



Demand Forecasting for Controlled Substances

SUMMARY REPORT

ABOUT THE REAGAN-UDALL FOUNDATION FOR THE FDA

The Reagan-Udall Foundation for the FDA (the Foundation) is an independent 501(c)(3) created by Congress to advance the mission of the FDA to modernize product development, accelerate innovation, and enhance product safety. The Foundation works to advance regulatory science, support development and dissemination of reliable information, and facilitate engagement and information exchange.

This activity is one part of a multi-part Foundation project related to substance use disorder. The multi-part project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an overall award of \$2,470,442 of federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit [FDA.gov](https://www.fda.gov).

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Introduction

Each year, the U.S. Food and Drug Administration (FDA) submits an estimate of domestic medical, scientific, and reserve stock needs for Schedule I and II substances, and other requested substances (together known as “quota-relevant substances”), to the Drug Enforcement Administration (DEA). Currently, this domestic estimate is prepared using the best available market data, which encompasses pharmaceutical sales distribution data from both retail and non-retail healthcare settings. In turn, DEA uses these estimates, along with data from other sources, to set an overall aggregate quota or limit for these substances, as well as individual quotas or allocations for each manufacturer, that covers both domestic and international needs.¹ The objective of this annual process is to ensure that the American public has sufficient medication to treat legitimate medical needs and to prevent the diversion of these controlled substances to non-medical or illicit uses. To inform potential improvements in the accuracy of these annual estimates, the Reagan-Udall Foundation for the FDA (Foundation), on behalf of the FDA’s Center for Drug Evaluation and Research, has conducted a review of data sources and forecasting techniques used by government agencies, the private sector, and academic researchers to predict demand for controlled substances.²

Demand forecasting is defined broadly as the process of predicting the quantity of goods and services that will be needed by each player in the supply chain and ultimately the final consumer at a future point in time. Demand forecasting helps industry estimate future customer demand based on historical sales data, market trends, and other external factors, and enables a company to avoid problems such as overproduction (leading to wastage) or underproduction (leading to shortage). In many cases, such as in heavily regulated markets, these inefficiencies can lead to market instability and price fluctuations, which can have negative consequences for both manufacturers and consumers.

Demand forecasting helps manufacturers and other players in the supply chain plan and allocate resources efficiently. Accurately predicting future demand also can help businesses prepare for potential disruptions, such as shortages or delays in access to raw materials or other ingredients, natural disasters, or changes in consumer behavior. Often, these internal processes rely on historical sales data (both from internal company data and third-party vendor data) as well as other external economic factors such as consumer behavior and market competition. Manufacturers also use forecasts to keep executive leadership and investors informed of business prospects. Forecasts used in the pharmaceutical industry often augment basic time series-based sales data with predictive analytics to more accurately predict customer demand and can help individual companies make informed decisions about production, inventory, pricing, and marketing specific to their company’s products and strategic niche. This contrasts with current statistical modeling methods used by FDA, which focus primarily on using the best available market data to estimate aggregate domestic needs for quota-relevant substances at a national level on an annual basis.

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- 1 Drug Enforcement Administration. Proposed aggregate production quotas for Schedule I and II controlled substances and assessment of annual needs for 2025. *Federal Register*. Published September 25, 2024. Accessed November 8, 2024. <https://www.federalregister.gov/documents/2024/09/25/2024-21962/proposed-aggregate-production-quotas-for-schedule-i-and-ii-controlled-substances-and-assessment-of>.
 - 2 This report focuses on the estimate of medical need, which is used to help determine annual aggregate production quotas. As such, this report does not include discussion of the process of allocating aggregate production quota among individual manufacturers, nor how DEA manages requests from manufacturers to increase or re-allocate an individual manufacturer’s quota in real-time in response to shortages of specific drugs in various areas of the U.S.

The Human Impact of Inaccurate Pharmaceutical Demand Forecasting

The consequences of overestimating or underestimating medical need for controlled substances impact individual patient care and broader public health. Excess production and availability of controlled substances can increase the opportunity for diversion and misuse. On the other hand, underproduction can lead to drug shortages and unmet treatment needs for patients. When drugs are unavailable through licensed pharmacies, patients may turn to the internet to obtain their medications and inadvertently receive falsified or adulterated products through illegal, online sources.

To gain an understanding of the current forecasting techniques used by the pharmaceutical industry, the Foundation carried out a review of current statistical modeling techniques used by industry to assess their strengths and weaknesses, and their applicability to the estimation of domestic medical need of controlled substances. Separately, the Foundation conducted a series of one-on-one interviews with industry and academic experts, some of whom were identified in the literature scan.

In addition, the Foundation gathered eight of these experts for an invitation-only roundtable in January 2025 to discuss current forecasting techniques (see roundtable agenda in [Appendix A](#)). The roundtable consisted of industry experts with experience at various points of the pharmaceutical supply chain, including active pharmaceutical ingredients (API) and finished dose formulation (FDF) manufacturers, contract manufacturers, and wholesale distributors. The academics were a combination of health economists and experts in supply chain and forecasting techniques. To encourage honest and candid discussion, the one-on-one interviews and roundtable meeting followed “Chatham House Rules.”³ Thus, no specific comments are attributed to any one person. Participants represented their own views reflecting on their personal or professional experiences. No attempt was made to corroborate or verify their statements.

Finally, the Foundation held a public meeting on August 27, 2025, with a panel of experts and 25 public commenters. The agenda for the public meeting can be found in [Appendix B](#), and a summary of the public comments can be found in [Appendix C](#).

3 Chatham House. Chatham House Rule. Chatham House. Accessed February 3, 2025. <https://www.chathamhouse.org/about-us/chatham-house-rule>.

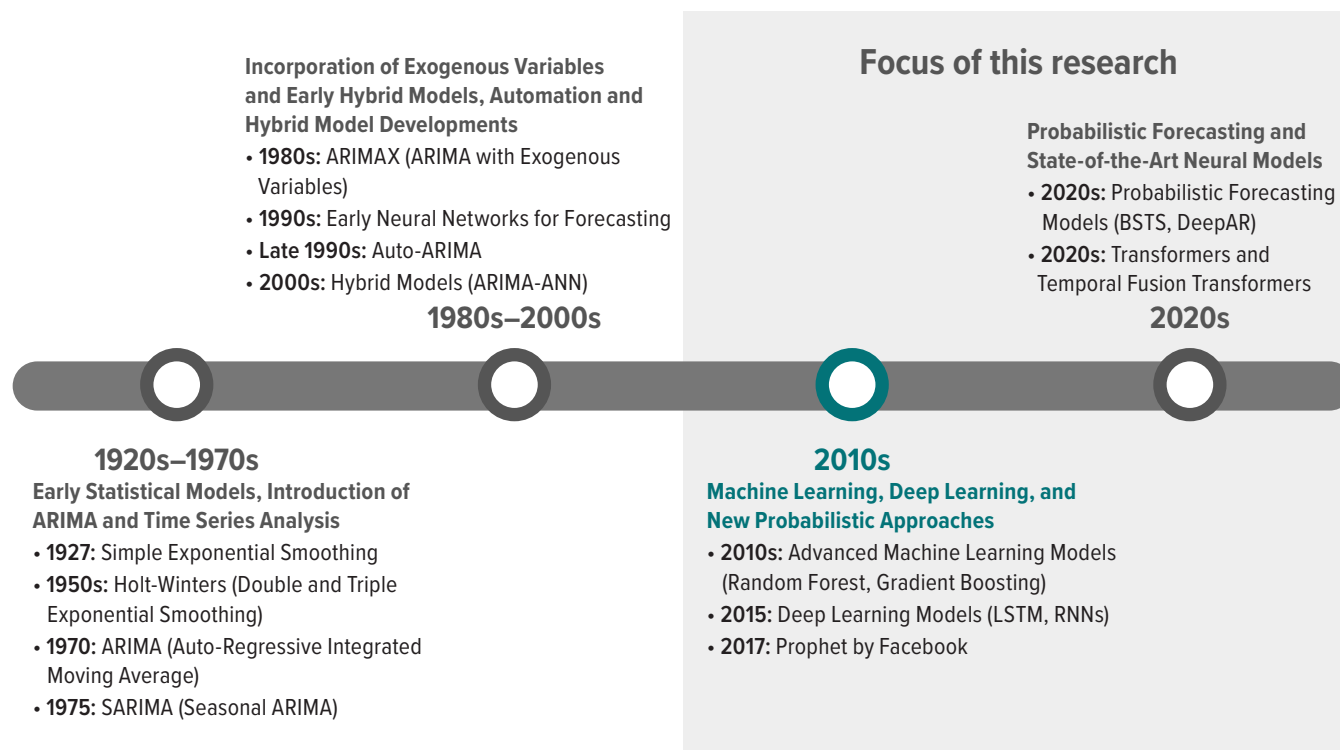
Forecasting Process

For manufacturers at large, when making up forecasts, there are two major categories of products. Each category entails a different set of factors built into the forecast and is developed by and for different audiences within and outside the organization. One category is “on-market products,” which are products currently being offered for sale that have a sales record that provides a historical basis for the forecast. The second category of product is “new entrants” or “new product launches.” These are products with no track record for sales, and thus the forecaster must use other data to help inform the forecast, such as the performance of competitors already on market and an estimate of the total addressable market.

Different statistical modeling techniques are available to forecasters. These techniques have been developed over the last 100 years, starting with moving averages and exponential smoothing (see Figure 1). Over the years, more sophisticated modeling techniques have been developed which attempted to incorporate more exogenous factors, such as changes in climate, policy or other macro-economic shifts. While the modeling has become more sophisticated, these newer models can be harder to use, require greater computational time and effort, and do not always result in more accurate predictions. See Appendix D for more information on the various types of statistical modeling techniques reviewed as part of this report.

FIGURE 1: TIMELINE OF MAJOR DEVELOPMENTS IN STATISTICAL MODELING TECHNIQUES^{4,5}

Despite Developments in Demand Forecasting, the Application of those Techniques in the Pharmaceutical Sector has Stagnated



4 Giri C, Chen Y. Deep learning for demand forecasting in the fashion and apparel retail industry. *Forecasting*. 2022;4(2):565-581. <https://www.mdpi.com/2571-9394/4/2/31>. 10.1111/poms.13426. <https://pure.psu.edu/en/publications/demand-forecasting-with-supply-chain-information-and-machine-lear>.

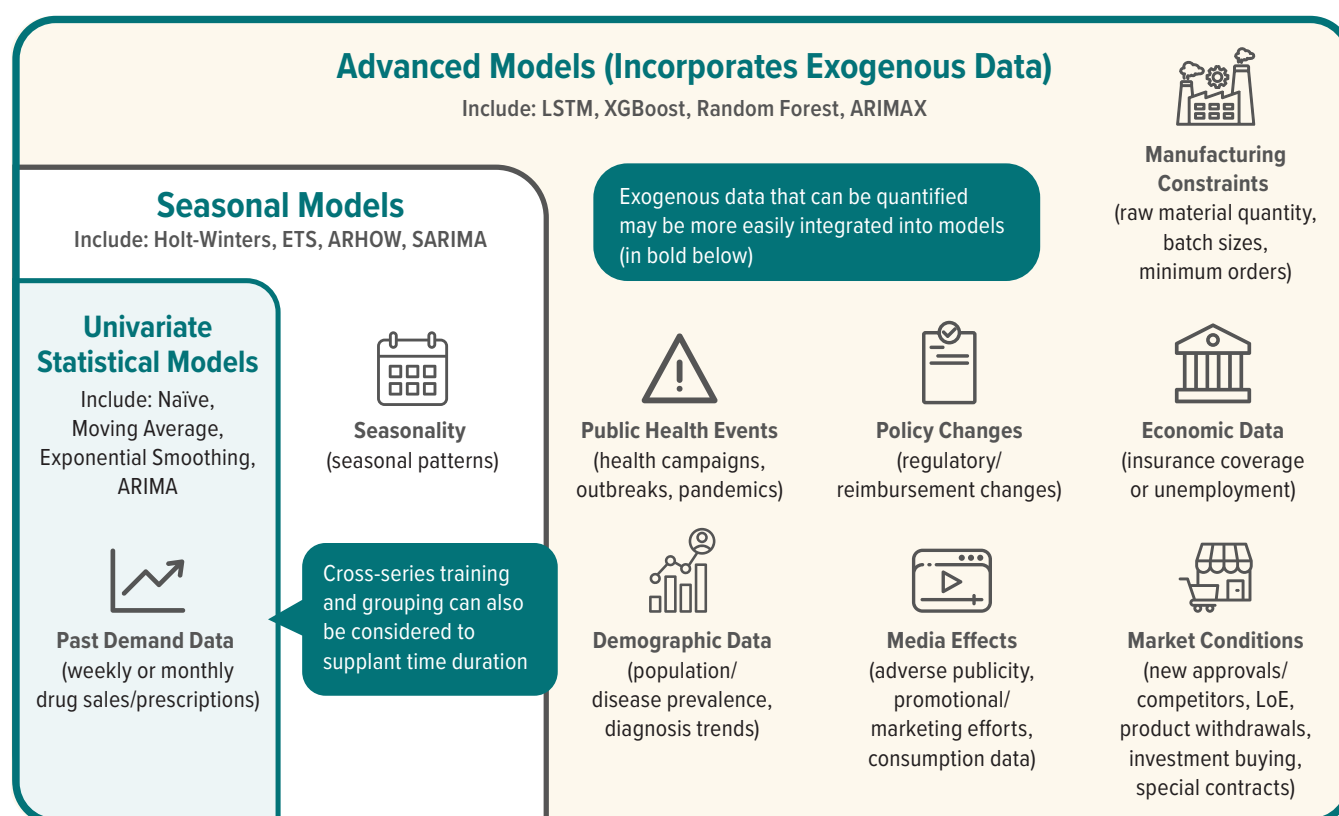
5 Zhu X, Ninh A, Zhao H, Liu Z. Demand Forecasting with Supply-Chain Information and Machine Learning: Evidence in the Pharmaceutical Industry. *Prod Oper Manag*. 2021;30(9):3231–3252. <https://doi.org/10.1111/poms.13426>.

As noted above, a key difference between the newer, more sophisticated statistical modeling techniques and the older, simpler techniques is the incorporation of exogenous or external factors. Exogenous factors are those real-time factors that can impact pharmaceutical demand but are not reflected in historical data (Figure 2). In other words, you cannot accurately predict the impact of these factors by simply looking backward in time. The latest models attempt to capture these factors using a method known as “demand sensing.” The concept of demand sensing focuses on identifying and including various exogenous factors affecting demand aside from historical demand (derived from product sales data).⁶ In these commercial enterprises, having an accurate and reliable demand forecast is seen as a clear business objective, along with having a necessary champion with authority to drive adoption and stress accountability while making the process sustainable into the future.⁷

FIGURE 2: EXOGENOUS FACTORS THAT CAN IMPACT PHARMACEUTICAL DEMAND^{8,9,10,11}

Integrating Prospective and Exogenous Data into Models to Better Predict Future Demand

The emerging concept of demand sensing, which focuses on identifying and including various factors affecting demand aside from historical demand, has attracted much attention.



6 Various commercial staff, Pfizer/J&J/Amgen/Kite/Gilead, personal communication, Nov.–Dec., 2024.

7 Chase CW. Next Generation Demand Management. Hoboken, NJ: John Wiley & Sons; 2016.

8 Ibid.

9 Cook AG. Forecasting for the Pharmaceutical Industry. Ashgate Publishing, Ltd.; 2015.

10 Zhu X, Ninh A, Zhao H, Liu Z. Demand Forecasting with Supply-Chain Information and Machine Learning: Evidence in the Pharmaceutical Industry. *Prod Oper Manag.* 2021;30(9):3231–3252. doi: 10.1111/poms.13426. <https://pure.psu.edu/en/publications/demand-forecasting-with-supply-chain-information-and-machine-learning>.

11 Bertolotti F, Schettini F, Ferrario L, Bellavia D, Foglia E. A prediction framework for pharmaceutical drug consumption using short time-series. *Expert Syst Appl.* 2024;253:124265. doi: 10.1016/j.eswa.2024.124265. <https://www.sciencedirect.com/science/article/abs/pii/S095741742401131X>.

While other industries have come to rely on advanced machine or deep learning methods in their demand forecasting, a 2021 survey identified during a systematic literature review revealed that pharmaceutical companies employed older methods such as exponential smoothing, moving average, linear regression, judgment, or a combination of these in their forecasting methods. These agile statistical methods, repeatedly fed with the latest data and coupled with experienced judgment about the impact of potential external factors to produce various scenarios, tended to provide the results for which these pharmaceutical companies were looking. None of the companies in the survey used machine learning models or other more advanced methods, although all mentioned they were considering it, especially for such high-impact areas as inventory and supply chain management.^{12,13}

On-Market Products

For on-market pharmaceutical products, short-term forecasting usually refers to time horizons that are 12 or 18 months long. Long-term forecasting usually refers to a rolling 36 months but can be up to 5- or even 10-year time horizons, and companies will make a habit of generating various combinations of these depending on their needs. For these needs, short-term forecasting is generally aimed at coordinating routine activities, such as managing raw materials, scheduling production activities, formulating pricing policy, and developing an appropriate sales strategy. In contrast, long-term forecasting is largely performed when anticipating a new product, expanding an indication, and/or upgrading a production or other supply chain facility (or even a fill-finish facility, or “vault” for storage), activities which require longer lead-time to be effectively managed.

There are important implications for the time horizon, especially the complexity of splitting an annual forecast into its monthly components. Ensuring a smooth transition from the exit forecast for one year to the entrance forecast of the subsequent year can be difficult. Similarly, creating a multi-year long-term forecast at the monthly level can be equally challenging. Various groups strive to provide their forecasts within the most suitable timeframe, which typically means an annual calendar. However, forecasts are sometimes generated for shorter or longer durations, sometimes with a base-case scenario along with multiple different forecasts having significantly different projections, which often rely on multiple external factors at play, such as pending litigation or regulatory oversight in which complex interactions make predicting the future difficult. Coordinating and ensuring alignment among these diverse forecasts can be a complex task.

Companies will commonly purchase datasets of pharmaceutical sales data from trusted data vendors, who often can provide both product-specific and market or therapeutic area-specific data, that will then be used to complement their own internal sales data, especially in competitive therapeutic indications/areas. While there are many different datasets available, it is widely recognized that no one dataset can perfectly meet all of the needs of the many different industry stakeholders, and companies routinely supplement commercially available datasets with additional data derived from both internal and external sources.

Many organizations also analyze their historical sales data, often revealing seasonal fluctuations, which can lead to irregular cash flow. These are areas where demand forecasting can minimize the risks and uncertainty associated with demand spikes or seasonal variations, especially from a supply chain and pricing perspective (which are generally intertwined for pharmaceuticals). In addition to the basic sales data, simple time-series analysis can also rely on prescriptions ordered (both total and new), total units, units by stock-keeping unit, units by strength, days of therapy, patient-days, retail units, hospital units, internet pharmacy units, sales to

12 Bertolotti F, Schettini F, Ferrario L, Bellavia D, Foglia E. A prediction framework for pharmaceutical drug consumption using short time-series. *Expert Syst Appl*. 2024;253:124265. doi: 10.1016/j.eswa.2024.124265. <https://www.sciencedirect.com/science/article/abs/pii/S095741742401131X>.

13 Zhu X, Ninh A, Zhao H, Liu Z. Demand Forecasting with Supply-Chain Information and Machine Learning: Evidence in the Pharmaceutical Industry. *Prod Oper Manag*. 2021;30(9):3231–3252. doi: 10.1111/poms.13426. <https://pure.psu.edu/en/publications/demand-forecasting-with-supply-chain-information-and-machine-lear>.

wholesalers, and wholesale and retail pharmacy inventories. However, comparison of trends across the different datasets can sometimes yield contradictory results, which can be difficult to reconcile or understand.

Manufacturers will often apply a wide range of external factors into their forecasts, including seasonality, but also rely on other expert opinions as well as economic trends. Many of these external factors (such as the COVID-19 pandemic, which lasted several years and had a variety of effects) can be difficult to assess, but including them affords a greater level of accuracy and results in a higher level of confidence. Often, expertise sharpened over years of forecast preparation, judgement, and validation can be the determining factors for how to apply these external factors properly, especially for such sensitive factors as the inter-relationship between new and total prescriptions, units and patients, and/or days of therapy and product strength.

In addition, there can be internal factors that have effects on the forecast, such as changes in marketing efforts or sales force allocation, as well as product formulation or packaging changes, regulatory policy or reimbursement changes, manufacturing constraints, market conditions such as competitive product entry (or even competitive product withdrawals), and therapeutic line extensions. Some product wastage occurs routinely when transferring product/intermediaries during a manufacturing run. Many companies also use software to keep track of wastage that occurs during the manufacturing process, which can then be incorporated into the forecasts.

Ultimately, forecasting will tend to include datasets that are both available and relevant to the particular therapeutic area under analysis to capture as many insights as possible. And further, trending market data relative to product data can lead to insights on product performance as well as overall market growth (or decline).

Market distortions are a crucial consideration in demand forecasting for pharmaceuticals. Factors such as binding quotas, drug shortages, and changes in the competitive landscape can significantly impact the accuracy and reliability of forecasts. These distortions can stem from regulatory policies, manufacturing constraints, or unexpected shifts in market conditions.

Binding quotas are upper limits on the production or distribution of particular drugs and can be applied in certain geographic markets by a regulatory body. If too restrictive, quotas can potentially lead to shortages that can disrupt supply chains and affect patient access to essential products. Quotas on quota-relevant substances are an example of binding quotas. Additionally, drug shortages can arise from manufacturing production issues, increased demand (sometimes driven by competitive brand or generic entry after loss-of-exclusivity), or supply chain disruptions, creating challenges for forecasting and inventory management.¹⁴

Changes in the competitive landscape are mostly external factors, such as new competitive entry or product withdrawals, but also include loss of brand exclusivity to competitors (either brands or generics) or new indications. Loss of exclusivity can be an especially dramatic market driver, especially in a therapeutic area having several brand competitors entering the market, where therapeutic interchangeability of other brands (or even generics) can push prices lower during contract negotiations year after year (or even more frequently in fragmented payer markets like the United States).¹⁵ Alternatively, the events could be internal (to the company), such as changes in marketing or sales force allocation, therapeutic line extensions, or new dosing and/or packaging. All these market distortions need to be considered during the forecasting process, and appropriate adjustments should follow.

14 Dave CV, Pawar A, Fox ER, Brill G, Kesselheim AS. Predictors of Drug Shortages and Association with Generic Drug Prices: A Retrospective Cohort Study. *Value in Health* 2018. (<https://doi.org/10.1016/j.jval.2018.04.1826>, accessed Feb. 26, 2025).

15 Effect of Entry on Generic Drug Prices: Medicare Data 2007-2022. Issue Brief No. HP-2025-06. Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services. January 2025. (<https://aspe.hhs.gov/sites/default/files/documents/510e964dc7b7f00763a7f8a1dbc5ae7b/aspe-ib-generic-drugs-competition.pdf>, accessed Feb. 26, 2025).

New Product Launches

Forecasting new product launches is usually conducted early in the development process, e.g., during Phase 1 or 2 clinical trials, and this is largely similar regardless of whether the drug sponsor is planning new innovator products or new generic launches. The basic process for new product forecasting can be separated into logically divided steps: 1) model the market/therapeutic area, 2) forecast the product using the target product profile (TPP), and 3) convert patients on product into revenue.

This first step of modeling the market and therapeutic area is critical to the new product forecast and involves a comprehensive analysis of the potential market environment (including the potential market size), mapping out the competitive landscape, and identifying key drivers and barriers to market entry. Detailed market models will allow companies to anticipate the potential uptake of their new products, estimate market share, and develop strategies to address any barriers, as well as scenario planning with recommendations for how to respond to any of these events to maximize potential revenue. This step includes assumptions about the supply chain, ensuring that production and distribution capacities align with the anticipated demand.

Often companies stagger their product entry into different therapeutic indications (such as for closely related indications, like rheumatoid arthritis and psoriasis), using these demand forecast models to plot the sequence of launches that will take advantage of the competitive landscape in each therapeutic area to minimize risk while providing revenue on an optimized schedule. Leveraging detailed market models allows companies to assess the uptake of their new products, develop strategies to maximize revenue, and thereby reduce the risks associated with new market entry.

Modeling the proposed market and therapeutic area is a critical step in the forecasting process for new product launches. This involves a comprehensive analysis of the potential market environment, including the (often dynamic) competitive landscape, and identifying key drivers and barriers to market entry. By leveraging detailed market models, companies can anticipate the uptake of their new products, estimate market share, and develop strategies to maximize revenue potential. This step also includes assumptions about supply chain resources, ensuring that production and distribution capacities align with the anticipated demand.

Occasionally, this step can also include taking regulatory actions, such as filing for new products or new dosages of existing products (or even a new route of administration such as a once-a-month injection or a pill), which can lead to a competitive or market access/reimbursement advantage that will have significant competitive effects on the overall market forecast. These product attributes, often organized during development into a TPP, help quantify the benefit-risk profile of the product, which is often used for internal discussions and external communications. The product forecast will often rely on these detailed product characteristics to help model a patient-based flow that will account for factors such as age, gender, diagnosis, provider specialty, route of administration, and even line of therapy. In planning for product launch, the company can then assess the various market segments and assign resources to maximize particular market access and reimbursement strengths and/or weaknesses within each segment. For global products, these processes can be highly complex, often necessitating multiple levels of internal review and strategic planning to mitigate regional or country-specific limitations and risks. While challenging to keep track of the various discussion points without becoming overwhelmed by the details, careful weighting and prioritization of the relevant factors can lead to a very effective model that is amenable to all the stakeholders.

Ultimately, this forecast model can provide a foundation for converting patients on the new product into revenue, thereby achieving the overall business objectives and supporting a successful product launch.

Forecasting Demand and Estimating Medical Need

As noted previously, FDA is interested in learning about best practices in industry for pharmaceutical demand forecasting, which may inform FDA's current thinking on best practices for estimating medical need for controlled substances.

Estimating the true medical need in the U.S. for any medication is a challenge. For example, there is no single source that provides comprehensive data on the number of prescriptions filled across the country by drug, dosage, and patient.¹⁶ Furthermore, there is no national database that reliably provides information regarding the number and type of diagnoses and what medications may have been prescribed to treat those diagnoses.

In the absence of reliable direct data on medical need in the U.S., FDA, DEA, and the pharmaceutical industry must rely on proxy data sources that help to estimate medical need for all controlled substances. However, those proxy data sources are several steps removed from true medical need and thus require cautious interpretation, particularly when a product is in shortage.

In addition to historical sales data, there are other data points or exogenous factors such as natural disasters or manufacturing quality issues which are important to consider when attempting to forecast demand for controlled substances. Because of the unusually rigid circumstances under which controlled substances are manufactured and sold, these pharmaceutical products are more challenging to forecast with implications for the availability of these important medications to patients. To the extent possible, exogenous factors such as these should be built into the estimate of medical need.

Limitations of Current Data Sources

Commercial third-party data aggregators provide the pharmaceutical industry and others with information regarding sales of pharmaceuticals in the U.S. These aggregators can provide useful details on specific pharmaceutical products by manufacturer, dosage, form, and sales channel. However, as many acknowledge, these data aggregators do not capture all data, resulting in substantial data gaps that can be critical when estimating medical need nationwide. For example, national data aggregators may be able to indicate that the volume of sales of a particular medication in a particular location has dropped, but not the reason behind that change, such as a natural disaster resulting in disruption of a pharmaceutical supply chain or preventing a patient from accessing their medication at their normal pharmacy.

Nonetheless, the pharmaceutical industry relies on these sales data, particularly in cases in which the drug of interest is not in shortage and/or for which demand is stable. In these cases, the data can be reasonably reliable and useful in estimating true medical need, perhaps utilizing some correction factor to compensate for known missing data. For these drugs, we can be reasonably assured that enough pharmaceutical product is being manufactured to meet the needs of patients in the U.S., even if the product is a controlled substance.

¹⁶ Datasets held by various integrated health systems, national pharmacy chains, and health insurers have relevant data, but cover only the patients in their system. Given that any one patient may visit multiple health facilities and pharmacies, and may change health insurers over time, these databases are not comprehensive enough to be useful.

However, when the pharmaceutical product is in shortage or the supply chain has been disrupted, actual sales data do not accurately reflect medical need. In this situation, sales data reflect only the amount of product dispensed and sold at the pharmacy level and in select other sales channels. The sales data do not record instances in which patients were unable to access their prescribed medications due to unavailability of the product. For controlled substances, DEA regulates the distribution of drugs as well as the transfer of prescriptions between pharmacies. These rigid factors can restrict patient access if a product is out of stock in their preferred pharmacy, leading to distortions in sales data. For example, when faced with a spot shortage of a specific medication, a prescriber may choose to substitute the out-of-stock medication with a second-choice medication. While the original medication is preferred, sales data will instead reflect lower sales of the original medication and increased sales for the second-choice medication, masking true demand for the original medication and further distorting the dataset that industry, FDA, and DEA rely on.

Supply Chain for Controlled Substances

Production of controlled substances is a multi-step process that can often take more than a year to get from raw materials to availability in a health care facility. The process is illustrated in [Figure 3](#).

FIGURE 3: EXAMPLE SUPPLY CHAIN FOR PRODUCTION OF A CONTROLLED SUBSTANCE



Note: These are estimated lengths of time intended to illustrate movement within the drug supply chain. Actual lengths of time will vary by specific drug and manufacturer.

For many controlled substances, the API is derived from agricultural products grown around the world. In both the northern and southern hemispheres, there is one growing season per year. API manufacturers rely on rolling forecasts to accurately predict the amount of raw material to order from farmers. Availability of agricultural products can be impacted by weather as well as regional infrastructure and instability (e.g., conflict). The International Narcotics Control Board and DEA regulate how much of a particular agricultural product can be legally planted as well as how much can be imported into the U.S.

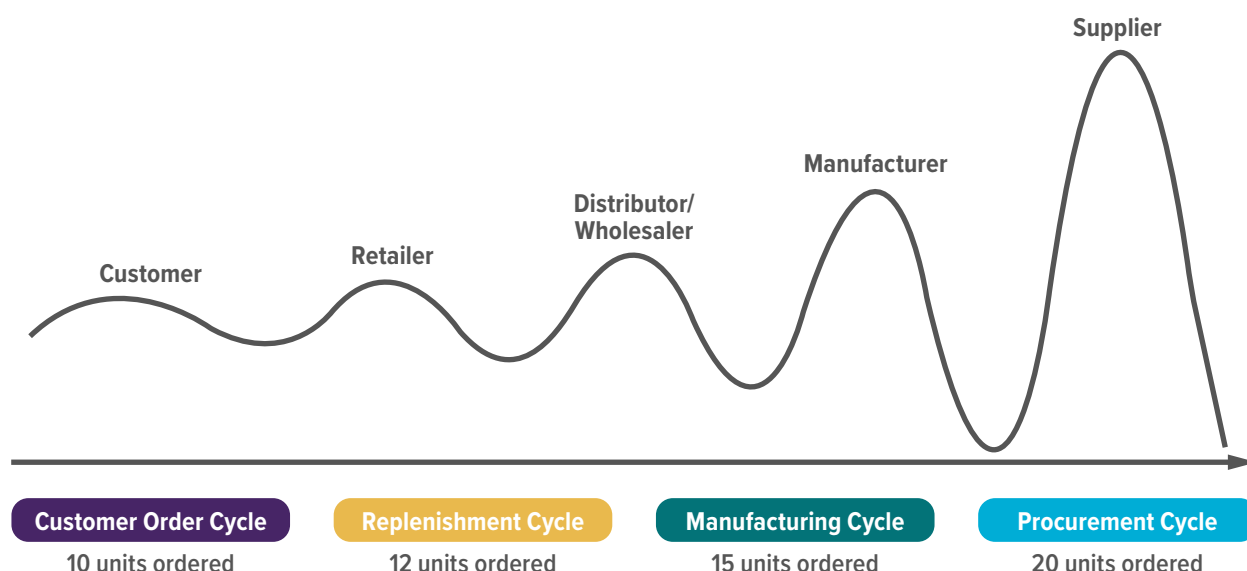
For both API and FDF manufacturers, production lines are usually planned a year in advance on a rolling basis, and changes cannot be made on short notice (i.e., less than two months from production). U.S.-based companies are incentivized to accurately forecast the amount of product they can manufacture and sell because they are limited by DEA in the amount of controlled product they can store (in accordance with 21 CFR § 1301.72). If manufacturers have a surplus of other kinds of pharmaceutical products, they can donate it to low- and middle-income countries. However, controlled substances cannot be donated; surplus must be destroyed.

Bullwhip Effect

In a typical market situation, one in which there are few if any regulatory constraints on manufacturing or sales of a product, e.g., common household products such as toilet paper, a sudden spike in customer demand for the product will reverberate throughout the supply chain in a predictable fashion. Known as the “bullwhip effect,”¹⁷ the demand at the retail level will be gradually exaggerated as one moves up the supply chain from retailer to wholesale distributors and ultimately to the manufacturer. What might hypothetically be a small increase in demand at the retailer, may ultimately be viewed as a much larger increase in demand at the manufacturer and supplier levels.

Retailers, facing uncertain demand and worried about meeting customer need, tend to request more product than absolutely needed from their distributors. In turn, distributors, sensing increased demand from their customers (the retailers), increase their orders from manufacturers, incorporating an excess buffer that amplifies the anticipated needs of retailers. This “whip” effect increases demand at every step, leading ultimately to over-supply in the next cycle. The longer the lead times from customers to manufacturers, the greater the bullwhip effect. See [Figure 4](#).

FIGURE 4: EXAMPLE OF THE BULLWHIP EFFECT ON THE SUPPLY CHAIN¹⁸



17 Yang Y, Guajardo M, Wallace SW. The behavioural causes of bullwhip effect in supply chains: a systematic literature review. *Int J Prod Econ*. 2021;236:108120. doi:10.1016/j.ijspe.2021.10812.

18 Adapted from Rodrigue JP. The Bullwhip Effect on Supply Chains. In: *The Geography of Transport Systems*. 6th ed. New York: Routledge; 2024. Available from: <https://transportgeography.org/contents/chapter7/logistics-freight-distribution/bullwhip-effect-supply-chains/>.

Typically, in the case of goods that do not change dramatically or expire from year to year, e.g., toilet paper, the impact is manageable. In a process known as “market clearing,” faced with excess inventory taking up valuable space, the retailers will discount the products until the excess is sold. Thus, the supply chain levels smooth out over time.

A Muted Bullwhip Effect for Quota-Relevant Controlled Substances

In the case of medications, particularly controlled substances subject to quotas, the market signals from the sudden increases in demand are considerably muted, with the result that manufacturers are unable to respond in a nimble fashion to increases in demand.

Controlled substances are regulated by the DEA, which by law determines the level of quota-relevant substances manufactured each year. These strict controls lead to the muting of market signals from patients to manufacturers.

Furthermore, due to concerns and subsequent lawsuits stemming from the opioid epidemic, pharmacies and wholesale distributors monitor closely the dispensing of all controlled substances. In part, they do this to avoid future liability from lawsuits alleging that pharmacies and distributors are abetting in the overuse and abuse of these controlled substances.¹⁹ As a result, pharmacies and distributors pay strict attention to the number of prescriptions and are disincentivized to increase orders. These anti-diversion controls are designed to slow down, minimize, or otherwise discourage increases. In this manner, the bullwhip effect is muted as market signals fail to pass accurately from pharmacies to distributors and ultimately to manufacturers. As a result, drug shortages can crop up as the market is unable to detect and respond to signals coming from patients.

Another place where the bullwhip effect is unintentionally muted is in the interactions between DEA and the manufacturers. DEA awards quotas to individual manufacturers (both API and FDF manufacturers) on an annual or semi-annual basis.²⁰ Under the quota system, manufacturers are not allowed to manufacture more than their assigned quota within a given year.

Because of delays and time lags in the calculation of historical sales orders, the data will be two years out of date by the time the quota is assigned, and the product has reached the market. Quotas for quota-relevant substances are set by DEA based primarily on historical sales orders.²¹ Preparation of the quota allocations requires manufacturers to submit data to DEA on both their historical and anticipated sales. Because the current year’s sales data and future sales orders are incomplete, DEA and the manufacturers must rely largely on prior years’ sales data. For example, to calculate the 2024 quotas, DEA prepared the quotas during the last six months of 2023, relying on sales data from 2022 and before. Using quotas which were granted by DEA at the beginning of 2024, the manufacturers (both API and FDF) would need 9–12 months to source the raw material, manufacture the product, and ship the finished doses to wholesale distributors. Thus, the quota-relevant substances manufactured based on 2022 sales data would not reach pharmacies and patients until 2025.

To illustrate this muted bullwhip effect, consider a hypothetical medical product that has been on the market for several years, with sales of 100 units per year for the past 5 years. Due to an exogenous factor, such as a medical journal article demonstrating evidence of increased effectiveness in a specific subpopulation, the

19 Minhee C. “Opioid Settlement Tracker”. <https://www.opioidsettlementtracker.com/>.

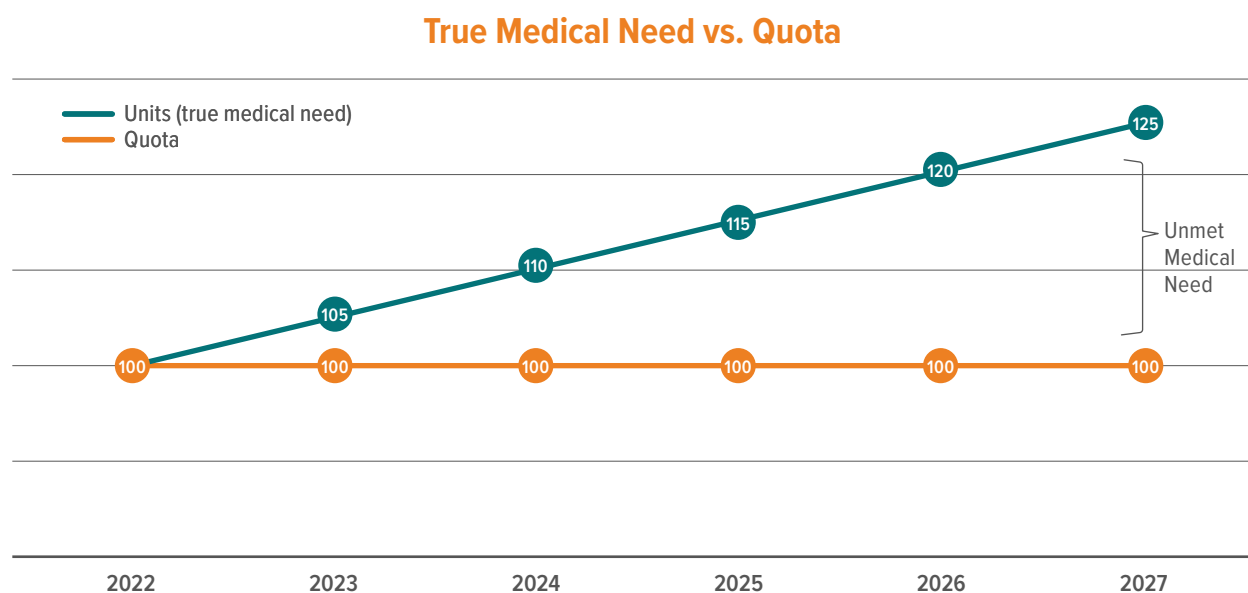
20 This report does not address the issues faced by API and FDF manufacturers in receiving and working with their assigned quotas, including issues of timing and wastage in the manufacturing process.

21 Drug Enforcement Administration. Established Aggregate Production Quotas for Schedule I and II Controlled Substances and Assessment of Annual Needs for the List I Chemicals Ephedrine, Pseudoephedrine, and Phenylpropanolamine for 2025. Federal Register. 2024;89(102649):102649-102662. Published Dec 17 2024. www.federalregister.gov/documents/2024/12/17/2024-30023/established-aggregate-production-quotas-for-schedule-i-and-ii-controlled-substances-and-assessment.

medical product starts to experience an increase in demand of 5 units per year for 5 years, then stabilizes. In other words, with no other constraints, growth in the sales of the product would increase year-over-year by 5 units each year. If 100 units were sold in 2022, 105 units would be sold in 2023, 110 units sold in 2024, and so on. By 2027, the demand for the medical product would be 125 units.

In the above example, sales of the medical product were 100 units per year up until 2022, the year the journal article was published. Based on these data, DEA allocated the manufacturer a quota of 100 units for 2024, which was manufactured and delivered to pharmacies by early 2025. At this point in 2025, true demand for the product is 115 units, resulting in a 15% shortage of the medication, that is, only 100 of 115 units needed to meet medical demand were manufactured and made available for sale. Furthermore, because the manufacturer was only able to sell 100 units in 2024 and before, historical sales data of 100 units sold will be used to make up the next quota allocation for 2026. As a result, by 2027 there is now a shortage of 25 units between available units (100) and true medical need (125 units), now representing 20% of the total need. Thus, in this hypothetical scenario, the bullwhip effect is entirely negated, and manufacturers are not able to respond to patient needs. (See [Figure 5](#).)

FIGURE 5: HYPOTHETICAL UNMET MEDICAL NEED AS A RESULT OF GAP BETWEEN QUOTA ALLOCATION AND TRUE MEDICAL NEED



In reality, drug manufacturers are able to incorporate some future sales orders in their quota request, backed up by sales contracts when available, which may or may not be factored into the quota allocated by DEA. Furthermore, while there are no penalties to manufacturers requesting more quota than necessary, manufacturers are in essence penalized for having excess inventory at the end of the year in the form of reduced quotas granted in the following year. Thus, while the bullwhip effect is not entirely negated, it is certainly muted.

Thoughts for the Future – Predictive Analytics

Recognizing the inadequacy of purely relying on historical sales data on drugs which are in shortage, several participants in the January 15 roundtable and August 27 public meeting advocated for some sort of estimate of the gap between true medical need and sales data. Referred to as “buffer” or “reserve,” some unspecified amount, e.g., a 20% boost to the forecasted need, could be added to the forecast to reduce the expected unmet medical need. While discussants did not specify how much should be added for any specific controlled substance, or how a reliable formula could be generated, the buffer could be implemented on an individual product basis based on known exogenous factors.

DEA has a mandate to provide for the estimated medical, scientific, research, and industrial needs of the U.S., lawful export requirements, and the establishment and maintenance of reserve stocks. and use the attached citation as a reference. Any manufactured product greater than the medical need has the potential to be diverted inappropriately, which DEA seeks to minimize.

As noted previously, the gap between historical sales data and true medical need for controlled substances is likely to be minimal for stable pharmaceutical products not in shortage, but significant for drugs which are in shortage. Introducing a buffer could potentially help to minimize that gap between recorded sales and true medical need.

While the calculation of the appropriate buffer for each controlled substance in shortage will be challenging, predictive analytics may be appropriately applied in this circumstance. For example, these analytics can factor in the age of the market sales data used to estimate future medical need and apply a small correction factor to the estimate. To estimate the size of the buffer, the reserve can be calculated by simply extending the growth curve of prior year sales at least three years out and using that figure for the reserve or buffer for the upcoming year. For products with stable sales, the buffer or reserve will be comparatively small or negligible, while for products which are in shortage, the reserve could be significant.

For drugs in shortage, those creating the estimates of medical need will want to evaluate the nature of the drug shortage, i.e., the reasons behind the shortage. If the factors leading to the shortage are temporary in nature, e.g., a short-term increase in demand, then the reserve may need to be adjusted in anticipation of the problem being adequately addressed. In this situation, the dip in sales is likely to be temporary and the market will return to a steady state of demand. However, if the reason is seen as permanent, e.g., an indication expansion that leads to greater numbers of patients who may benefit from the drug, then the buffer may need to be extended further out.

In addition to advanced estimation techniques, speakers at the public meeting highlighted the need to design and build new datasets that can provide better insight for demand forecasting and quota allocation. As previously discussed, historical sales data are a proxy for medical need, which are three years out of date by the time that medications are shipped to pharmacies. Prescriber, pharmacy, and distributor data derived from real-time electronic records could provide more up-to-date and accurate data from which to make estimates of medical need. Currently, many of these data are proprietary and not made available to the public or FDA.

Additionally, given that DEA has shifted to making semi-annual quota allocations to industry for many quota-relevant substances, FDA may wish to consider issuing refined estimates for products in shortage more frequently and incorporating new sales data, assuming refreshed data are made available every quarter. These refined estimates could subsequently be incorporated into the quota allocations made to industry by DEA.

Conclusion

Pharmaceutical demand forecasting is a useful if limited tool for estimating medical need across the country. Traditional methods for demand forecasting in the pharmaceutical industry rely heavily on past sales to estimate future need, tempered with experience and judgment regarding the impact of exogenous factors.

Relying on sales data is generally adequate for most pharmaceutical products, including quota-relevant substances subject to the rigid quota allocation system. However, in unusual market conditions such as drug shortages due to sudden increases in demand, historical sales alone cannot adequately reflect the increase in medical need, potentially contributing to current and ongoing drug shortages. In those situations, sales data do not reflect patient needs, particularly given the rigid quota allocation system mandated by the Controlled Substances Act.

Given the long time span between when the data that are used to set quota limits on quota-relevant substances are compiled, and when the pharmaceutical product reaches the patient, it is important to consider and appropriately incorporate the short- and medium-term increase in legitimate medical need. This may be achieved by introducing some sort of buffer or reserve by estimating the growth over the next 3+ years and applying this estimate to contemporaneous quota grants.

A November 1, 2023, letter from the DEA Administrator noted a shortfall of 1 billion doses of mixed amphetamine salts that were not produced in 2022 due to problems with the drug supply chain.²² Assuming that these doses were truly needed by U.S. patients, it is incumbent upon all players in the drug supply chain to ensure that the estimates of medical need in any given year are as accurate as possible to minimize these kinds of mismatches between patient need and available medication.

22 Drug Enforcement Administration. Letter to registrants regarding quota and shortages. Published November 2023. Accessed March 24, 2025. <https://www.dea.gov/sites/default/files/2023-11/Quota-Shortages%20Letter.pdf>.

Appendix A

Virtual Roundtable Agenda

Methods for Demand Forecasting for Controlled Substances

January 15, 2025 | 1–3 pm ET

Roundtable Goal: Gather experts to discuss various data sources and methods used by different stakeholders for forecasting annual demand for controlled substances. Participants will include representatives from pharmaceutical/biotech companies, data and consulting companies, academia, professional societies, and federal agencies.

1:00 pm	Welcome
	SPEAKERS: Susan C. Winckler, RPh, Esq , CEO, Reagan-Udall Foundation for the FDA
1:05 pm	Participant Introductions
1:20 pm	Background Presentation
	SPEAKER: James Wu, MSc, MPH
1:30 pm	Group Discussion
	MODERATOR: Susan C. Winckler, RPh, Esq QUESTIONS: • What methods and processes do you use to forecast demand for pharmaceutical products? – What data sources do you use for forecasting, including drug demand, drug shortage, and drug diversion? – Who within the company prepares the forecast and how is the forecast used? – How do you validate the forecast methodology? • Controlled substances are impacted by various factors which do not impact non-controlled substances. For example, we are concerned about the potential for misuse and diversion of these products for non-medical uses. We are also concerned about how to factor drug shortages into the demand forecasting. – How should those factors be incorporated into demand forecasting? – What other factors should be considered for controlled substances that might not apply to other pharmaceutical products? • Are there other resources we should include in this activity? • How did Covid-19 impact processes used to adjust demand forecasting and was there a difference between controlled and non-controlled substances?
2:55 pm	Closing Remarks
	Susan C. Winckler
3:00 pm	Adjourn

Appendix B

Hybrid Public Meeting Agenda

Demand Forecasting for Controlled Substances

**August 27, 2025 | 2–5 pm ET | Rooftop Meeting Space
1333 New Hampshire Ave NW | Washington, DC 20036**

2:00 pm	Welcome
	Susan C. Winckler, RPh, Esq , CEO, Reagan-Udall Foundation for the FDA
2:05 pm	FDA Opening Remarks
	Lowell Zeta, JD , Deputy Commissioner for Strategic Initiatives and Special Counsel, U.S. Food and Drug Administration
2:10 pm	CDER Fireside Chat
	Marta Sokolowska, PhD , Deputy Center Director for Substance Use and Behavioral Health, Center for Drug Evaluation and Research, U.S. Food and Drug Administration Susan C. Winckler, RPh, Esq
2:20 pm	Overview
	Amar Bhat, PhD, COO , Reagan-Udall Foundation for the FDA
2:35 pm	Public Comment
4:00 pm	Demand Forecasting Panel
	PANELISTS: Laura Bray, MBA , Chief Change Maker and Founder, Angels for Change John A. Gilbert, JD , Director, Hyman, Phelps & McNamara Nicolette Louissaint, PhD , Chief Policy Officer, Healthcare Distribution Alliance Emily Tucker, PhD , Dean's Assistant Professor, Department of Industrial Engineering, Clemson University Jillanne Schulte Wall, JD , Senior Director of Health and Regulatory Policy, American Society of Health-System Pharmacists
5:00 pm	Adjourn

Appendix C

Key Themes from Public Comments

During the public meeting on August 27, 2025, twenty-five stakeholders, representing a wide range of backgrounds, were provided up to three minutes each for public comment. Twenty-four commenters participated virtually, and one public commenter presented in-person. The commenters included patients and caregivers who have been impacted by challenges with accessing controlled substances, advocacy groups, representatives of pharmaceutical manufacturers, and others involved in the supply chain for controlled substances.

Commenters were asked to address at least one of the following topics:

1. Methods and processes used in forecasting demand and considerations for the unique circumstances of estimating demand for controlled substances
2. The effects of misuse/diversion on controlled substances and how they should be considered in demand forecasting
3. Potential impacts of underestimation or overestimation of demand on patients who are prescribed Schedule II substances

Below are key themes of the comments regarding demand forecasting and factors that impact access to controlled substances. Commenters referenced their personal experiences, and where applicable their professional experiences, to describe how current quota practices can result in underproduction of quota-relevant controlled substances.

Topic 1: Methods and Processes

Commenters used terms such as “limited transparency” and “opaque decision-making” to reflect the frustration they feel when urging federal agencies to change the way they present and make quota decisions.

Commenters representing manufacturers noted that in addition to underestimated quota, DEA’s sudden changes from an annual then quarterly and finally semi-annual quota allocation system has “severely disrupt[ed] manufacturing supply chains.” Due to continuous issues with requests for additional quota and lack of timely responses, commenters made a few requests for DEA which included: returning to the previous quota system that restores 50% year-end inventory allowance for API suppliers, awarding manufacturing quotas at least 90 days in advance of procurement quotas, awarding 75–80% of quota at the beginning of the year to allow better utilization of manufacturing plants which make more than one pharmaceutical product, and finding a way to respond to quota requests faster.

Commenters from a trade association said that underestimation causes logistical and economic challenges for generic pharmaceutical manufacturers as they serve high-volume, low-margin markets.

Participants also emphasized that by requiring pharmaceutical compounders known as 503B outsourcing facilities, which do not manufacture additional product, to obtain a quota, DEA may be led to believe there is more product in the market than there actually is.

Topic 2: Effects of Misuse and Diversion

Commenters provided personal stories about the impact of drug shortages and access limitations at pharmacies for controlled substances, especially prescription opioid medications. In some cases, patients noted that the inability to obtain a prescription through a pharmacy can turn patients to the illicit market, which may contain medications adulterated with substances such as fentanyl.

Participants also noted that there is a focus on lives lost due to harm from opioid overdose, but not enough focus on the lives lost due to harm from losing access to these same medications. Participants from various backgrounds also mentioned how the current overdose crisis is driven by illicit drugs rather than legitimate prescription use of opioid or stimulant medications. Others questioned whether there was documented evidence that the current quota allocation system leads to prevention or diversion.

Topic 3: Potential Impacts of Underestimation or Overestimation

Many public commenters across the board mentioned that when supply is underestimated, patients will face shortages and seek relief in the illicit market to ease their pain. Because the substances from the illicit market are “unregulated and highly variable,” the risk of death and other health complications are higher. Commenters stated that these deaths are often reported as caused by “diversion,” but are actually due to patients taking fentanyl-laced illicit products.

Many participants expressed anger at the fact that patients are punished when they attempt to seek out prescriptions at pharmacies other than their main dispenser. For example, commenters noted that when a patient goes to a new pharmacy seeking to fill a prescription, they are red-flagged in the Prescription Drug Monitoring Program. Participants highlighted that risk algorithms like NARx Scores can make it difficult for patients who are prescribed medication to get their prescriptions filled, as they eventually become “cut off” and labeled with opioid use disorder just because a pharmacy was out of the medication. Furthermore, commenters also noted that demand is not accounted for when patients go to the pharmacy and the prescription is not filled due to a shortage, contributing to a negative feedback loop.

Appendix D

Comparison of Statistical Models and their Application to Pharmaceutical Demand Forecasting

Features of Importance for Model Tradeoffs

Accuracy	Description: <i>How accurate is the model at predicting demand?</i> Inclusion Reason: Ensures the model reliably predicts demand, reducing overstocking and shortages.
Handling Seasonality and Simple Trends	Description: <i>How well can it adjust to seasonal and linear phenomena?</i> Inclusion Reason: Captures predictable fluctuations like school season or flu/allergy season; crucial for planning and inventory management.
Exogenous Data Adaptability	Description: <i>Can exogenous data, beyond historical demand, be integrated into the model?</i> Inclusion Reason: Reflects the model's ability to integrate external factors that significantly influence pharmaceutical demand.
Handling Complex Trends	Description: <i>Can it adjust to unseen phenomena?</i> Inclusion Reason: Addresses dynamic, nonlinear demand patterns driven by factors like new drug launches, black market/diversion dynamics, and regional variability.
Level of Model Complexity	Description: <i>What is the model's transparency in terms of implementation and intelligibility?</i> Inclusion Reason: Focuses on balancing ease of implementation and complexity of inputs, with the need for transparency in understanding
Forecast Horizon	Description: <i>For what time span?</i> Inclusion Reason: Assesses how well the model performs over short- and long-term periods. Two-year production times have been reported by controlled substance manufacturers.
Industry Prevalence	Description: <i>What is the usage in practice?</i> Inclusion Reason: Indicates the model's trustworthiness and real-world applicability based on its adoption and proven track record in the pharmaceutical sector.
Computational Cost	Description: <i>What is the resource usage during processing?</i> Inclusion Reason: Evaluates resource efficiency of model, balancing performance against time and infrastructure requirements; especially important for scalability (across products or classes).

Overview of Various Statistical Models

Moving Average²³

Overview

An average of the last N observed values

Advantages:

- Extremely simple and intelligible, no advanced statistical knowhow required
- Computationally efficient, possible to calculate MA for numerous NDCs

Limitations:^{24,25}

- Does not capture trends or seasonality
- **Does not incorporate exogenous factors**
- Always trails the data, delayed detection of sudden changes
- Highly sensitive to the chosen window size (N)
- Not suitable for long-term forecasting sequential

ARIMA [Autoregressive Integrated Moving Average]²⁶

Overview

Regression-based model tailored for time series data with Autoregressive (AR), Differencing (I), and Moving Average (MA) components

Advantages:

- Highly effective for short-term forecasting with consistent patterns¹
- Widely available tools and software implementation
- Can be extended to capture seasonality and exogenous variables with SARIMA and ARIMAX

Limitations:

- **Does not inherently capture seasonality nor exogenous factors nor multivariate time series**
- Assumes linear relationships, unsuitable for complex nonlinear patterns
- Not ideal for long-term forecasts

23 Zhu X, Ninh A, Zhao H, Liu Z. Demand Forecasting with Supply-Chain Information and Machine Learning: Evidence in the Pharmaceutical Industry. *Prod Oper Manag.* 2021;30(9):3231-3252. doi: 10.1111/poms.13426. <https://pure.psu.edu/en/publications/demand-forecasting-with-supply-chain-information-and-machine-lear>.

24 Sousa RM, Hannachi S, Ramos GN. Statistical and Deep Learning Models for Forecasting Drug Distribution in the Brazilian Public Health System. 2019 8th Brazilian Conference on Intelligent Systems (BRACIS). 2019:723–728. doi: 10.1109/BRACIS.2019.00130. <https://ieeexplore.ieee.org/document/8923953>.

25 Mbonyinshuti F, Nkurunziza J, Niyobuhungiro J, Kayitare E. Health supply chain forecasting: a comparison of ARIMA and LSTM time series models for demand prediction of medicines. *Acta Logistica.* 2024 Jun 1;11(2):269–80. https://www.actalogistica.eu/issues/2024/II_2024_10_Mbonyinshuti_Nkurunziza_Niyobuhungiro_Kayitare.pdf.

26 Nikolopoulos K, Buxton S, Khammash M, Stern P. Forecasting branded and generic pharmaceuticals. *Int J Forecast.* 2016;32(2):344-357. doi: 10.1016/j.ijforecast.2015.08.001. <https://www.sciencedirect.com/science/article/pii/S1877050919301061>.

Exponential Smoothing²⁷

Overview

Smooth forecasted in which most recent values carry more weight than previous values

Advantages:

- Adequate accuracy for short-term forecasts
- Computationally efficient, possible to calculate ES for numerous NDCs
- Can be extended with Holt's Linear and Holt-Winters

Limitations:

- Does not inherently capture trends nor seasonality
- **Cannot incorporate exogenous factors**
- Assumes linear relationships, unsuitable for complex nonlinear patterns
- Not suitable for long-term forecasting

Holt-Winters²⁸

Overview

An extension of exponential smoothing that incorporates level, trend, and seasonality components

Advantages:²⁹

- **Adequate accuracy for short- and medium-term forecasts**
- Captures trends and seasonality
- Computationally efficient
- Widely available tools and software implementation

Limitations:

- Requires **consistent seasonality** (either additive or multiplicative)
- **Cannot incorporate exogenous factors**
- High parameter sensitivity
- Not suitable for long-term forecasting

27 Nikolopoulos K, Buxton S, Khammash M, Stern P. Forecasting branded and generic pharmaceuticals. *Int J Forecast.* 2016;32(2):344–357. doi: 10.1016/j.ijforecast.2015.08.001. <https://www.sciencedirect.com/science/article/pii/S0169207015001181>.

28 Burinskiene A. Forecasting Model: The Case of the Pharmaceutical Retail. *Front Med (Lausanne).* 2022 Aug 3;9:582186. doi: 10.3389/fmed.2022.582186. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9381873/>.

29 Sousa RM, Hannachi S, Ramos GN. Statistical and Deep Learning Models for Forecasting Drug Distribution in the Brazilian Public Health System. 2019 8th Brazilian Conference on Intelligent Systems (BRACIS). 2019:723–728. doi: 10.1109/BRACIS.2019.00130. <https://ieeexplore.ieee.org/document/8923953>.

ARHOW [Autoregressive Holt-Winters Method]³⁰

Overview

Hybrid model with optimal weighted contributions from an ARIMA forecast and a Holt-Winters forecast³¹

Advantages:

- Blends ARIMA's robust handling of trends and residual dependencies with Holt-Winters' ability to manage seasonal variations
- Mitigates the limitations of each model
- Highly capable for short- and medium-term forecasts, possibility for long-term forecasts

Limitations:

- **Does not incorporate exogenous factors**
- Requires careful integration and parameter selection
- Higher data requirement, must effectively train both models
- Computationally expensive compared to the models by themselves

LSTM [Long Short-Term Model]³²

Overview

Deep neural network suitable for capturing sequential dependencies and long-term patterns

Advantages:

- **Adept at capturing complex dependencies and nonlinear trends**
- Natural work-in with cross-series training, exogenous grouping, and inclusion of exogenous variables
- Designed for time series data
- High accuracy potential across long-term forecasts

Limitations:

- Complex setup and data preparation required; requires hyperparameter fine-tuning
- Extensive data to train
- Computationally expensive
- **Limited transparency in “black-box” models may complicate quota justification**

30 Siddiqui R, Azmat M, Ahmed S, Kummer S. A hybrid demand forecasting model for greater forecasting accuracy: the case of the pharmaceutical industry. *Supply Chain Forum Int J*. 2021;23(2):124–134. doi: 10.1080/16258312.2021.1967081. <https://www.tandfonline.com/doi/full/10.1080/16258312.2021.1967081?scroll=top&needAccess=true#abstract>.

31 Azmat M, Siddiqui R. Enhancing supply chain efficiency: a holistic examination of hybrid forecasting models employing mode and PERT technique as deterministic factors. *Int J Logist Res Appl*. 2023;1–19. doi: 10.1080/13675567.2023.2280094. <https://www.tandfonline.com/doi/full/10.1080/13675567.2023.2280094#abstract>.

32 Mousa B, Al-Khateeb B. Predicting medicine demand using deep learning techniques: A review. *Journal of Intelligent Systems*. 2023;32(1): 20220297. <https://doi.org/10.1515/jisys-2022-0297>.

XGBoost [Extreme Gradient Boosting]³³

Overview

Machine learning algorithm that sequentially builds decision trees, summing their outputs to iteratively correct errors and optimize predictive accuracy

Advantages:

- High accuracy potential across short-, medium-, and long-term forecasts
- **Adept at capturing complex dependencies and nonlinear trends**
- Fast for a machine learning algorithm
- Widely available tools and software implementation

Limitations:³⁴

- Not specifically designed for time series, requires engineered features and statistical knowhow
- Requires fine tuning of hyperparameters
- Computationally expensive
- **Limited transparency in “black-box” models may complicate quota justification**

33 Fourkiotis KP, Tsadiras A. Applying Machine Learning and Statistical Forecasting Methods for Enhancing Pharmaceutical Sales Predictions. *Forecasting*. 2024;6(1):170–186. doi: 10.3390/forecast6010010. <https://www.mdpi.com/2571-9394/6/1/10>.

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Appendix E: Acronyms and Definitions

API	Active Pharmaceutical Ingredient
Controlled Substance	A drug or substance that has potential to cause dependence, abuse, and/or create a risk to public health. There are five classes, or schedules, of controlled substances, with Class I and II being the highest potential for abuse and thus, subject to quotas by the federal government.
DEA	Drug Enforcement Administration
ES	Exponential Smoothing
ETS Method	Exponential Smoothing State Space Model that captures Error, Trend, and Seasonality to forecast time series data.
FDA	U.S. Food and Drug Administration
FDF	Finished Dose Formulation
HHS	U.S. Department of Health and Human Services
MA	Moving Average
Naïve Method	A simple forecasting approach where the next period's forecast is the same as the last observed value.
NDC	National Drug Code
TPP	Target Product Profile



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