INTRODUCTION TO FDA'S OPIOID SYSTEMS MODEL

A WHITE PAPER

Office of Program and Strategic Analysis
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

March 2021

TABLE OF CONTENTS

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: 1) to help FDA and other stakeholders identify high-impact interventions; 2) to assess potential unanticipated consequences of policies; and 3) to identify needs for further research. Model development began in 2018 and has involved a strong collaboration of experts across opioids, modeling, and policy domains. To date, this effort has produced an initial model and a framework for its use in policy analysis. Continued work 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 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.

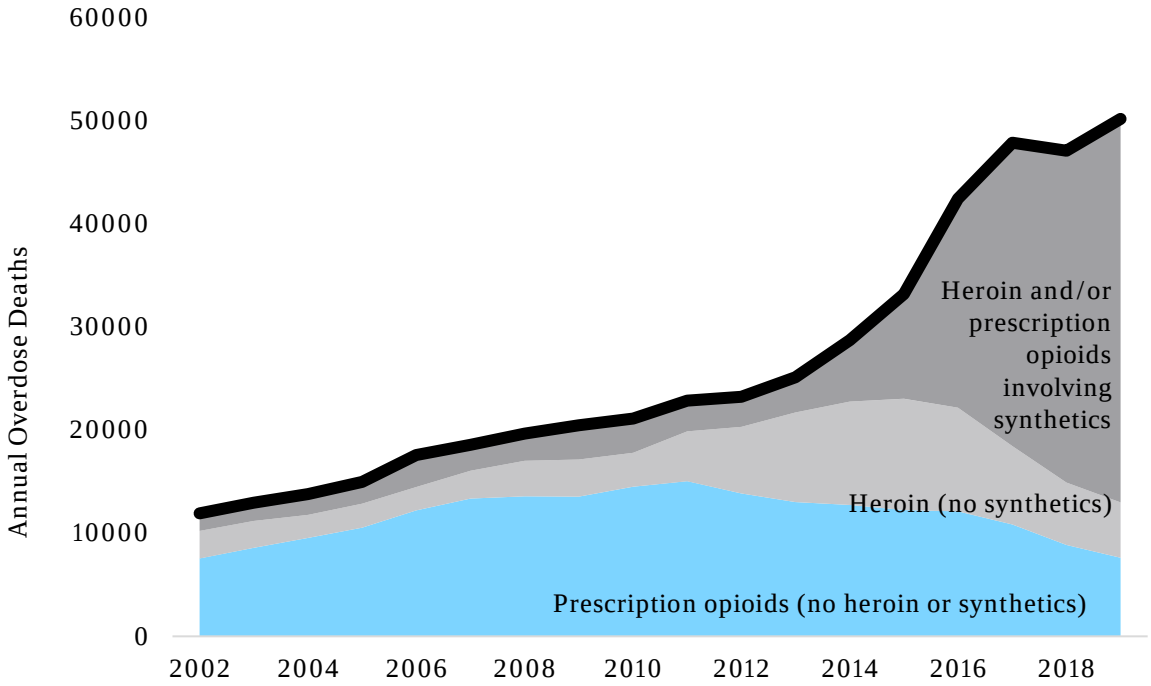
INTRODUCTION TO FDA'S MODELING EFFORT

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 2019, over 50,000 people lost their lives to overdoses involving opioids—more than four times the roughly 12,000 people who lost their lives to the same cause in 2002. Cumulatively, over 471,000 people lost their lives to overdoses involving opioids between 2002 and 2019.[1] As illustrated in Figure 1, while prescription opioids*,[2] were responsible for most overdose deaths early in the crisis, deaths involving heroin and illicitly-manufactured synthetic opioids, primarily fentanyl, have increased rapidly over the last ten years.[3] 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.

* In this context, prescription opioids (may also be referred to as Rx Opioids) include opioid analgesic medications prescribed for pain, such as morphine, hydrocodone, and oxycodone, as well as prescribed synthetic opioids like fentanyl.

Figure 1: Overdose Deaths Involving Opioids, 2002-2017[4]



FDA's Role in Responding to the Crisis

As the agency responsible for regulating opioid medications marketed in the United States, 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.[5] FDA detailed an approach to reducing the misuse of opioids in a "2018 Strategic Policy Roadmap".[6] For additional information on FDA's response to the opioid crisis, see FDA's homepage for opioid medications.[7]

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 opioid 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.** The physiological, social, and organizational influences on individuals' interactions with opioids are complex. This heterogeneity makes it difficult to understand underlying mechanisms, identify patterns, and predict effects of interventions.

2. **Myriad stakeholders are involved in the crisis response**, each with their own jurisdiction, priorities, capacities, and constraints. Coordination across these stakeholders is challenging, and ineffective coordination can result in unintended consequences.
3. **There are delays between actions and effects**, which complicates assessment of causes 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.** The landscape of opioid prescribing has fluctuated greatly over the past 30 years. There are multiple actions and drivers in effect at any given time, so discerning the impact of any singular action in isolation is challenging.
6. **Data gaps limit our understanding of the crisis.** The complexity of the crisis coupled with limitations of current data leave large uncertainties about many important and interconnected aspects of the crisis, such as the prevalence of opioid use and polysubstance use, risks of overdose, the development and progression of substance use disorders, and the effects of treatment.[8]

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

The Value of Systems Modeling

In 2017, at the request of FDA, National Academies of Science, Engineering and Medicine (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.[9]

Systems modeling combines systems thinking and computerized simulation to quantitatively model complex systems. In so doing, it can assist policy makers in exploring potential future states of the crisis, and assess how the future may be affected by policy changes, in both intended and unintended ways. 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 important reinforcing or balancing feedbacks within the boundary of the model (i.e., endogenously), 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.
- **Supporting purposeful discussions.** Analysis conducted with models (employing a user interface to explore different scenarios in real-time) can facilitate interactions among experts and policy makers to build a shared understanding of underlying phenomena, key assumptions, and potential effects.

System dynamics models have often been used for decision support; notable examples include the Millennium Institute's Integrated Sustainable Development Goals model,[10] Climate Interactive's C-ROADS climate change policy simulator,[11] and ReThink Health's regional health systems model.[12] Similar models have been used to inform policy-making and analysis in various parts of the Federal Government, including the Department of Health and Human Services' tobacco control simulation models,[13] the Department of Defense's Project Stoddert,[14] and the Department of Energy's Integrated Framework for Modeling Multi-System Dynamics.[15]

The umbrella of systems modeling encompasses several different modeling approaches. FDA's model of the opioid crisis employs a system dynamics approach, which emphasizes endogenous feedback processes and changing behaviors over time.[16,17] Other systems modeling and opioid research teams have already undertaken similar efforts, applying a range of systems approaches to examine the crisis.[18, 19] Previously published opioids modeling efforts, however, are limited in that they do not include aspects of the crisis of particular relevance to FDA's regulatory context, were constructed prior to the fentanyl surge, do not make full use of other relevant existing data (e.g., prescribing data), or have narrow model boundaries that do not account for important feedbacks (e.g., regarding the role of risk perception). Therefore, FDA's effort aligns with both NASEM's and other researchers' call for more applications of systems modeling in the opioid space.[20]

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: 1) to help FDA and other stakeholders identify interventions that have potential to yield high-impact gains in the crisis; 2) to assess the intended and potential unanticipated consequences of policies or actions that may be considered; and 3) to identify needs for further research to address uncertainties that have the greatest effect 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 modeling effort. The Workgroup consists of experts in decision science, modeling and data analysis, economics, and evaluation.[21] 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).[22] Through this research collaboration, model development has been guided by a team of 13 renowned opioid and system dynamics modeling experts, as well as 13 expert advisors.[23]

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. FDA began using 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 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 represents populations in each opioid use state as state variables (similar to compartment models used in epidemiology), and incorporates dynamic transition rates, such as estimates of 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.[24] A follow-up meeting occurred in October 2020 and focused on the process of translating questions from decision-makers into model analyses and results.

OVERVIEW OF THE MODEL

Model Scope

The FDA model focuses on tracking people through various opioid use states and characterizing 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 the U.S. 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 opioid 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, each of which is defined below. Note, although therapeutic use, as shaped by prescribing practices (depicted in Figure 2), is not represented as an explicit use state, it is included as one potential pathway to the initiation of misuse and potentially use disorder.

Misuse: Misuse captures people who engage in the nonmedical use of prescription opioids as defined in the National Survey on Drug Use and Health (prior to 2015): use of one's own medication for reasons other than pain (e.g., for the feeling it causes), or any use of another individual's medication for any purpose, including the feeling it causes.[†] It also includes use of heroin or illicit opioids that does not rise to the level of disorder (i.e., non-disordered use).[25]

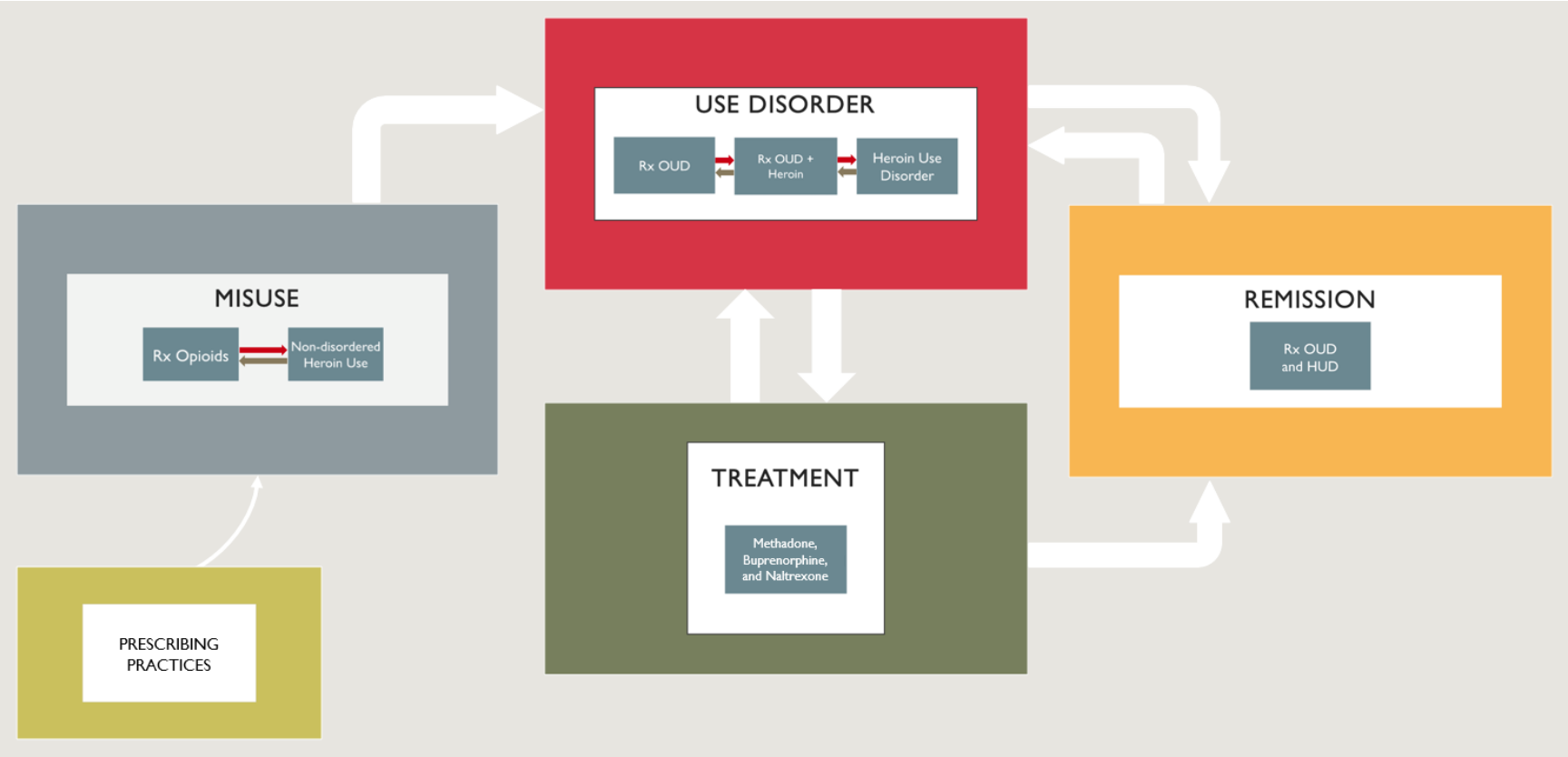
Use disorder: Use disorder captures people who meet the use disorder criteria described by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for prescription opioids and/or heroin.[26] The model differentiates people with opioid use disorder (OUD) whose use is limited to prescription opioid use (Rx OUD) and 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 naltrexone (also known as 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. [27] The model represents groups of people who are in remission and not currently in treatment.

[†]Prior to 2015, use of one's own medication not as directed but specifically to treat pain is not considered misuse by NSDUH. Post-2015, NSDUH considers any use of one's own medication not-as-directed to be misuse. This difference has been accounted for in the model by adjusting the post 2015 NSDUH data.

Figure 2: Misuse, Use Disorder, Treatment, and Remission Structure



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.

Model Quantification

Model quantification is a complex process including iterative consultation of literature and experts, calibration to historical data, and extensive testing. Our forthcoming technical publication will describe the quantification process and data sources in more detail. 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®.

Additionally, like every model, this model is predicated on a number of assumptions, derived by expert opinion and literature review and undergo sensitivity testing. All assumptions are fully documented and as part of the modeling and analysis process, any assumption can be further tested and modified.

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. [28] 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. Notwithstanding these limitations, the model replicates historical trajectories reasonably well while providing quantified uncertainties in near-term projections. Both estimated and assumed model inputs can also be easily varied to test for sensitivity to these assumptions and limitations in the process of analysis.

In some cases, data limitations necessitate scope limitations. For example, the model does not explicitly represent treatments for OUD that do not incorporate one of the three FDA-approved medications. Mental health and other health comorbidities, as well

as polysubstance use, are also currently not included in the model on the basis of limited data and the complexity of their relationship to the opioid crisis. Future research is planned to to appropriately incorporate 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 the 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. These analyses 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 about 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 2021.

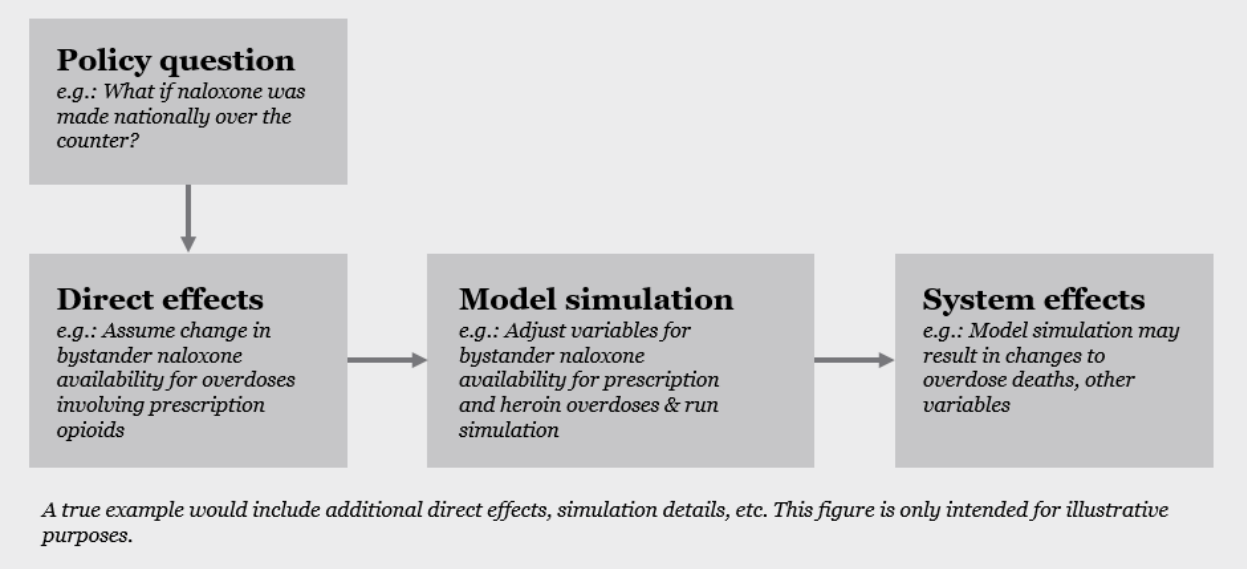
Inevitably, policy questions will not always fit clearly into one category. Depending on the analysis goals and questions, both approaches or a hybrid approach could be applied. With support from Booz Allen Hamilton, we are developing a policy simulation

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 increasing the availability of naloxone. The model is best designed to address strategic, "what if" questions (e.g., What if naloxone was available over the counter in every U.S. state?), rather than operational questions (e.g., How should the public be educated about naloxone availability?). 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 judgment to inform assumptions about the direct impacts of potential policies or changes. In the case of over-the-counter naloxone, for instance, we may assume (among other assumptions) that the availability of naloxone to bystanders witnessing an overdose involving prescription opioids changes by some percentage over some time period. (It is important to note, of course, that the accuracy of important assumptions is paramount to a successful policy outcome and not guaranteed in any particular case.)

These assumptions are used as inputs into the model, or changes to relevant model values (e.g., the parameter for "bystander naloxone availability for prescription overdoses"). The model simulates the effects of these changes and shows outcomes across model variables. For instance, a change in the availability of naloxone may affect 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.

POTENTIAL ANALYSIS TOPICS & NEXT STEPS

Potential Analysis Topics

FDA's opioid systems model was developed first and foremost to support the FDA mission to address the opioid crisis. Using it, FDA will continue to address 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 and within the constraints posed by data limitations. In its current state, the model can best address policy questions related to prescribing practices, naloxone distribution, and OUD treatment, among other topics. Figure 4 includes example questions. These topics are not necessarily indicative or representative of what regulatory actions or policies FDA is currently considering or anticipating; rather, they are potential use cases for the model.

We continue to 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, our modeling experts will assess what parts of the question can be addressed within the scope of the model and whether any expansions in scope are warranted.

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 size or duration per prescription?* **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 prescription drug market?** *What if a new opioid drug was added to the prescription drug market?*
Naloxone distribution	**What if the probability of naloxone administration changed?** *What if the probability of naloxone administration by bystanders increased? By law enforcement officers? What if naloxone was available over-the-counter in every U.S. state? What if harm reduction and OUD 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 opioid 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 others enter treatment and remission)?* **What if outcomes (i.e., remission) for people in treatment improved?** *What if the rate of relapse out of treatment decreased? 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 opioid use disorder and incorporation of cost-effectiveness and social outcomes (e.g., pain, quality of life) into model analyses.

In 2021, 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.

---

[1] Ahmad FB, Rossen LM, Sutton P. (2020) Provisional drug overdose death counts. National Center for Health Statistics.
[2] *Opioid Medications*. (2020, August 4). U.S. Food and Drug Administration. https://www.fda.gov/drugs/information-drug-class/opioid-medications
[3] National Center for Health Statistics. (2020, January). *NCHS Data Brief* (No. 356). https://www.cdc.gov/nchs/products/databriefs/db356.htm
[4] Ahmad FB, Rossen LM, Sutton P. (2020) Provisional drug overdose death counts. National Center for Health Statistics.
[5] *What We Do*. (2018, March 28). U.S. Food and Drug Administration. https://www.fda.gov/about-fda/what-we-do
[6] U.S. Food and Drug Administration. (2018, January). *Healthy Innovation, Safer Families: FDA's 2018 Strategic Policy Roadmap*. https://www.fda.gov/media/110587/download
[7] *Opioid Medications*. (2020, August 4). U.S. Food and Drug Administration. https://www.fda.gov/drugs/information-drug-class/opioid-medications
[8] Jalali, M.S., Botticelli, M., Hwang, R.C. et al. The opioid crisis: need for systems science research. Health Res Policy Sys 18, 88 (2020). https://doi.org/10.1186/s12961-020-00598-6
[9] National Academies of Sciences, Engineering, and Medicine. 2017. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24781.
[10] *iSDG: Integrated Simulation Tool*. (2020). Millennium Institute. https://www.millennium-institute.org/isdg
[11] *C-ROADS*. (2020, January 15). Climate Interactive. https://www.climateinteractive.org/tools/c-roads/

[12] Rippel. (2019, October 16). *Dynamics Model*. Rethink Health. https://www.rethinkhealth.org/our-work/dynamics-model/
[13] U.S. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
[14] *Project Stoddert, A System Dynamics Model of Affordability Using Utility Theory | SBIR.gov*. (1997). U.S. Small Business Administration. https://www.sbir.gov/sbirsearch/detail/310290
[15] *An Integrated Framework for Modeling Multi-System Dynamics*. (2016). Earth and Environmental System Modeling. https://climatemodeling.science.energy.gov/projects/integrated-framework-modeling-multi-system-dynamics
[16] Sterman, J. D. (2000). *Business dynamics: Systems thinking and modeling for a complex world*. Boston: Irwin/McGraw-Hill.
[17] Forrester, Jay W. (1961). *Industrial dynamics*. Cambridge, Mass : M.I.T. Press
[18] Pitt AL, Humphreys K, Brandeau ML. Modeling Health Benefits and Harms of Public Policy Responses to the US Opioid Epidemic. *Am J Public Health*. 2018;108(10):1394-1400. doi:10.2105/AJPH.2018.304590
[19] Wakeland, W., Nielsen, A., & Geissert, P. (2015). Dynamic model of nonmedical opioid use trajectories and potential policy interventions. *The American journal of drug and alcohol abuse, 41*(6), 508–518. https://doi.org/10.3109/00952990.2015.1043435
[20] Jalali, M.S., Botticelli, M., Hwang, R.C. et al. The opioid crisis: need for systems science research. Health Res Policy Sys 18, 88 (2020). https://doi.org/10.1186/s12961-020-00598-6
[21] Members of the FDA Workgroup include: Reza Kazemi-Tabriz, Sara Eggers, Emily Ewing, Tse Yang Lim, Lukas Glos, Calvin (Blake) Bannister, and Blair Coleman Nesmith.
[22] U.S. Food and Drug Administration. (2019, May 9). *RFA-FD-19-026: Cooperative Agreement to Support Regulatory Research Related to the 2018 Prescription Drug User Fee Act and the 21st Century Cures Act (U01) Clinical Trials Not Allowed*. Grants.Nih.Gov. https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-19-026.html
[23] *Opioid Systems Modeling*. (2020). Harvard.Edu. https://projects.iq.harvard.edu/osm
[24] Jalali MS, Ewing E, Bannister CB, Glos L, Eggers S, Lim TY, Stringfellow E, Stafford C, Pacula RL, Jalal H, Kazemi-Tabriz R. Data Needs in Opioid Systems Modeling: Challenges and Future Directions. American Journal of Preventive Medicine (forthcoming)
[25] Substance Abuse and Mental Health Services Administration. (2012). *2012-2013 National Survey on Drug Use and Health: Guide to State Tables and Summary of Small Area Estimation Methodology*. https://www.samhsa.gov/data/sites/default/files/NSDUHStateEst2012-2013-p1/Methodology/NSDUHsaeMethodology2013.htm
[26] American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5* (5th ed.). American Psychiatric Publishing.
[27] American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5* (5th ed.). American Psychiatric Publishing.
[28] Jalali MS, Ewing E, Bannister CB, Glos L, Eggers S, Lim TY, Stringfellow E, Stafford C, Pacula RL, Jalal H, Kazemi-Tabriz R. Data Needs in Opioid Systems Modeling: Challenges and Future Directions. American Journal of Preventive Medicine (forthcoming)