INTRODUCTION TO FDA'S OPIOID SYSTEMS MODEL

A WHITE PAPER

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EXECUTIVE SUMMARY

In response to recommendations from the National Academies of Sciences, Engineering and Medicine (NASEM), the U.S. Food and Drug Administration (FDA) is developing a national-level system dynamics model of the opioid crisis, with the goal of informing potential regulatory actions that may make meaningful gains in addressing the crisis. The primary objectives of the model are threefold: help FDA and other stakeholders identify high-impact interventions, assess potential unanticipated consequences of potential policies, and identify needs for further research. Model development began in 2018 and has involved a strong collaboration of opioids, modeling, and policy experts. To date, this effort has resulted in development of an initial model and a framework for its use in policy analysis. Continued efforts will further enhance the model, implement a policy analysis service and disseminate findings.

This paper introduces FDA's opioid systems modeling effort, discusses potential uses of the model, provides an overview of the model's scope and structure, highlights preliminary areas for potential policy analysis and outlines on-going work. This paper does not provide complete documentation of the model or discuss findings; both will be included in a publication expected in the next year.

INTRODUCTION TO FDA'S MODELING EFFORT

The Opioid Crisis

The opioid crisis is among the most serious public health problems of the 21st century. Opioid overdose deaths have increased dramatically over the last 20 years. In 2017, more than 47,000 people lost their lives to overdoses involving opioids – almost four times the roughly 12,000 people who lost their lives to the same cause in 2002. Cumulatively, almost 375,000 people lost their lives to overdoses involving opioids between 2002 and 2017.[1] While prescription opioids were responsible for most overdose deaths early in the crisis, deaths involving heroin and synthetic opioids, primarily illicit fentanyl, have increased rapidly over the last ten years.[2] Beyond overdose deaths, comorbidities such as untreated pain and infectious disease, as well as the broader socioeconomic impacts of addiction, also add to the toll of the crisis.

Figure 1: Overdose Deaths Involving Opioids, 2002-2017[3]
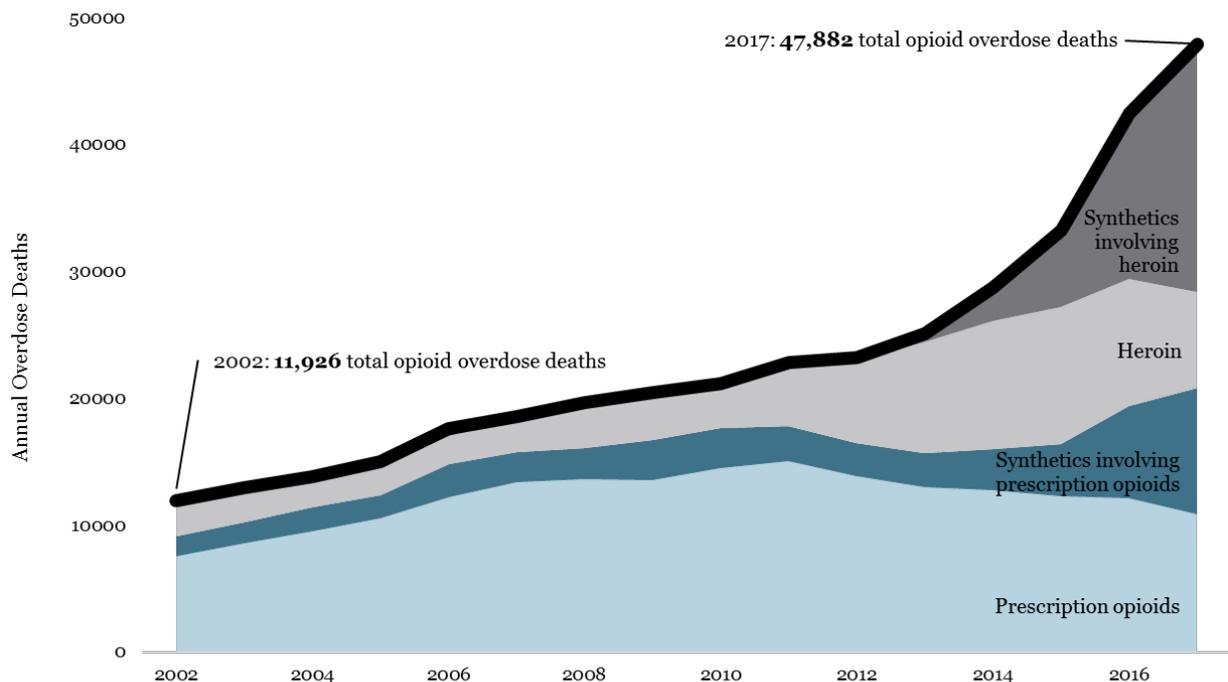
FDA's Role in Responding to the Crisis

As the agency responsible for regulating opioid medications marketed in the U.S., FDA plays a critical role in responding to the opioid crisis. FDA's decision-making is guided by its fundamental goals to protect and advance public health, including enabling the availability of medical therapies that meet the medical needs of people living with pain and reducing harms associated with opioids, such as overdose and addiction.[4] FDA detailed an approach to reducing the misuse of opioids in a "2018 Strategic Policy Roadmap".[5] For additional information on FDA's response to the opioid crisis, see FDA's homepage for opioid medications.[6]

Effectively addressing the crisis requires multiple interventions— products, technologies, policies, and communications— working together. Evaluating the overall public health impact of any one intervention is extremely challenging in light of the ever-changing opioids landscape and the many concurrent interventions being undertaken. Incomplete information and the constant evolution of the crisis limits decision-makers' ability to predict the impacts of regulatory actions. Multiple key factors complicate decision-making:

1. **The crisis is heterogeneous.** Every individual's interactions with opioids is unique. This heterogeneity makes it difficult to understand underlying mechanisms, identify patterns, and predict effects of interventions.
2. **Myriad actors are involved in crisis response**, each with their own jurisdiction, priorities, capacities, and constraints. Coordination across these

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actors is challenging, and ineffective coordination can result in unintended consequences.

3. **There are delays between actions and effects**, which complicates assessment of cause and effects.
4. **Actions to address one aspect of the crisis may have unintended consequences elsewhere.** For example, attempts to limit opioid prescribing may have unintended consequences on illicit use and overdose deaths.
5. **The crisis is evolving at an unrelenting pace.** For example, the landscape of opioids prescribing has fluctuated greatly over the past 30 years. More acute changes are the proliferation of illicit fentanyl and the sudden impacts of Coronavirus Disease 2019 (COVID-19).

To address these challenges, FDA is increasingly incorporating systems approaches to inform our understanding of the potential impacts of regulatory actions for opioids.

Systems Modeling

In 2017, at the request of FDA, NASEM published recommendations for FDA and other stakeholders regarding effective responses to the opioid crisis. In its report, NASEM called on FDA to employ a systems approach for incorporating individual and societal considerations into its decision-making regarding opioids. NASEM further recommended that FDA develop a systems model that would include prescribed and illicit opioid use and establish the needed data infrastructure to predict the effects of changes in policy or other changes in the opioid ecosystem. [7]

A systems approach, or systems thinking, is the recognition that an identified problem is the manifestation of a system of people and organizations who make choices and exhibit behaviors that are influenced by their environment. Systems thinking emphasizes the integrated nature of systems, considering their components collectively rather than in isolation. Systems approaches draw on techniques ranging from qualitative frameworks to quantitative modeling.

Systems modeling, the focus of this initiative, combines systems thinking and computerized simulation to quantitatively model complex systems. Systems modeling is well-suited to the opioid crisis for:

- **Framing the crisis on a broad scale and highlighting relationships between actors.** As a conceptual framework, a model enables decision-makers to visualize the interconnected nature of the crisis and consider ripple effects of actions.
- **Endogenously capturing important causal processes.** By incorporating endogenous feedbacks, a systems model can account for the dynamic nature of the problem, including the shifting drivers of various important transitions.
- **Providing quantified estimates.** In addition to providing a conceptual framework, models can help estimate the relative magnitude of proposed decisions on indicators of interest, such as overdose death.

- **Explicitly accounting for uncertainty.** Models use historical data to rigorously estimate unknown model parameters and quantify uncertainty. Models can also run sensitivity analyses to help decision-makers visualize a range of possible outcomes.
- **Ensuring adaptability by design.** Models can be adjusted to reflect new conditions and data as the crisis evolves. Models can also be calibrated to different populations of interest, data permitting.

System dynamics models have often been used for decision support; notable examples include the Millennium Institute's Integrated Sustainable Development Goals model,[8] Climate Interactive's C-ROADS climate change policy simulator,[9] and ReThink Health's regional health systems model.[10] Similar models have been used to inform policymaking and analysis in various parts of the Federal Government, including HHS's tobacco control simulation models[11], the Department of Defense's Project Stoddert[12], and the Department of Energy's Integrated Framework for Modeling Multi-System Dynamics[13].

The umbrella of systems modeling encompasses several differentiated modeling approaches. FDA's model of the opioids crisis employs a system dynamics approach, which emphasizes endogenous feedback processes and changing behaviors over time.[14,15] Various systems modeling and opioids research teams have already undertaken efforts, applying a range of systems approaches to examine the crisis.[16, 17] Previously published opioids modeling efforts, however, do not include aspects of the crisis of particular relevance to FDA within their scope, were constructed prior to the fentanyl surge, do not make full use of existing national-level data, or lack an endogenous perspective. Therefore, FDA's effort aligns with both NASEM's and other researchers' call for more applications of systems modeling in the opioid space.[18]

FDA's Opioid Systems Model & Modeling Approach

In 2018, in response to NASEM's recommendation, FDA's Center for Drug Evaluation and Research (CDER) launched an initiative to develop a system dynamics model of the opioid crisis. The primary objectives of FDA's model are threefold: a) to help FDA and other stakeholders identify interventions that have potential to yield high-impact gains in the crisis; b) to assess the intended and potential unanticipated consequences of policies or actions that may be considered; and c) to identify needs for further research to address important uncertainties that have the greatest impact on our ability to assess impacts.

An Opioid Systems Modeling Workgroup (hereafter referred to as "the Workgroup" or "we"), situated within CDER's Office of Program and Strategic Analysis, initiated model building and currently oversees model development and manages projects related to the initiative. The Workgroup consists of experts in decision science, modeling and data analysis, economics, and evaluation.[19] The Workgroup led the first year of model development and then transitioned the lead technical model development (in close collaboration with the Workgroup) to Harvard Medical School (HMS) and Massachusetts General Hospital (MGH).[20] Through this research collaboration, model

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development has been guided by a team of 13 renowned opioid and system dynamics modeling experts, as well as 13 expert advisors.[21]

To date, the Workgroup and HMS/MGH team have focused on the development of a quantified, U.S. national-level model, which tracks populations through major opioid use states. The model development process has involved consultation with subject matter experts, robust internal validation, and formal review of the model by two third-party system dynamics modeling experts to ensure the integrity and transparency of the model. The HMS/MGH team routinely conducts standard tests to check for historical accuracy and realistic representation of real-world trends. We anticipate that FDA will begin use of the model in an exploratory capacity in late 2020, and the collaboration team plans to publish the complete model and initial findings in 2021. Documentation of modeling procedures, assumptions, definitions, data sources, and rationale will be included in this publication.

As a system-wide model with a fundamentally broad perspective, the model necessarily touches on aspects of the opioid crisis beyond FDA's jurisdiction, such as the supply of illicit drugs and community-based harm-reduction and treatment practices. Incorporating these aspects in the model allows FDA to account for the interconnections between FDA's and other stakeholders' actions and enable identification of potential synergies and/or unintended spillover consequences among policies. While the model is intended specifically to guide FDA policies, it could potentially be adapted for use by others. It could also help inform efforts to leverage inter-agency coordination around the opioid crisis, across the U.S. Department of Health and Human Services (HHS) agencies and possibly beyond.

Parallel Efforts within Health and Human Services

FDA's systems modeling initiative coincides with complementary research and modeling efforts undertaken by HHS partners at the National Institute on Drug Abuse (NIDA) and the Centers for Disease Control and Prevention (CDC). The models under development by FDA, NIDA, and CDC apply different modeling scopes and strategies (e.g., agent-based modeling and compartmental models) to provide unique insights that complement one another. FDA's system dynamics model is a continuous-time, differential equation compartment model. This model uses state variables to depict populations in each opioid use state, and it incorporates dynamic transition rates, such as drug use initiation and endogenous feedback effects. The Workgroup and MGH/HMS team engage regularly with NIDA, CDC, and other stakeholders across HHS to discuss data sources, methodological considerations, and prioritized research needs. For example, in April 2019, we convened data experts and modelers to discuss best practices in data use and approaches to data gaps.[22] A follow-up meeting is occurring in October 2020 and will focus on the process of translating questions from decision-makers into model analyses and results.

OVERVIEW OF THE MODEL

Scope of the Model

The FDA model focuses on tracking people through various opioid use states and the factors that affect transitions between those states. It depicts the U.S. population, allowing FDA and other policy makers to consider the crisis on a national scale. In so doing, it does not account for geographic variability in population or effect sizes.

The FDA model includes important drivers not yet included in other models, such as the relationship between fentanyl penetration into the illicit opioid market and overdose death. Additionally, the FDA model is unique in that it differentiates and includes each of the FDA-approved medications for opioid use disorder separately and includes remission as a modeled use state. We also include important feedback dynamics around social influence, risk perception, and availability of both prescription and illicit opioids. Although they are outside of FDA's jurisdiction, the model includes illicit prescription opioids and heroin because they are crucial dimensions of the crisis. Further, escalation to illicit use may be an unanticipated consequence of interventions related to opioids prescribing.

The model currently excludes explicit factors such as social determinants of health and comorbid health conditions. The model does not include use of illicit substances that are not opioids, such as cocaine or methamphetamines. Finally, the model does not include the criminal justice system and other complex sub-systems at this time, as these require extensive further modeling research.

As FDA continues to enhance the model and as data become available, the scope of the model may change. Planned expansions include the incorporation of additional social outcome variables (e.g., untreated pain, quality of life) and the cost-effectiveness of interventions.

Model Structure

The model tracks people through four categories of opioid use, each of which includes multiple possible use states. Figure 2 provides a high-level overview of the current model structure. The four categories are (1) misuse, (2) use disorder, (3) treatment, and (4) remission:

Misuse: Misuse includes prescription opioid misuse that reflects the pre-2015 National Survey on Drug Use and Health definition of nonmedical use: any use of another individual's medication, for any purpose including the feeling it caused, as well as use of heroin or illicit opioids that does not rise to the level of disorder (i.e., non-disordered use).[23]

Use disorder: Use disorder captures people who meet the use disorder criteria described by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for prescription opioids and/or heroin.[24] The model differentiates people with prescription

opioid use disorder (OUD) who do not use heroin, people with OUD who use heroin but do not have heroin use disorder (HUD), and people who have HUD, regardless of whether they also use prescription opioids or have OUD.

Treatment: Treatment includes people who are actively receiving one of the three FDA-approved medications for OUD – methadone, buprenorphine, and Vivitrol. These individuals may or may not also receive psychosocial treatment and may or may not be in remission.

Remission: Remission is defined as at least one year without any symptoms of OUD or HUD, consistent with the DSM-5. [25] The model represents groups of people who are in remission and not currently in treatment.

In addition to transitions between specific use states, the model tracks fatal and nonfatal overdoses and non-overdose deaths. The model also incorporates factors that affect the rate of transition between states and the rate of overdose. Major factors include prescribing practices for opioids, the availability of prescription opioids and heroin, social influence, perceived risk of use, the penetration of fentanyl into the opioid supply, treatment duration, access to naloxone, and access to treatment, among others. Full model documentation will accompany its published version.

Figure 2: Misuse, Use Disorder, Treatment, and Remission Structure
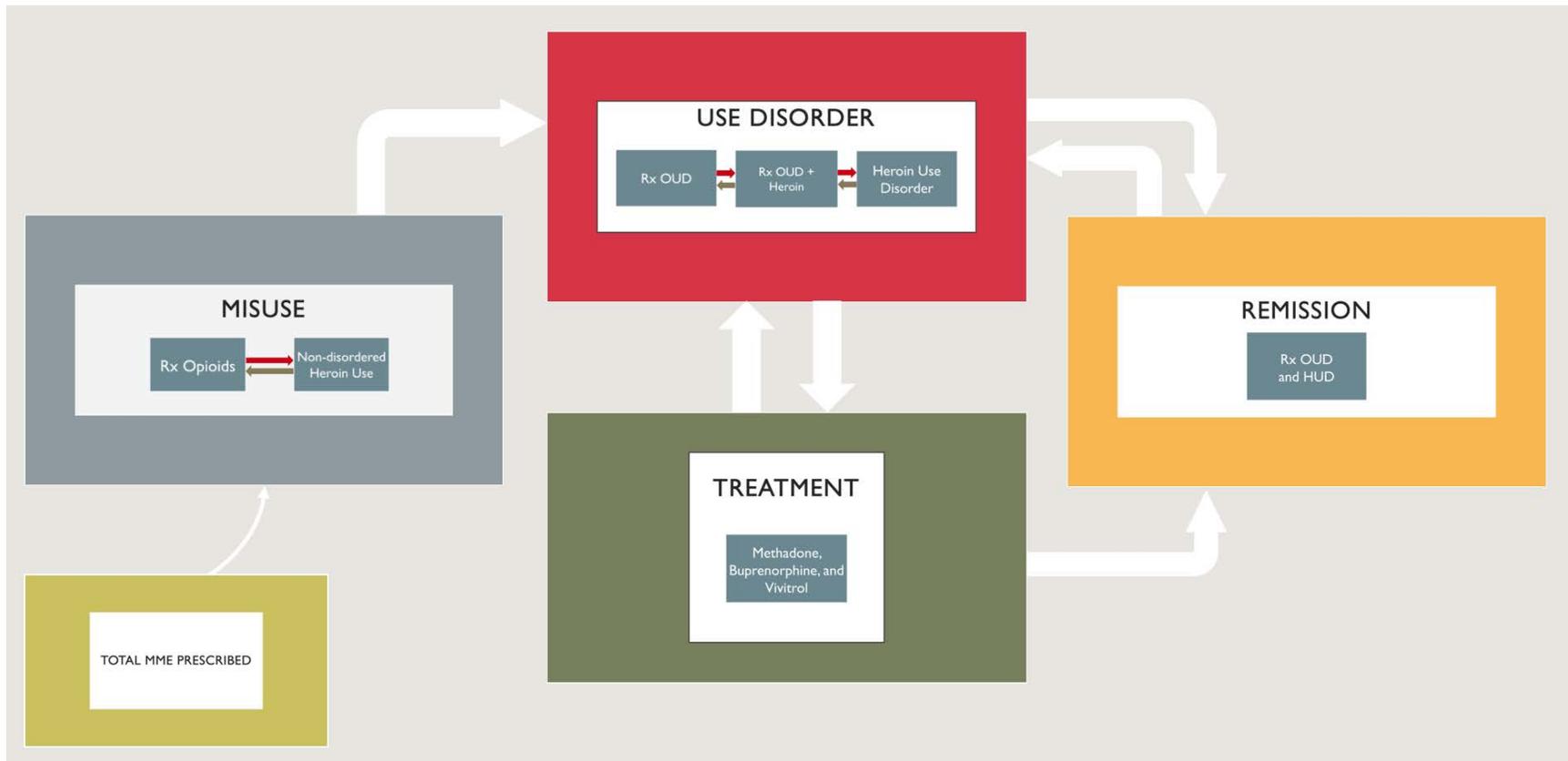
Quantification of the Model

Model quantification is a complex process including iterative consultation of literature and experts, calibration to historical data, and extensive testing. We have quantified the model's use states, the transitions between them, and other relevant variables to estimate model parameters. When available, we rely on national datasets that are representative of the U.S, population (or projected to be representative of the U.S. population), consistently collected over time and geographic areas, and reflective of relevant concepts pertaining to the opioid crisis. These sources include, among others, the National Survey on Drug Use and Health, National Vital Statistics System, National Survey of Substance Abuse Treatment Services, and IQVIA's National Sales Perspective®, National Prescription Audit®, and Total Patient Tracker®. Our forthcoming technical publication will describe the quantification process and data sources in more detail.

Limitations of the Model

Model limitations fit into two general categories: data limitations and scope limitations. The FDA model necessarily relies on imperfect data. We have identified prevalent gaps in the existing data, which continue to limit model development. [26] We regularly engage with other HHS agencies, as well as non-government modelers, to identify data challenges and discuss paths forward. An example of a major challenge is the lack of longitudinal data to support quantification of transitions between use states. Most available national data sources reflect snapshots in time, which allow us to quantify use states but provide little insight into transitions between those states. Information about illicit use and the illicit market is also limited by the likely presence of reporting bias in the available sources. Despite data limitations, the model is able to replicate historical data well and produces reasonable estimates.

In some cases, data limitations necessitate scope limitations. For example, the model does not explicitly represent treatments for use disorder that do not incorporate one of the three FDA-approved medications. Mental health and other health comorbidities, as well as polysubstance use, are also excluded from the model on the basis of limited data and the complexity of their relationship to the opioid crisis. Sub-models may be required to appropriately reflect such topics in the future.

We are committed to transparency regarding the model's capabilities and limitations. As we begin exploratory use of the model, we prioritize user awareness of the existing limitations and appropriate applications of model results.

USING THE MODEL TO INFORM DECISION-MAKING

Modes of Model Analyses

Broadly speaking, there are two ways to approach the analysis of policy questions using the FDA model, depending on the uncertainty associated with the policy question and the intended goal of analysis:

Rapid thought-experiment analyses aim at developing intuitions and exploratory learning. Model users may develop their own questions, hypotheses, and assumptions, and test these questions in the model to obtain a general understanding of trends and system behavior. This approach produces simulation results quickly and provides information about the relative magnitude or directionality of effects but with limited quantitative precision. Model users may wish to conduct rapid thought-experiments when there is high uncertainty around a policy question, such that rigorous definition of the question and assumptions are not possible. They may also be particularly valuable in the early 'brainstorming' or learning stages of policy exploration. In these cases, the model can provide insight into the range of possible outcomes and help decision-makers prioritize further research around areas with projected favorable impacts.

Guided analyses intended to inform decision-making with more quantitative precision require a more structured approach. In these cases, a decision-maker may pose a policy question that will inform some regulatory action or provide insight into a more narrowly-defined topic area (e.g., prescribing guidelines, naloxone distribution). A decision-maker may also pose a policy question around which sufficient research exists to carefully define the analysis question(s) and develop quantitative assumptions with reasonable confidence. In order to produce robust results, we anticipate a structured process through which the Workgroup, subject matter experts, and decision-makers work together to design and interpret model simulations, assess uncertainties, and document analysis processes. With support from Booz Allen Hamilton, we are currently developing a roadmap for this guided analysis process, termed the "Opioid Systems Analytics Service". We expect to test this process in conjunction with exploratory model use in late 2020.

Inevitably, policy questions will not always fit clearly into one category. Depending on the analysis goals and questions, both approaches or a hybrid approach could be applied. With support from Booz Allen Hamilton, we are developing a policy simulation tool interface in which users can interact with the model, run and store simulations, and produce visualization of model results, to aid in both modes of use.

Translating Policy Questions into Model Analyses

The Workgroup's current framework for approaching policy questions using the FDA model is outlined in Figure 3.

Figure 3: Translation of a policy question into model analyses
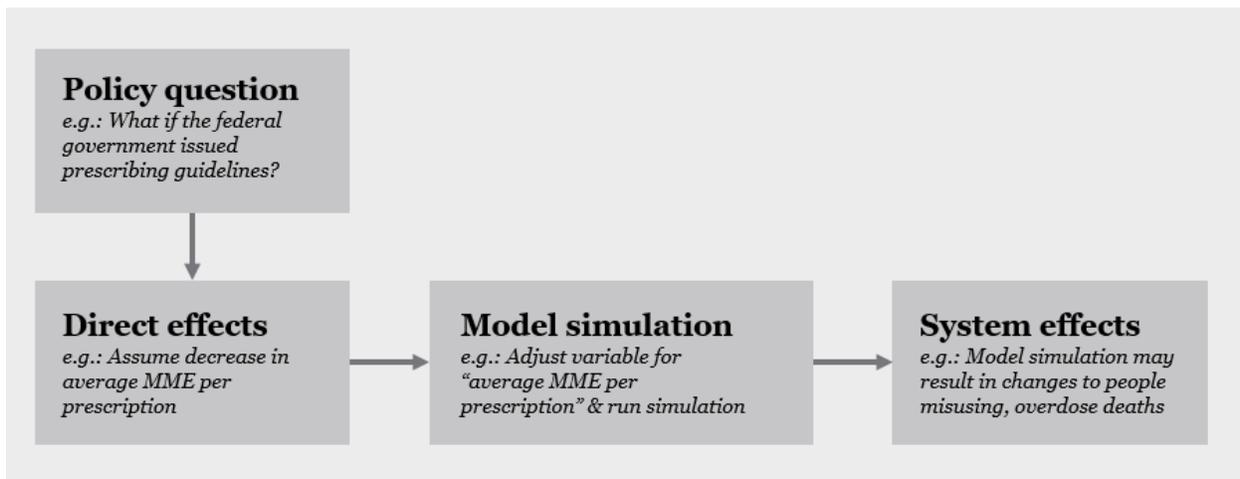
First, a decision-maker encounters a question relevant to the opioid crisis. For example, a decision-maker may wish to understand the potential impacts of changing specific opioid prescribing guidelines. The model is best designed to address strategic, "what if" questions (e.g., What if the Federal Government issued particular guidelines on prescribing?), rather than operational questions (e.g., How should prescribing guidelines be communicated to the public?). The model can also address questions about shocks to the system, e.g., "what is the impact of the COVID-19 pandemic on the opioid crisis?". Refinements may be required to suit the question to the scope of the model or split the overarching question into specific sub-questions.

With a policy question defined, we use a combination of existing data, research, and expert judgement to inform assumptions about the direct impacts of potential policies or changes. In the case of new prescribing guidelines, for instance, we may assume that the average morphine milligram equivalent (MME) per prescription or the number of people receiving prescriptions decreases by some percentage over some time period.

These assumptions are used as inputs into the model, or changes to relevant model values (e.g., the parameter for "average MME per prescription"). The model simulates the effects of these changes and shows outcomes across model variables. For instance, a change in the average MME per prescription may affect the number of people misusing prescription opioids and ultimately the overdose death rate, among other components of the model. Depending on the time horizon across test scenarios, the model may reveal different short- and long-term trends, which can be reviewed both qualitatively and quantitatively.

Development of assumptions, model simulation, and review of outcomes is an iterative process. The FDA model allows us to easily simulate and compare results across a wide range of scenarios.

DISCUSSION OF POTENTIAL ANALYSIS TOPICS & NEXT STEPS

Potential Analysis Topics

FDA's opioids systems model addresses a wide range of topics pertaining to the opioid crisis, with particular focus on aspects of the crisis most pertinent to interventions that may exist within FDA's purview. We continue to invest in research and modeling work to expand the model's depth and scope. At the time of any analysis, some questions may be well suited to the model's existing capabilities, while other questions may require new model structure or otherwise fall outside the model's scope. Based on the importance of a given question and the resources required to analyze it, modeling analysts, as part of the Opioid Systems Analytics Service, will work with FDA's opioids and policy experts to assess what parts of the question can be addressed within the scope of the model. In its current state, the model can address policy questions related to prescribing practices, naloxone distribution, and treatment, among other topics. These topics are not indicative or representative of what regulatory actions or policies FDA is currently considering or anticipating; rather, they are potential use cases for the model. Figure 4 includes example questions that the model has been designed to provide insight into.

Figure 4: Sample policy analysis topics

TOPIC	EXAMPLE QUESTIONS
Prescribing practices	**What if prescribing guidelines changed for all or a subset of indications?** *What if these guidelines changed the total number of people receiving an opioid prescription? The average morphine milligram equivalents per prescription? The average prescription duration?* **What if additional abuse-deterrent formulations were introduced to the market?** *What if these formulations replaced non-abuse-deterrent formulations? What if abuse-deterrent formulations were removed from the market?* **What if a specific opioid drug or class of drugs was removed from the prescribed market?** *What if a new opioid drug was added to the prescribed market?*
Naloxone distribution	**What if the probability of naloxone administration changed?** *What if the probability of naloxone administration by bystanders increased? Law enforcement officers? What if naloxone was universally available over-the-counter? What if harm reduction and treatment programs distributed naloxone for free?* **What if the probability that there is a timely overdose intervention changed?** *What if naloxone could be administered more quickly in the presence of a fentanyl overdose?*
Treatment	**What if treatment capacity for people with use disorder increased?** *What if the prescribing waiver policy changed? What if pharmacists could prescribe medication for OUD?* **What if intake delays for treatment programs decreased?** *What if access to telehealth increased? What if prior authorization requirements changed?* **What if treatment-seeking increased?** *What if increased treatment engagement created a feedback loop whereby more people entered treatment as a result of social influence (i.e., observing other enter treatment and remission)?* **What if outcomes (i.e., remission) for people in treatment improved?** *What if the rate of relapse out of treatment reduced? What if average duration in treatment changed?*

Next Steps

Over the last two years, the collective efforts of the Workgroup and our collaborators have focused on model development and quantification. With the completion of an initial version of the model imminent, we are shifting focus to exploratory use of the model within FDA and incorporation of model enhancements.

Our intent is to continue to enhance the model as the crisis – and our collective understanding of it – evolves. The Workgroup has partnered with Booz Allen Hamilton to develop formal plans for model maintenance and strategic use of the model. Funded research projects to support future model enhancements include efforts to improve quantitative estimates related to utilization of treatment for use disorder and incorporation of cost effectiveness and social outcomes (e.g., pain, quality of life) into model analyses.

In late 2020, FDA will begin exploratory use of the model, through the Opioid Systems Analytics Service, to inform decision-making. Within the next year, we will work to submit peer-reviewed publications detailing the model and initial findings.

We believe that the FDA opioid systems model has the potential to serve as a valuable tool to help FDA and others assess the system-wide impacts of changes to the opioid crisis and identify areas for further research. We recognize that this model is only one step toward addressing the crisis. We strive for full model transparency and collaboration across stakeholders, in hopes that this work contributes to the broader FDA goal of furthering the public health.

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