Qualify AI Drug Discovery Tools through FDA ISTAND Program to Model Responsible Drug Discovery AI and Mitigate Dual Use Concerns

[Rachel Cherney](#)[1], [Rami Major](#)[1], [Tara Fitzpatrick](#)[2]

[1]University of North Carolina at Chapel Hill, Curriculum in Genetics and Molecular Biology, Chapel Hill, NC, USA

[2]University of North Carolina at Chapel Hill, Department of Environmental Sciences and Engineering, Chapel Hill, NC, USA

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Corresponding author: rcherney@email.unc.edu

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Executive Summary: Artificial intelligence (AI) is poised to revolutionize many fields of science and technology. One field that stands to benefit significantly is drug discovery, which is a time-consuming and expensive process. AI can predict compounds and some of their relevant characteristics, including their efficacy and toxicity. In doing so, AI can help refine the pool of potential compounds that progress in the drug discovery pipeline, while excluding those that will later likely prove to be too toxic or ineffective (Tran et al. 2023). Essentially, AI can make the early stages of drug discovery more efficient by helping to avoid unnecessary human clinical trials and prevent costly, late-stage failures (Tran et al. 2023). Yet, as drug design AI capabilities burgeon, so does the concern that these algorithms could be used for malicious purposes, such as harnessing AI to instead predict compounds that are both highly effective and highly toxic, posing biosecurity risks. Although concerns about the dual-use potential of AI are warranted, there is great potential for AI's beneficial application in drug discovery, so eliminating the use of AI in this space altogether is undesirable. We recommend that the Food and Drug Administration (FDA) place a special call for submissions of drug design AI with safeguards in place to prevent dual-use to its Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program. This would allow the FDA to open up a line of communication with drug design AI creators, educate the broader public on the potential for dual-use of these technologies and emphasize the need for safeguards, and select a drug design AI that models responsible AI applications for the field at large.

I. Introduction

Recent amalgamation of faster computer processing, larger data libraries, and a growing pool of AI-talent has catalyzed the rapid development and adoption of powerful AI tools (Bohr & Memarzadeh 2020). People already engage with numerous technologies that leverage AI, including customer support chat-bots, navigation apps that predict traffic flows and optimize routes, and text-editors and grammar checks (Reeves 2023). Furthermore, tools like the language model, ChatGPT, the text-to-graphic generator, Dall-E 2, and the automated music generator, Soundraw, allow people and companies alike to use powerful AI technologies for the pursuits of their choosing (Marr 2023). The drug discovery space is particularly poised to benefit from this boom since specialized AI applications show great potential for generating novel compounds. This, in turn, could boost the earliest phases of drug design, helping to accelerate the identification and creation of promising drug candidates (Mouchlis et al. 2021). However, risks posed by open-access, dual-use drug technology come with elevated gravity, as nefarious actors could design compounds that are

intentionally toxic, addictive or produce inequitable impacts (Sohn 2022). In fact, a pharmaceuticals company found that toggling their drug discovery AI program to predict the most toxic compounds to humans could be accomplished in just six short hours (Urbina 2022).

The federal government has attempted to regulate the drug discovery space and incentivize progress. Congress passed the 21st Century Cures Act in 2016, which set aside $500 million dollars over nine years for the Food and Drug Administration (FDA) with the goal of accelerating the development and review of innovative medical technologies, including those related to drug development (21st Century Cures Act 2016). The Cures Act introduces the process of qualification for drug development tools (DDTs) to accelerate approval across the pipeline. DDTs are "methods, materials, or measures that have the potential to facilitate drug development", such as biomarkers and clinical outcome assessments (US Food and Drug Administration 2023b). When a DDT is qualified, this entails "a determination by the Secretary that a [DDT] and its proposed context of use can be relied upon to have a specific interpretation and application in drug development and regulatory review under [the Cures Act]" (21st Century Cures Act 2016). A qualified DDT would be publicly available and open for use in any new drug development program, allowing its use in a variety of drug submissions to the FDA without the DDT itself necessitating subsequent FDA review (US Food and Drug Administration 2023a). However, it is unclear how drug discovery regulation would apply to AI.

The technology's rapid growth, paired with its potential to yield novel compounds that could be intentionally designed for harm, or employed as biological ammunition, emphasizes the need for proactive regulatory action. Therefore, we will introduce and discuss three policy responses aimed at preserving and supporting access to the beneficial sides of AI in drug development, while mitigating the risks posed by potential nefarious actors employing the technology to cause harm. Our first option consists of placing a temporary pause on open-source AI-powered DDTs, our second proposes expanding the FDA's oversight for life science research that has dual use risks to include AI-powered DDTs, and our third entails calling for drug design AI algorithms to be submitted to the

FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program.

II. Policy Options

i. Option 1: The FDA supports a temporary moratorium on open-source AI-powered DDTs
Employing AI DDTs necessitates reckoning with the technology's dual-use potential, especially in open-access contexts. Open-access AI provides transparency, promotes innovation, and gives developers the power to wield and adapt the technology in the domains of their choosing (Forbes 2019). Yet, such innovation and freedom often come at the expense of oversight and regulation. Given that the improvement and proliferation of AI has outpaced both regulatory response and research, these risks necessitate urgent action. The Future of Life Institute, an organization aimed at reducing existential risks posed by AI, petitioned for a six-month moratorium on large scale experiments training and developing powerful AI systems, which has amassed over 27,000 signatures from people working in and adjacent to technology (McNamee 2023). The FDA could support a temporary moratorium specifically on developing and using AI DDTs to give themselves, researchers, and other agencies the time needed to create risk-mitigating policies and safeguards.

Advantages
A pause on open-sourced AI-powered DDTs would give the FDA the opportunity to prepare for future iterations, design and implement guardrails, and cultivate a society educated on the social and ethical dimensions of AI. Such an intervention could be an impetus for pivoting the field's focus and resources towards creating a regulatory architecture capable of optimizing and sustaining AI. The EU's High-Level Expert Group on AI identified ethical principles that AI applications are expected to meet: respect for human autonomy, prevention of harm, fairness, and explicability (Van de Poel 2020). By suspending the race-to-develop, a pause could foster interdisciplinary collaboration among a range of stakeholders in the United States to identify societal values and goals for the technology and craft a shared mission. Consequently, the FDA would be better positioned to create policies, grounded in ethical principles and intentions, to realize those aims. For example, regulation could shape how tools

collect, use, and store personal data, thereby addressing potential security weaknesses, while reflecting societal values of privacy and confidentiality (Center for American Progress 2021). Similarly, a supposed value of transparency could be incorporated into a range of policies surrounding AI, potentially manifesting in expectations around disclosing how a model was trained or garnering informed consent from people engaging with a system.

Broadly, this iterative and intentional process would provoke discussion, rousing a society that is posited to be impacted by an increasingly powerful technology. Given that AI stands to revolutionize pharmaceutical development, educating students, industry professionals, and consumers alike is imperative, and would be more feasible if the dynamic field was temporarily stabilized. The pause could then serve as an inflection point, after which society progresses forward with policies and careful consideration for mitigating AI's dual-use potential.

Disadvantages
The Future of Life Institute's petition calls for all AI labs to agree upon a "public and verifiable" pause on AI development, and if such cannot be enacted upon and implemented quickly, the petition calls for government intervention (Future of Life 2023). Regardless of industry, it's difficult to foresee all involved labs, researchers, and actors voluntarily stopping training and developing their models, especially if they think they could gain a competitive advantage by continuing to work during a pause. The efficacy of this option rests on the assumption that nefarious actors would be restricted, and since they would not be incentivized to voluntarily comply, an enforceable directive or intervention would likely be needed to ensure the moratorium is unilateral. However, enforcing a nation-wide moratorium on the training of large AI systems would be an ambitious and unprecedented move against a fairly new technology, and there is "no US federal or state government entity that has clear legal authority" to issue such (Villasenor 2023). Verifying compliance would require significant resources and personnel, and it would be challenging to detect if a company is continuing to train their AI models behind closed doors (Villasenor 2023). Some regulated industries can more easily be monitored by tracking their associated inputs and activities; for example, nuclear

weapons require materials that are hard to come by, work with, and hide or disguise from oversight, whereas the inputs training AI tools are essentially data and computing power, and therefore enforcement would likely rely on, in part, whistleblowers (Villasenor 2023). Overall, the logistical and legal weight of enforcing a moratorium is dubious, and the FDA would likely be immediately challenged in court if they attempted to do so, since they don't have clear legal authority to intervene on companies, organizations, and researchers, private and public, across the industry. Drawn-out court proceedings would drain resources and waste time that could be better used regulating AI in tandem with its continued growth and diffusion.

Additionally, a temporary moratorium would impede economic growth by stifling innovation and compromise the benefits of open-source AI. Stifling innovation in this space could be hard to justify, especially given the critical need for new drugs for conditions with few or no effective treatments. While a freeze could prevent pernicious applications, it would do so at the cost of restricting well-intended actors in the short-term and jeopardizing the community's ecosystem in the long-term (Engler 2021).

i. Option 2: Expand the scope of FDA's Dual Use Research of Concern (DURC) to include AI DDTs
Dual Use Research of Concern (DURC) is life science research, including bioinformatics and modeling, that has the potential for misuse in ways that can harm the environment, human health, or national security. To mitigate potential DURC threats, the United States Government (USG) issued a policy for all federally funded research, requiring that each federal department and agency implement a governing body for regular review of high consequence DURC research in order to mitigate any potential risks and to gather information for development of updated policies for DURC oversight. Regular review of DURC research includes biannual reports to the Department of Homeland Security and Counterterrorism on DURC projects and proposals, including risks and implemented or planned methods to mitigate risks. In 2013, the FDA established an Institutional Biosafety Committee (IBC) which reviews FDA research involving DURC (US Food and Drug Administration 2013).

The federal DURC policy currently comprises 15 pathogens and toxins such as anthrax or the plague; however, the USG is open to expanding the scope to include additional agents, and states it is up to the discretion of institutions to evaluate and expand their oversight to include additional types of DURC. The increased use of AI in biomedical sciences, combined with the current lack of regulations, could lead AI DDTs to be considered DURC. Expanding the FDA's IBC DURC scope to include AI DDTs would require projects funded by the FDA to have their research reviewed by the FDA's IBC. Regular review of FDA DURC research would maintain vigilance over the development of AI DDT and would require immediate action to rectify any identified risks (US Department of Health and Human Services 2015).

Advantages

The FDA structure of drug and medical device regulation has been touted as a paradigm for implementing AI regulation (US Chamber of Commerce 2023). By classifying AI DDTs as DURC, the FDA would continue to set an example of government and industry standards for responsible research regulations and would lead the development of regulation for AI use in biomedical research. This would apply to entities that are funded by or collaborate with the FDA. This option would set a framework through which to monitor dual-use concerns from bad actors using AI DDTs. The FDA already has a dual-use regulatory system in place, so expansion of it to cover AI DDTs would not require a lengthy program development process.

Disadvantages

Inclusion of AI DDTs in the FDA's DURC plan would only apply to FDA-funded research; other funding institutions would have to include AI DDTs in their own DURC plans for this policy to affect funding decisions more generally. Additionally, this option would not halt the fast pace of advancements made by AI DDTs; rather, it would allow the continued development and use of AI DDTs in the private sector without official regulatory or ethical considerations, unless any of the companies developing AI DDTs were receiving FDA funding. Additionally, due to the increase of AI DDTs, including them in the FDA's DURC scope may increase the amount of personnel required to efficiently screen projects, potentially resulting in a need to hire more employees, increasing FDA costs.

iii. Option 3: Increase visibility of the potential for dual-use AI DDTs by calling for submission of drug design AI algorithms to the ISTAND program.

The FDA's Center for Drug Evaluation and Research (CDER) has several programs under which DDTs can qualify, one of which is the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program, which attempts to keep pace with developments in the biomedical space. Unlike established DDT qualification programs like the Biomarker Qualification Program or the Animal Model Qualification Program, which expedite FDA regulatory approval when qualified biomarkers or animal models are used in the drug development process, ISTAND expands the scope of metrics that could inform DDT qualification and subsequent expedited approval pathways by encompassing technologies that are not as easily categorized or that are novel, like AI or tissue chip assays (US Food and Drug Administration 2021a, US Food and Drug Administration 2021b US Food and Drug Administration 2023b). When the ISTAND Pilot Program was announced in 2020, the FDA expected to accept 2-4 submissions annually (US Food and Drug Administration 2023b). However, only two submissions total have been accepted for qualification under the ISTAND Program: a molecular biologic that measures drug response (US Food and Drug Administration 2022) and a monitoring biologic that measures exposure (US Food and Drug Administration 2023c). The ISTAND home page specifically references the use of AI algorithms in clinical trial contexts — for patient evaluations, prediction of surrogate endpoints, and informing study design (US Food and Drug Administration 2023b). Although it is possible that the ISTAND would cover an AI DDT, this is not an example provided on the ISTAND home page, nor is there any clarification around whether such an algorithm would be qualified or relegated to an alternative outcome (US Food and Drug Administration 2023b). By calling for submission of an AI DDT for ISTAND qualification, the FDA can choose to model an exemplary algorithm that has safeguards in place to prevent dual-use and encourage widespread use of the algorithm.

Advantages

By calling for AI DDTs to be submitted to ISTAND, the FDA will increase visibility around the potential for

the dual-use of AI DDTs. This option would open a line of dialogue between the FDA as a regulatory body and companies seeking to utilize AI DDTs in their pipelines. Even if submission does not result in qualification, the FDA lists alternative paths through which submitters can receive more feedback on their technology, including drafting a white paper or FDA position statement, or organizing meetings between the FDA and the submitter. This option would allow the FDA to set standards for what AI DDTs should do, and what safeguards should be installed, before qualifying the DDT and therefore recommending it for broader use. The ISTAND program is already funded by the Cures Act and is not operating at its intended capacity, so the FDA should not incur additional costs from soliciting more specific submissions.

Disadvantages

The dual-use of AI DDTs is difficult to regulate, yet this option does not attempt to regulate AI DDTs nor does it mitigate the concerns of drug design AI being used for nefarious purposes. Although it seeks to increase dialogue between AI DDT creators and the FDA, calling for ISTAND submissions does not alone recommend any standards for companies to adhere to. It instead places the burden on independent bodies to create appropriate safeguards within their AI DDT. Further, a call for additional submissions does not guarantee that researchers will submit their AI DDTs. ISTAND qualification requires public availability of the DDT, which may not be amenable to companies that seek to commercialize their AI DDT, despite the potential rewards of qualification. If

the FDA wants to incentivize private companies to interface with them regarding their AI DDT, they could ensure that qualified AI DDTs that pose potential security risks would not be publicly available. This would likely necessitate the creation of a new program, as submissions that qualify under ISTAND would likely fall under the scope of the transparency provisions of the 21st Century Cures Act (21st Century Cures Act 2016). Alternatively, the FDA could call for AI DDT submissions to ISTAND without qualification, avoiding potential concerns of private companies that their AI DDT would become available to the public once qualified. Instead, the FDA could emphasize alternative ISTAND submission outcomes like increased dialogue with the FDA or publication of a white paper, which would still deliver benefits to the submitter.

III. Recommendation

To mitigate dual-use AI DDTs, we recommend implementing option 3. By specifically requesting submission of AI DDTs, the FDA ISTAND Program publicizes interest in reviewing AI in drug discovery and development. Through the process of being qualified, an AI DDT would be able to "be relied upon to have a specific interpretation" for its use, and would have developed safeguards in place to prevent misuse (US Food and Drug Administration 2023b). ISTAND would initiate dialogue around AI DDT oversight through its publicized interest and would model pathways for AI DTT management. As the power of AI exponentially rises, so must the degree to which it must be monitored to ensure use for the betterment of the world.

References

21st Century Cures Act, Public Law No. 114-225, 130 Stat. 1033 (2016). https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf

Bohr, Adam and Memarzadeh, Kaveh. 2020. "The Rise of Artificial Intelligence in Healthcare Applications." In *Artificial Intelligence in Healthcare*, edited by Adam Bohr and Kaveh Memarzadeh, 25–60. Cambridge: Academic Press. https://doi.org/10.1016/b978-0-12-818438-7.00002-2

Center for American Progress. 2021. "How To Regulate Tech: A Technology Policy Framework for Online Services," November 16, 2021. https://www.americanprogress.org/article/how-to-regulate-tech-a-technology-policy-framework-for-online-services/.

Engler, Alex. 2022. "How Open-Source Software Shapes AI Policy." *Brookings*, March 9, 2022. https://www.brookings.edu/research/how-open-source-software-shapes-ai-policy/

Future of Life Institute. 2023. "Pause Giant AI Experiments: An Open Letter." *Future of Life Institute,* March 22, 2023. https://futureoflife.org/open-letter/pause-giant-ai-experiments/

Marr, Bernard. 2023. "Beyond ChatGPT: 14 Mind-Blowing AI Tools Everyone Should Be Trying Out Now." *Forbes*, February 28, 2023. https://www.forbes.com/sites/bernardmarr/2023/02/28/beyond-chatgpt-14-mind-blowing-ai-tools-everyone-should-be-trying-out-now/.

McNamee, Roger. 2023. "There Is Only One Question That Matters with AI." *Time*, April 5, 2023.

https://time.com/6268843/ai-risks-democracy-technology/

Mouchlis, Varnavas D., Antreas Afantitis, Angela Serra, Michele Fratello, Anastasios G. Papadiamantis, Vassilis Aidinis, Iseult Lynch, Dario Greco, and Georgia Melagraki. 2021. "Advances in De Novo Drug Design: From Conventional to Machine Learning Methods." *International Journal of Molecular Sciences* 22(4): 1676. https://doi.org/10.3390/ijms22041676

Reeves, Sasha. 2023. "8 Helpful Everyday Examples of Artificial Intelligence." *IoT For All,* January 24, 2023. https://www.iotforall.com/8-helpful-everyday-examples-of-artificial-intelligence.

Sohn, Rebecca. 2022. "AI Drug Discovery Systems Might Be Repurposed to Make Chemical Weapons, Researchers Warn." *Scientific American.* https://www.scientificamerican.com/article/ai-drug-discovery-systems-might-be-repurposed-to-make-chemical-weapons-researchers-warn/

Tran, Thi Tuyet Van, Agung Surya Wibowo, Hilal Tayara, and Kil To Chong. 2023. "Artificial Intelligence in Drug Toxicity Prediction: Recent Advances, Challenges, and Future Perspectives." *Journal of Chemical Information and Modeling* 63(9): 2628–43. https://doi.org/10.1021/acs.jcim.3c00200

Urbina, Fabio, Filippa Lentzos, Cédric Invernizzi, and Sean Ekins. 2022. "Dual Use of Artificial Intelligence-powered Drug Discovery." *Nature Machine Intelligence* 4: 189-191. https://doi.org/10.1038/s42256-022-00465-9

US Chamber of Commerce. 2023. "Commission on Artificial Intelligence Competitiveness, Inclusion, and Innovation." March 29, 2023. https://www.uschamber.com/assets/documents/CTEC_AICommission2023_Report_v5.pdf

US Department of Health and Human Services (HHS). 2012. "United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern." March 28, 2012. https://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf

US Food and Drug Administration (FDA). 2013. "Establish the FDA Institutional Biosafety Committee". October 16, 2013. https://www.accessdata.fda.gov/scripts/fdatrack/view/track_project.cfm?program=operations&id=Operations-ESEM-Institutional-Biosafety-Committee

US Food and Drug Administration. 2021a. "Biomarker Qualification Program," July 7, 2021. https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program

US Food and Drug Administration. 2021b. "The Animal Model Qualification Process," August 5, 2021. https://www.fda.gov/drugs/animal-model-qualification-program-amqp/animal-model-qualification-process

US Food and Drug Administration. 2022. "DDT-IST-000006, Submission Title: Specificity Screening of Biotherapeutics for Improved Safety Profiling in IND Applications Using the Membrane Proteome Array (MPA)." July 1, 2022. https://force-dsc.my.site.com/ddt/s/ddt-project?ddtprojectid=156

US Food and Drug Administration (FDA). 2023a. "Drug Development Tool (DDT) Qualification Programs." April 6, 2023. https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs#:~:text=DDT%20acceptance%20in%20the%20drug,Cures%20Act%20(Cures%20Act).

US Food and Drug Administration (FDA). 2023b. "Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program." April 6, 2023. https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program

US Food and Drug Administration. 2023c. "DDT-IST-000015, Local Tolerance of Epidurally/Intrathecally Administered Leachables in Vitro." January 23, 2023. https://force-dsc.my.site.com/ddt/s/ddt-project?ddtprojectid=173.

Van de Poel, Ibo. 2020. Embedding Values in Artificial Intelligence (AI) Systems. *Minds & Machines* 30: 385–409. https://doi.org/10.1007/s11023-020-09537-4

Villasenor, John. 2023. "The Problems with a Moratorium on Training Large AI Systems." *Brookings,* April 11, 2023. https://www.brookings.edu/blog/techtank/2023/04/11/the-problems-with-a-moratorium-on-training-large-ai-system

Rachel Cherney recently received her Ph.D. in the Curriculum in Genetics and Molecular Biology from the University of North Carolina at Chapel Hill.

Rami Major is a fourth-year Ph.D. candidate in the Curriculum in Genetics and Molecular Biology at the University of North Carolina at Chapel Hill. Her research interests lie in the use of gene editing to treat disease from both a technical and ethical perspective. Beyond the bench, she is involved in many science policy, communication, and outreach initiatives, including as President of the Science Policy and Advocacy Group (SPAG) at the University of North Carolina at Chapel Hill.

Tara Fitzpatrick is a Master of Public Health Student, concentrating in Environmental Health Solutions, at the University of North Carolina at Chapel Hill. She is also completing a graduate certificate in Literature, Culture and Medicine. Her interests include environmental risk assessment, zoonotic and infectious disease, and climate change and health, as well as science communication and patient narratives.