leverage the State of California's purchasing power to buy naloxone at a reduced cost.

Another HCAI program addressing healthcare costs is its Hospital Bill Complaint Program, part of the Hospital Fair Pricing Act. Under the Act, hospitals are required to have both discount payment and charity care policies to provide financial assistance to qualified patients. HCAI's Hospital Bill Complaint Program helps patients who have been wrongly denied financial assistance.

Executive Summary

As required under the Affordable Drug Manufacturing Act of 2020, this report examines the feasibility of the State of California engaging more directly in drug manufacturing in response to market failures that result in drugs with excessively high prices. Specifically, it evaluates the feasibility of directly manufacturing generic prescription drugs and selling generic prescription drugs at a fair price. This report will also compare this approach to entering into strategic public-private partnerships with existing manufacturers or other entities. This report also considers possibilities for governance, including the establishment of a private company, a public-private partnership, or a publicly managed entity via a public board of directors.

The generic drug sector provides critical health care access by offering more affordable alternatives to higher cost branded medications without compromising on quality or efficacy. Any form of State involvement in generic drug manufacturing has several benefits which include eliminating costs associated with the use of intermediaries, guaranteeing a more stable and reliable supply of drugs, and ensuring essential medications are more affordable for Californians.

State-owned and operated manufacturing would grant California the most direct control in setting its own prices and increasing transparency in production costs. However, this endeavor requires a significant upfront investment, has a steep industry learning curve, and faces operational, legal, and regulatory challenges with a potentially lengthy timeframe for return on investment. Upfront costs for establishing a new generic drug manufacturing facility range from $100 million to $300 million initially with ongoing costs between $20 million to $50 million incurred annually.

Alternatively, continuing to partner with existing drug manufacturers or entities leads to immediate industry expertise, shared responsibility for costs, and quicker market entry as demonstrated by CalRx's Naloxone Access Initiative. Partnerships could include white labels and strategic investments. While public-private partnerships require the State to share decision-making in setting prices and rely on an industry partner, this more flexible model avoids holding full risk for investments. Such public-private partnerships merge the strengths of the private sector's agility, expertise, and experience with the oversight, scale, and public welfare focus of the State. These partnerships still concentrate public investment to correct pharmaceutical market failures, but do not carry the same risks and upfront costs associated with direct manufacturing.

Ultimately, pharmaceutical market distortions for specific medications tend to change quickly, and committing a large investment into an entirely State-owned facility reduces the State's ability to be flexible in this fluid environment. The State should proceed with leveraging public-private partnerships with drug manufacturers as this approach leads to the best balance of flexibility and control so long as there is detailed planning and strategic collaboration.

Introduction

As part of public policy considerations for the State to address high drug prices, the California Affordable Drug Manufacturing Act of 2020 requires a legislative report with the following information:

> (1) An assessment on the feasibility of directly manufacturing generic prescription drugs and selling generic prescription drugs at a fair price.
>
> (2) An analysis of governance structure options for manufacturing functions, including chartering a private organization, a public-private partnership, or a public board of directors.

This report provides background information on the generic drug market, drug manufacturing, and regulatory requirements before considering the benefits and costs of direct manufacturing.

Background

The Generic Drug Market

Generic drugs are copies of branded drugs that have the same dosage, safety, effectiveness, strength, stability, quality, and intended usage, but they are often attainable at a lower cost. Once the patent and market exclusivity of a brand-name drug expires, other manufacturers can produce and sell generic versions which leads to competition and reduced prices.

The global generic drug market has grown substantially in recent years. One of the primary drivers behind this growth is the expiration of patents on several major brand-name drugs, paving the way for generic manufacturers to introduce their versions to the market. Economically, the introduction and proliferation of generic drugs has helped curb health care expenditures. In the last decade, the U.S. health care system has saved $1.67 trillion due to the availability of low-cost generics.[1] Savings incurred by the two largest government health care programs, Medicare and Medicaid, totaled $77 billion and $37.9 billion, respectively, in 2016.[2]

Challenges in the generic market include price erosion, intense competition, regulatory hurdles, and anticompetitive market behaviors. This has led to the need for public-driven investment and intervention in the generic pharmaceutical sector to balance against profit-seeking interests and an opaque pricing system.

[1] Association for Accessible Medicines. (2017). Generic Drug Access & Savings in the U.S.
[2] Ibid.

Drug Manufacturing Complexities

Drug manufacturing is not a one-size-fits-all operation. The specific physical and operational needs of a drug manufacturing facility are influenced by the nature of the drugs being produced, manufacturing methods, the product's critical quality attributes which must be met, and the associated regulatory requirements. Every drug manufacturing facility, irrespective of its specialization, is governed by strict regulations and quality benchmarks established by the U.S. Food and Drug Administration (FDA).

Formulation and Method of Administration

One element of manufacturing complexity is the formulation of the final drug product. Common formulation types, ordered by level of manufacturing complexity, include:

1. **Oral Solid Dose Drugs** include tablets, pills, capsules, and powders for oral consumption. Manufacturing is considered easier and less complex due to more stable, well-established formulations and standardized manufacturing processes. These drugs do not have sterility requirements, are less likely to have microbial contamination or proliferation concerns and are simpler to produce. They also have longer shelf lives and reduced stability testing needs. Quality control is more straightforward due to their physical form, and packaging and storage are, typically, uncomplicated and lower risk.

2. **Oral Liquid Drugs** include suspensions, syrups, and liquids for oral administration. Manufacturing is, typically, straightforward with established ingredients and are non-sterile, requiring less stringent microbial control. However, ensuring an oral liquid maintains evenly distributed active ingredients and stable chemical, physical, and microbiological properties requires additional testing to ensure quality throughout its intended shelf life. Filling and packaging may require specialized equipment. Viscosity control and flavor and palatability concerns add to the complexity.

3. **Topical and Dermatological Drugs** include creams, patches, ointments, lotions, and gels for external use on the skin. Formulating topical and dermatological products is moderately complex due to formulation variability, microbial control considerations, stability issues, and the need for homogeneity. Ensuring stability over the shelf life may require additional testing. Achieving uniform distribution of active ingredients can be challenging, especially for complex formulations. Viscosity must be controlled for texture and dispersibility, and sterility measures are necessary for certain products.

4. **Inhaled Drugs** include respiratory medications, such as asthma inhalers. Inhaled medication can be formulated with either liquid or dry-powder ingredients. Manufacturing is more complicated due to varying user requirements, delivery device design, microbial control or sterility, product flow resistance and fluid dynamics, and specialized filling and finishing requirements.

5. **Injectable Drugs** are administered via intravenous, intramuscular, or subcutaneous injections. Common examples include influenza vaccines, insulin, and many chemotherapy drugs. Manufacturing injectable drugs is a highly complex and intricate process that requires specialized knowledge, equipment, and potential aseptic manufacturing or terminal sterilization procedures. Packaging must maintain sterility, and stability challenges require careful formulation and storage.

Biologics and Biosimilars (vs. “Small-Molecule” Drugs)

Biologics, or “large molecule” drugs, are made from natural sources, such as living or once-living organisms from human, animal, or microbial sources. Common examples include vaccines, insulin, and anti-inflammatory injectable medications, such as Humira. Generic versions of biologics are referred to as biosimilars. Due to the highly complex structures of biologic drugs, the biosimilar development and manufacturing process may involve additional analytical comparability studies, clinical trials, and complex production techniques involving cell culture, fermentation, and purification. Quality control involves advanced analytical techniques, sterility assurance, and extensive documentation.

Handling Considerations

Drugs that are high-potency, have a need to avoid cross-contamination, may be cytotoxic, or carry risk of abuse require specialized documentation, handling, and processing.

High-potency drugs are those where very small doses can have large effects. Common examples include fentanyl, clozapine, and tacrolimus. Safety concerns for personnel, including the risk of inhalation or skin contact, require specialized containment measures, physical controls, and training. Preventing cross-contamination within the facility is critical, necessitating separate handling for potent compounds. Some high potency drugs can be made in shared facilities, while others require dedicated facilities (e.g., certain antibiotics or cytotoxic chemotherapy drugs). Cleaning validation, analytical challenges, packaging requirements, waste disposal, and rigorous regulatory oversight are additional complexities.

Controlled substances are those that have additional oversight and regulatory requirements from the U.S. Drug Enforcement Administration (DEA) due to their abuse potential. Examples include fentanyl, oxycodone, and amphetamine/ dextroamphetamine. Manufacturing controlled substances is complex and highly regulated. Security measures, extensive record-keeping, and accurate reporting are required to prevent theft and unauthorized access. Preventing diversion to the illicit market or abuse is a major concern, necessitating robust control systems. Quality control, specific packaging and labeling, inventory management, supply chain oversight, and addressing public health concerns related to addiction are essential components of controlled substance manufacturing.

Manufacturing Stages

Drugs go through several stages of manufacturing before they are considered final, ready-to-use products, which includes packaging in the final container closure system. Each type of facility is an important part of the drug-making process. Moving smoothly from raw materials to the final product requires planning, capital support, and technical knowledge.

First, the **Active Pharmaceutical Ingredient (or API)** must be created. These are the raw substances that actively lead to the intended effect of the drug. Manufacturing APIs can be a complex process due to many factors, including the chemical complexity of APIs, stringent purity and quality control standards, the need for special equipment such as reactors and mixers, and the challenges of scaling up from laboratory synthesis to commercial production. Furthermore, making some APIs, including the APIs needed to manufacture chemotherapy drugs such as cisplatin and carboplatin, can be dangerous and require adherence to strict safety rules.[3]

Next, APIs are **formulated** into usable products, including pills, creams, injectables, or liquids. These facilities combine APIs with inactive ingredients that help stabilize, dilute, or improve usability of the drug. Inactive ingredients include fillers, binders, flavors, suspension agents, and film coatings. The plants also use advanced machines to make sure each drug dose is precise and consistent.[4] Some bulk drugs or their components may also have sterilization steps.

Finally, drugs go through **packaging**. Here, drugs are put in packages, labeled, and made ready for distribution. These units need to be flexible to package drugs in ways that meet local or specific patient needs. Packaging protects the product, makes it identifiable to consumers, and includes all FDA-required information. There are three layers of packaging: primary packaging that touches the drug, such as blister packs and bottles; secondary packaging that holds the primary packages and includes safety inserts with product information; and tertiary packaging that protects the drug during the shipping and handling process.[5] Labeling is also a critical component of a drug product and is reviewed and assessed by regulators, as it needs to be supported by data. Additionally, a new and complex area of packaging is unit-level sterilization and the related requirements for interoperable traceability systems.

Regulatory and Legal Environment

Becoming a drug manufacturer in the U.S. is a complex and highly regulated process that involves meeting a range of requirements established by the FDA and other agencies. The process can be lengthy and resource-intensive, but these requirements are in place to ensure the safety, efficacy, and quality of pharmaceutical products.

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[3] Campbell, John (2018). Understanding Pharma: The Professional's Guide To How Pharmaceutical And Biotech Companies Really Work. Third Edition. Syneos Health.
[4] Ibid.
[5] Ibid.

FDA Requirements

Before a drug enters the U.S. market, it must undergo a rigorous regulatory pre-market approval process by the FDA. This process encompasses several stages of clinical trials assessing the drug's safety and effectiveness. The FDA also regulates and inspects component supplier and manufacturing facilities to ensure they meet safety and quality standards. Beyond the approval phase, the FDA monitors drug safety reporting for potential adverse effects or long-term complications and potentially performs post-approval inspections of the related facilities (e.g., surveillance and/or for cause inspections).

Specific FDA requirements include:[6]

1. **Establishment registration with the FDA:** All drug manufacturers, re-packagers, or re-labelers must register their establishment with the FDA. This registration must include a list of all manufactured drugs and downstream entities. Initial drug listings should be submitted within three days of registration.

2. **Drug development and review materials:** When developing a new drug, manufacturers first submit and obtain approval of an Investigational New Drug Application before starting clinical trials. If the clinical trials are successful, manufacturers must submit a New Drug Application, including data summaries and findings supporting drug approval. Generic drug manufacturers are required to submit an Abbreviated New Drug Application (ANDA), which allows them to skip some of the clinical trial steps if they can prove their drug is bioequivalent (i.e., generic product exhibits similar pharmacokinetics) and therapeutically equivalent (i.e., generic product achieves same therapeutic outcomes) to the reference drug. Manufacturers who are developing a biologic or biosimilar drug must file a Biologics License Application (BLA). These submissions must provide comprehensive data on safety and efficacy, with biosimilar applications including data demonstrating equivalence to the reference biologic.

3. **Facility safety compliance:** The FDA requires all drug manufacturing facilities to comply with Current Good Manufacturing Practices (“CGMPs”), or standards for manufacturing, processing, and packing drugs that help ensure the drugs are safe and effective, as outlined in the Code of Federal Regulations (CFRs). CGMP standards cover cleanliness, equipment, quality control, and detailed record-keeping. The FDA conducts routine inspections of manufacturing facilities to ensure compliance with CGMP regulations. Non-compliance can lead to regulatory actions, including warning letters, consent decree, import alerts, fines, and product recalls.

[6] U.S. Food and Drug Administration. (n.d.). Guidance for Industry Providing Regulatory Submissions in Electronic Format Drug Establishment Registration and Drug Listing.

4. **Labeling:** Drug labeling and packaging must comply with FDA regulations. This entails providing accurate information regarding identity, strength, dosage form, indications, warnings, and usage instructions.

5. **Serialization:** Systems must be in place to exchange transaction information and statements electronically, verify products at the package level, promptly respond to verification requests, and use the product identifier for tracing in compliance with the Drug Supply Chain Security Act (DSCSA) serialization requirements.[7]

6. **Post-market surveillance:** After the drug enters the market, the manufacturer is obligated to promptly report adverse events and safety information to the FDA. This supports ongoing drug safety monitoring.

7. **Fee payment:** Certain user fees are associated with FDA drug approval and inspection processes, with fee amounts contingent on factors such as application type and facility size. Additionally, the Prescription Drug User Fee Amendments (PDUFA) apply to specific drugs and devices, while the Generic Drug User Fee Amendments (GDUFA) apply to generic drug manufacturers, providing funds for FDA activities related to drug reviews and inspections. The Biosimilar User Fee Act (BsUFA) provides funds for FDA activities related to biosimilar and interchangeable biologic products (biosimilars). Medical Device User Fee Amendments (MDUFA) support the FDA's efforts to increase patient access to safe and effective medical devices. Some product categories also have ongoing annual fees.

Other Federal Requirements

If manufacturing involves controlled substances, drug manufacturers must register with the U.S. Drug Enforcement Administration (DEA).

State Regulations

Facilities in California must conform to the California Environmental Quality Act (CEQA) and associated State regulations, the California Occupational Safety and Health Act (Cal/OSHA), and State pharmaceutical manufacturer licensing requirements. This license must be obtained through the California Department of Public Health. The license is valid for two calendar years from the date of issue, unless it is revoked. A separate license is required for each manufacturing location.

Legal Considerations

Considering the litigation-heavy nature of pharmaceuticals, preparation for potential legal challenges is crucial. There might also be situations where post-market drugs are

[7] Elisabeth Cuneo, Key Concepts of the FDA's Drug Supply Chain Security Act Serialization Laws, October 4, 2024

deemed unsafe, necessitating recalls. In such instances, the State should be equipped with an efficient plan and mechanism to manage these events.

Compliance with intellectual property laws is another pivotal area to ensure that the State does not infringe upon pre-existing patents.

If California imports any ingredients or materials from outside of the country, manufacturing operations should be in line with U.S. importation rules and standards.

Business Considerations

Before starting drug or biologic production, it may be advisable to formally establish a legal business entity, such as a corporation or Limited Liability Company (LLC), in accordance with state and federal business laws and regulations. Some key reasons for this include liability protection, fundraising, intellectual property, or tax purposes.

Other State-Led Manufacturing Initiatives

Beyond traditional manufacturing initiatives, California has developed specialized programs to address unique public health challenges, as exemplified by California's Infant Botulism Treatment and Prevention Program (IBTPP). The IBTPP operates under the California Department of Public Health (CDPH), focusing on infant botulism's public health implications. Established in the late 1970s after the identification of infant botulism, the IBTPP has been pivotal in diagnosing, treating, and researching the disease. A notable accomplishment is the creation of BabyBIG®, an orphan drug treating infant botulism types A and B, which has shortened hospital stays for affected infants. BabyBIG® is manufactured through a partnership with CDPH, Baxalta, Inc., and Cangene bioPharma, Inc.[8]

Federal Policy

Some federal policymakers are supportive of improving domestic manufacturing capabilities. Recent executive orders as well as White House reports have addressed the need to strengthen and secure the nation's supply chains and boost domestic production capabilities to reduce reliance on foreign production and supply.[9] According to the U.S. Department of Health and Human Services (HHS), only half of the approximately 120 medications on the FDA's 2020 Essential Medications List have domestic API facilities.[10] The report also advises ensuring a diversification of supply sources for APIs and finished dosage forms (FDFs), aiming to prevent over-reliance on any single supplier or country. Despite these reports, there are few instances where

[8] California Department of Public Health (2021). Infant Botulism Treatment and Prevention Program.
[9] Executive Order No. 14017, 86 FR 11849 (2021); Executive Order No. 13944 (2020); The White House. (2023, November). Fact Sheet: President Biden Announces New Actions to Strengthen America's Supply Chains, Lower Costs for Families, and Secure Key Sectors.
[10] The White House. (2021, June). Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-based Growth, Page 219.

federal policy supports domestic manufacturing through tax incentives or domestic procurement preferences.

Relatedly, recent studies have found that leveraging underused U.S. manufacturing infrastructure and investing in advanced technologies can revitalize domestic production of critical medicines, enhancing the supply chain's resilience and national security within a two to three-year timeframe.[11] One study, which surveyed 37 manufacturing sites, indicated that 30 percent of those facilities operate below 50 percent utilization.[12]

CalRx Manufacturing Analysis

Benefits of State-Owned Manufacturing

The benefits associated with California establishing its own drug manufacturing program include total pricing control, greater influence on supply chains within the health care system, and economic development.

Total Pricing Control

With complete control over pricing, the State could set prices at the cost of production and distribution with no markup or rebates. This could improve price transparency within the pharmaceutical sector and could lead to savings in the specific markets that CalRx enters. However, the rest of the pharmaceutical supply chain is set up in a way that prefers products with rebates and markups. For example, pharmacy benefit managers earn profits from the rebates they receive on brand pharmaceuticals, and wholesalers and pharmacies retain profits on price markups for generics. While these incentive structures continue to exist, it could be difficult for CalRx to attract and maintain sales volume without alternative distribution structures.

Eventual Cost Savings

By producing its own pharmaceuticals and taking a direct-to-consumer approach—bypassing traditional pharmaceutical distribution channels and selling medications directly to health care providers or patients—California could reduce certain costs along the supply chain, thereby reducing the expenses associated with intermediaries and their added markups.[13] This approach aligns with the emerging trend of alternative distribution models in the pharmaceutical industry which aim to streamline the supply chain and reduce costs.[14] Direct-to-consumer models usually (but not always) bypass health plans and pharmacy benefit managers.

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[11] Sardella, A. (2022, September 30) U.S. Generic Pharmaceutical Manufacturer Available Capacity Research Survey. Center for Analytics and Business Insights, Washington University in St. Louis.
[12] Ibid.
[13] Kaiser Family Foundation. (2005, March). Follow the Pill: Understanding the U.S. Commercial Pharmaceutical Supply Chain.
[14] Plumptre, E. (2024, March 26). Exploring alternative distribution models for pharma supply chains.

Supply Chain Stability

With its own manufacturing capabilities, California would be somewhat less susceptible to international supply chain disruptions, whether they arise from geopolitical tensions, transportation obstacles, or global health crises.[15] If California also manufactures APIs directly, this could further bolster this stability and reduce lead times. Additionally, having direct control over the manufacturing process could ensure that the quality of medications remains consistent, lowering the risk of recalls or other quality-related setbacks. However, continued reliance on the global supply chain for equipment and component parts would still impact operations.

Job Creation

A California manufacturing facility would be a significant source of employment, generating job opportunities spanning from research roles to factory positions and managerial capacities. Beyond direct employment, there may be increased employment in related sectors, such as logistics, packaging, equipment upkeep, and raw material procurement.

Control Over Targeted Indications

A State-owned manufacturing facility could prioritize the production of essential medications with low profit margins, addressing critical drug shortages. Medications such as vincristine (for pediatric cancers), bupivacaine (for local and regional anesthesia), and metoprolol (for heart conditions) are examples of drugs with low profit margins that are currently experiencing shortages.[16] This approach would focus on drugs that are not as attractive to private manufacturers due to limited financial incentives or consistent demand.

Challenges of State-Owned Manufacturing

Direct manufacturing also comes with challenges, including significant initial investment costs, additional legal risks, and less flexibility in operations.

Significant Initial Investment Required

One of the first hurdles is the initial capital investment required. Costs span from land acquisition to infrastructure development to specialized labs and manufacturing units. Moreover, the industry mandates advanced machinery and cutting-edge technology to chemically develop, test, and purify the drug. Lastly, the State would need to attract the best talent in the pharmaceutical sector, which necessitates competitive salaries, benefits, and comprehensive training.

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[15] U.S. Food & Drug Administration. (2019, October 30). Safeguarding Pharmaceutical Supply Chains in a Global Economy.

[16] Abramowitz, P.W. (2024, April 11). ASHP Calls for Policy Solutions as Drug Shortages Reach All-Time-High.; Drugs.com. (2024, May 6). Drug Shortage Data.

Cost Estimations for a State-Owned Facility

Table 1 displays the potential costs associated with setting up a drug manufacturing plant, which range from $100 million to $300 million in startup costs and $20 million to $50 million in annual operational costs. Exact costs can fluctuate based on multiple factors, including location, scale, and technological advancements. Advanced biotech facilities, considering their specialized nature, can cost even more, especially when factoring in the costs of continuous research and development (R&D). Additionally, financial viability in the generic drug manufacturing space may require a facility to manufacture 20 to 40 products.

Table 1: Drug Manufacturing Plant Setup Cost Estimates

Category	Item	Factors/Notes	Setup Costs	Annual Costs
Land and Infrastructure	Land Acquisition	Cost varies based on location. A moderately sized plant might need 10 to 50 acres.	$20,000+ per acre	$25,000 - $5M for mortgage, taxes, etc.
	Infrastructure Development	Facility development including labs, manufacturing units, utility equipment and systems, storage, and administrative blocks	$500 to $900 per sq. ft.	
Research and Development	R&D	Formulation development, analytical testing, and bioequivalence studies	$3M per generic drug; biologics could be much higher	
Equipment and Technology	Basic Machinery	This includes mixers, granulators, tablet presses, and coating machines	$1M - $5M for a medium-scale setup	
	Specialized Equipment	Biotech may require fermenters/bioprocess supporting vessels, chromatography systems, microscopes, cell culture systems, processing filtration	$2M - $100M, depending on the scale and specificity	

Category	Item	Factors/Notes	Setup Costs	Annual Costs
		equipment, single-use systems, component depyrogenation equipment, autoclave(s), filling isolator(s), and aseptic filling machine(s)		
	Laboratory Equipment	Used for testing in pharmaceutical and biologics, specifically for quality control, stability testing, microbiological analysis, physical testing, packaging integrity testing, and compliance	Pharmaceutical testing lab: $200K - $1.7M Biologics lab: $500 - $2.0M+	
	Technology Integration	Systems for quality control, monitoring systems, and automation tools	$500K - $5M	$100K - $500K
Operational Costs	Utilities	This includes water, electricity, HVAC, water for injection (WFI), clean steam, various gases, and waste management		$120,000 - $5M
	Salaries	A medium-sized plant might employ anywhere from 100 to 500 employees, ranging from laborers to Ph.D.-level researchers[17]	$5M - $50M, depending on the scale and expertise required	$1M - $35M

[17] For more information on the types of staffing needed in drug manufacturing facilities, see the Appendix.

Category	Item	Factors/Notes	Setup Costs	Annual Costs
	Raw Materials and Ingredients	Costs vary by volume and drug type		$2M - $20M
	Maintenance	Regular maintenance of machinery and infrastructure can add another 5-10% in costs annually		5-10% of the initial equipment cost
Regulatory and Compliance Costs	Licensing	Costs vary depending on the type of drugs being produced and the scale of operations	$100K - $500K per filing fee	
	Quality Control (QC) and Testing	Establishing in-house QC labs or outsourcing testing		$100K - $2M
	Insurance			$100K - $5M
	Regulatory Filing Fees	Abbreviated New Drug Applications (ANDAs) for each drug manufactured		$500K per filing fee over a multi-year period

Potential Gap in Technical Expertise

Hiring for and maintaining technical expertise is another significant domain of challenges. The pharmaceutical sector is diverse and complex, demanding proficiency in areas such as chemical engineering, biotechnology, and pharmacology. Some of this expertise can be difficult, or rare, to find and expensive to hire. The ever-evolving nature of the industry also requires continuous workforce training.

Competitive & Complex Market

Navigating a market dominated by existing leading pharmaceutical companies, with some in existence for over a century, requires strategic positioning. Although the State's

primary aim may be to lower the prices of essential medicines within California, the State must be prepared for global pricing dynamics which are often swayed by factors beyond the State's immediate control, including channel dynamics that can affect the end-user price even without changes in the manufacturing selling price. Additionally, carving out a niche for CalRx in an already saturated market, where trust in established brands is deeply entrenched, will be a significant undertaking. For this reason, CalRx may want to consider only manufacturing medications where an additional market player would lower costs or improve access.

Significant Regulatory and Legal Needs

Obtaining approvals from the FDA is an intricate and a protracted process with each drug, manufacturing facility, and associated vendors having to adhere to rigorous standards. This adherence is not a one-time effort; continuous monitoring, regular audits, and inspections are essential to ensure compliance with regulations. Additionally, even with in-house manufacturing capabilities, the facility will still rely on external vendors for container/closure systems and filters. This dependence may lead to significant supply chain challenges beyond the State's control, potentially affecting consistent product supply. Lastly, there are risks associated with potential adverse effects leading to significant liabilities and navigating legal challenges, such as intellectual property law.

Less Flexibility

Lastly, inefficiencies and drug shortages in the pharmaceutical market are constantly changing, and new drugs are always being developed. The types of medications that CalRx may want to target to address a market problem could fluctuate and shift over time. If CalRx invests in a specific type of manufacturing for a target drug, that manufacturing facility may not be suitable for other target drugs, which would require CalRx to pursue other production methods.

While the development of advanced manufacturing technology could help improve the flexibility of a future plant, many of these advances are still years away from commercialization. For example, 3D bioprinting—where drugs are 3D-printed at a micro level using cells, growth factors, and biomaterials—would lead to more flexibility in a manufacturing plant, but this technology is still in early stages of development and faces technical and regulatory barriers.[18] Other techniques, like single-use or modular systems that manufacturers can swap in and out to manufacture different drugs in the same facility, also have drawbacks. These systems have much smaller capacity than typical systems, add supply chain complexities due to the need to source single-use items, and contribute to more environmental waste.[19]

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[18] Li, Y., Jiang, X., & Huang, K. (2020). 3D Bioprinting for Drug Development and Screening: Recent Trends Towards Personalized Medicine. ScienceDirect.
[19] Deloitte. (2015). Advanced Biopharmaceutical Manufacturing: An Evolution Underway; National Academies of Sciences, Engineering, and Medicine. (2021). Innovations in Pharmaceutical Manufacturing on the Horizon: Summary. National Academies Press.

Alternative: Strategic Partnerships and White Labels

The alternative to an entirely State-owned and operated manufacturing facility is to continue to engage in partnerships with existing manufacturers or entities and associated vendors. These partnerships could include:

- White labels, where another drug manufacturer manufactures a drug under the CalRx label with its own pricing structure and commercialization strategy (i.e., CalRx's naloxone model);
- Strategic investments with partners that share the same mission of making medications more affordable and accessible (i.e., CalRx's insulin model); and
- Targeted funds or guaranteed volume purchasing for manufacturers to make essential medications with low profit margins.

Since May 2024, CalRx has demonstrated success and efficiencies through a white label partnership for its Naloxone Access Initiative. By leveraging California's Naloxone Distribution Project (NDP) as substantial purchasing power, CalRx successfully negotiated a reduced price of $24 per twin-pack of generic naloxone nasal spray with Amneal Pharmaceuticals. This white label collaboration resulted in a 40 percent savings off the State's previous contracted rate for naloxone and provided immediate market share to Amneal Pharmaceuticals as a new entrant to the naloxone market. Between May and November 2024, internal calculations suggest that CalRx generic naloxone has saved the State over $4.4 million. This cost savings has allowed California's NDP to stretch their budget further in purchasing additional units for free distribution to harm reduction groups, schools, emergency responders, and more. Additionally, all California business and governmental entities can now purchase CalRx generic naloxone at this price, further expanding access to this life-saving medication.

These partnerships still concentrate public investment to correct pharmaceutical market failures, but do not carry the same risks and upfront costs associated with direct manufacturing. Strategies such as guaranteed volume purchasing have the potential to help lower prices. However, California would not be able to keep total control over pricing and would need to manage conflicts of interest in a profit-seeking partner, likely through contract negotiations.

Pros and Cons of Different Structural Approaches

Table 2 provides a summary of potential pros and cons associated with State-owned manufacturing versus public-private partnerships. Note that an entirely State-owned manufacturing program could be governed by a public board, while a public-private partnership would have a range of different governance options depending on the partner and structure of the partnership.

Table 2: Pros and Cons of Drug Manufacturing Approaches

Approach	Pro	Con
Entirely State-Owned Facility	Direct control over operations; greater influence over more parts of the supply chain; transparent production; potentially more sustainable for long term; better customization; spillover economic benefits	Significant upfront costs; longer turnaround time; high financial and legal risks; industry learning curve; need for in-house technical expertise for navigating the regulatory environment; ongoing staff costs; operational challenges
Partnering with a Drug Manufacturer (Recommended)	Instant expertise; cost-sharing; quicker market entry; leverage existing relationships/ processes with major health care systems; shared responsibility; potential spillover economic benefits; minimal staff costs	Shared decision-making; medium financial risks; potential conflicts of interest; profit margin-seeking from industry partner; dependency on external partnerships; potential for lack of transparency or control over confidential information, vendor agreements, and/or regulatory communications; partner's other products might take priority over State product(s)

Conclusion

While there are several benefits of a State-owned facility for generic drug manufacturing, the challenges are considerable. Advantages include direct control over pricing, improved ability to address specific health needs in California, and fostering job creation and economic growth within the state. However, possible challenges include high capital requirements, the need for technical expertise, navigating complex regulatory requirements, dependency on vendors (e.g., contract laboratories, component and/or container-closure suppliers, testing laboratory), contending with established global pharmaceutical companies, and decreased flexibility due to the need to commit funds to specific manufacturing capabilities.

This report recommends that CalRx continue partnering with existing manufacturers on white label solutions or focused investments. Such collaboration merges the strengths of the private sector's agility, expertise, and experience with the oversight, scale, and public welfare focus of the State. These public-private partnerships still concentrate public investment to correct pharmaceutical market failures, but do not carry the same risks and upfront costs associated with direct manufacturing. This solution also leads to more flexibility for the State to adjust its strategy based on the changing pharmaceutical market.

Appendix: Staffing Needs for Drug Manufacturing

The staffing needs for a pharmaceutical manufacturing facility vary depending on the size, scope, and complexity of the operation as well as the types of pharmaceuticals produced. For example, a facility producing sterile injectables would have different staffing needs compared to a facility manufacturing oral solid dosage forms. Additionally, depending on the organization, some roles may overlap or be outsourced to external contractors, particularly in areas such as cleaning, cafeteria services, and security.[20]

Below are representative key roles that are, typically, required to ensure the facility runs efficiently, safely, and in compliance with regulatory standards:

1. **Senior Management**
    - Site Leader: In charge of the overall facility, ensuring all operations align with company goals and compliance standards.
    - Quality Leader: Heads the quality department, overseeing all quality-related activities and regulatory compliance.
2. **Engineering and Maintenance**
    - Engineering Manager: Manages the engineering team, overseeing the design, implementation, and maintenance of production systems.
    - Process Engineer: Focuses on optimizing equipment reliability and maintenance strategies to reduce downtime.
3. **Production Management**
    - Production Manager: Oversees the manufacturing process, managing staff, schedules, and production goals.
    - Production Technicians: Responsible for production activities, ensuring targets and quality standards are met.
4. **Quality Management and Inspection**
    - Quality Engineer: Ensures all products meet internal and regulatory quality standards throughout the production process.
    - Quality Assurance Specialists: Conduct investigations into quality deviations and implement corrective actions.

[20] Donagh Fitzgerald and Claire Wilson, What Types of Jobs and Careers are there in the Pharmaceutical and Medical Device Industry, https://www.getreskilled.com/types-of-pharma-jobs/#Production

- Quality Systems Manager: Manages the quality systems and ensures they are compliant with regulatory requirements.

5. **Environmental Health and Safety (EHS)**
    - EHS Lead: Ensures that all operations comply with environmental regulations and maintain workplace safety protocols.
6. **Research and Development (R&D)**
    - Formulation Scientists: Develop generic drug formulations that are bioequivalent to the branded products.
    - Process Development Scientists: Work on scaling up laboratory processes to manufacturing scale and optimizing production methods.
    - Analytical Chemists: Develop and conduct analytical tests to ensure that the generic drug matches the reference drug in terms of purity, potency, and other quality attributes.
7. **Laboratory and Testing**
    - Lab Manager: Oversees the laboratory operations and ensures accurate testing and reporting of results.
    - Chemistry Supervisor: Supervises chemists and oversees chemical testing and analysis.
    - Microbiology Supervisor: Supervises microbiology staff and oversees microbial testing processes.
    - Chemistry Technician: Conducts chemical testing and analysis of raw materials and products.
    - Microbiology Technician: Performs microbiological testing to ensure products are free from contamination.
8. **Production and Machine Operation**
    - Production Operators: Operate production equipment and participate in manufacturing processes.
    - Machine Technicians: Maintain and troubleshoot manufacturing machines to keep them operating effectively.
    - Utility Technician/Operator: Supports production by managing utilities and assisting with equipment setups.
    - Manufacturing Operators (aseptic require additional training/expertise)

9. **Technical and Information Technology (IT) Support**
    - Calibration Technician: Specializes in calibrating manufacturing and laboratory instruments to ensure accurate measurements.
    - Electrician: Maintains and repairs electrical systems within the facility.
    - Automation/IT Technician: Supports manufacturing automation systems and IT infrastructure.
10. **Warehouse and Logistics**
    - Warehouse Operations Staff: Manage inventory, storage, and material movement within the warehouse.
    - Warehouse Supervisor: Oversees warehouse operations, including staffing, logistics, product distribution, and inventory management.
11. **Validation and Process Optimization**
    - Validation Engineer: Designs and executes validation protocols for equipment, processes, and cleaning procedures.
    - Validation Technician: Assists in the validation process, performing tests and collecting data to ensure compliance.
    - Process Engineer: Optimizes manufacturing processes for efficiency, quality, and compliance.
12. **Training and Development**
    - Trainer: Develops and delivers training programs to enhance employee skills and ensure compliance with operational standards.
13. **Human Resources (HR) and Administrative Support**
    - General Administration: Provide administrative support across various departments, handling clerical and organizational tasks.
14. **Marketing**
15. **Legal Support** (either in-house or provider)
16. **Finance**