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The Regulatory Landscape for Synthetic Biology

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Working Paper

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This publication was produced in collaboration with Rice University's Baker Institute for Public Policy. It has not been through editorial or peer review. Any errors are the authors' alone.

The Regulatory Landscape for Synthetic Biology

Executive Summary

Biotechnology is regulated in the United States via a mosaic of statutes enforced by three government agencies: Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and United States Department of Agriculture (USDA). This paper provides a broad overview of the United States' regulatory approach for biotechnology, describing specific pathways for oversight and gaps in regulation. We primarily focus on the EPA's Toxic Substance Control Act (TSCA) regulation of environmental applications and FDA's Food, Drug, and Cosmetic Act (FDCA). The majority of synthetic biology products produced by the synthetic biology will likely be regulated by one of these agencies. Anticipating regulatory pathways can inform how experiments are designed to facilitate a smoother assessment process. Researchers may identify ways that their work could inform regulatory gaps (i.e., gene transfer in complex open environments, frequency of off-target events in cell therapies). Finally, researchers can use their expertise to inform regulatory policy or decisions via public comments, meeting with policymakers, or other mechanisms. This document guides researchers towards areas where they can be more involved if they wish to engage in policy more directly.

Abbreviations: Code of Federal Regulations (CFR); US Department of Agriculture (USDA); US Environmental Protection Agency (EPA); US Food and Drug Administration (FDA); Genetically-Engineered Microorganisms (GEMs) (see Table 1 for more department/agency specific abbreviations).

Acknowledgements: Funding for this project was provided by grants from: Rice University's Synthetic Biology Institute (Matthews and Beth Beason-Abmayr), the Rita Allen Foundation Civic Science Fellow Award (Matthews and Johnson), and the National Science Foundation (#2223678). We thank Rice undergraduate students Elizabeth Craig, Caroline Snider, and Michelle Oyoo Abiero for their assistance in graphic design and referencing.

Introduction

In the United States, biotechnology regulation relies on a mosaic of statutes spread across three agencies: the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and the United States Department of Agriculture (USDA) (Figure 1, Table 1). This is collectively known as the Coordinated Framework (OSTP 1986). The US system focuses on the end result, employing a product-based regulatory system that focuses on characteristics and applications of the final product as opposed to the methods used to make the product. These characteristics and applications determine which regulations apply and which agency has oversight. In contrast, other jurisdictions (such as the United Kingdom) assess biotechnology based on a systems-based approach or how the product is made. Due to this product-based system, in the United States, it is possible for the product to be regulated across multiple agencies. For example, a genetically-engineered microorganism (GEM) that has a plant pest component would be regulated across two agencies. The plant pest component would be regulated by USDA under the Plant Protection Act and the EPA under the Federal Insecticide, Fungicide, & Rodenticide Act.

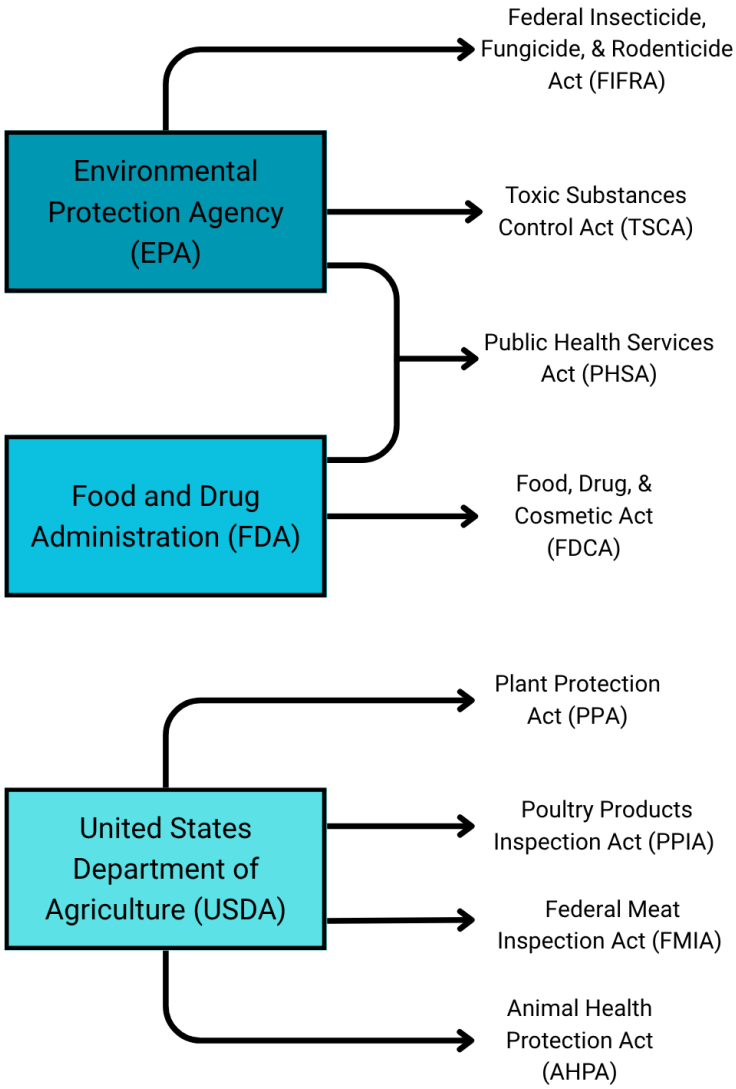
The US regulatory and governance structures oversee synthetic biology (SynBio) products with increased capability to design genetic circuits that do not exist in nature, synthesize genes *de novo*, and construct entire genomes. However, there is a "pacing problem" in which technology development outpaces the development of appropriate legal structures (Marchant 2011). As SynBio innovation moves from the lab to the real world, researchers should be aware of how the regulatory and broader political environment can impact the translatability of their work and vice versa.

An awareness of the regulatory structures of SynBio ensures that the intensive resources (e.g., time, money, and effort) that go into research and development are well-utilized. This lesson can be heeded from prior applications of gene-drives to eliminate disease-carrying mosquito populations. Oxitec developed a genetically-engineered mosquito that carried a "self-limiting" gene that prevents their offspring from surviving which ultimately drives down the mosquito population. This product has remained in regulatory limbo for more than ten years bouncing around between the FDA, USDA, and EPA before it was determined that the EPA has lead regulatory authority (Maxon 2023; George et al. 2025). In contrast, MosquitoMate, which infected the mosquito with *Wolbachia,* a naturally-occurring bacteria that was not genetically engineered, was ultimately approved by the EPA after six years. These technologies challenged the product-based regulatory system in the US. Although both companies had the same goal to decrease mosquito populations and mosquito-borne diseases, the difference in approaches (or process) resulted in different regulatory outcomes.

There are also regulatory gaps that exist due to a lack of evidence or lack of awareness of evidence. It is possible for researchers to identify how their studies may inform these regulatory gaps. For example, GEMs designed for bioremediation have had difficulty being approved by the EPA due to uncertainties in their long-term effects on native

microbial populations and broader ecosystems. One step in filling this gap may be identifying ways to study gene transfer events in complex environments. Another example is the uncertainty associated with long-term stability of genetically-engineered cell therapies.

Figure 1 — Statutes and Agencies Associated With Regulation of US Biotechnology



Sources: Authors' analysis; and OSTP 1986.

It is likely that the enforcement and interpretations of these regulations will change in the near future. The 2024 US Supreme Court Ruling in *Loper Bright Enterprises v. Raimondo* overturned the *Chevron Doctrine* and introduced an additional layer of uncertainty regarding the interpretations of regulatory policy in biotechnology (Kumar 2025). When regulatory decisions were challenged, *Chevron* compelled the courts to defer to agency interpretation of regulatory statutes in a two-step process. The 2024

court ruling created a precedent for federal judges to in interpret ambiguous rules and regulations instead of deferring to federal agencies in these cases. This means that the interpretation of highly technical, complex statutes may be more subject to the legal expertise of federal court judges, who are generalists by nature, than the scientific and technical expertise of federal agencies in these cases. The full scope of impacts of this change in agency deference is not entirely clear. However, this uncertainty makes it even more important for researchers to be aware of regulatory processes and how their work may be impacted.

Table 1 — Different Centers, Programs, and Terms Associated With the Agencies Regulating SynBio

Department/Agency	Associated Centers/Programs/Terms
US Department of Agriculture (USDA)	"Am I Regulated?" (AIR)
	Animal Plant Health and Inspection Service (APHIS)
	Biotechnology Regulatory Services (BRS)
	Petition for Determination of Non-Regulated Status (PDNS)
	Plant Protection Act (PPA)
	Regulatory Status Review (RSR)
	Sustainable, Ecological, Consistent, Uniform, Responsible, Efficient rule (SECURE rule)
US Environmental Protection Agency (EPA)	Engineered Microorganisms for Environmental Release (EMER)
	Generally Recognized as Safe (GRAS)
	TSCA Experimental Release Application (TERA)
	Toxic Substances Control Act (TSCA)
US Food and Drug Administration (FDA)	Cell and Gene Therapies (CGTs)
	Center for Biologics Evaluation and Research (CBER)
	Center for Drugs Evaluation and Research (CDER)
	Chemistry, Manufacturing, and Controls (CMC)
	US Department of Health and Human Services (HHS)
	Drug Product (DP)
	Drug Substance (DS)
	Food, Drug, and Cosmetic Act (FDCA)
	Human Cell- and Tissue-Based Products (HCT/Ps)
	Investigational New Drug (IND)
	Public Health Service Act (PHSA)

Source: Authors' analysis.

EPA Regulation of SynBio

The EPA is the primary agency responsible for regulating engineered microorganisms for environmental release (EMERs) outside of non-agricultural applications through Section 5 of TSCA. The Office of Pollution Prevention and Toxics is responsible for managing programs under TSCA. Applications like environmental biosensing, bioremediation, and biofuel production would qualify for TSCA regulation. TSCA is a notable exception to the product-based regulatory system in the United States as it specifies that intergeneric microorganisms are regulated. Intergeneric is defined as: "a microorganism that is formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera." Developments in DNA synthesis and engineering technology challenge this strict definition. For example,

the ability to build a synthetic genome based on a naturally occurring organism leaves a gray area as to how an organism would be regulated, if at all. However, the EPA has offered formal, though not codified, guidance regarding chemically synthesized genes. If a synthesized gene's sequence is identical to a known sequence that exists within the same genus of the recipient organism, it is considered intrageneric and thus not "new" (EPA 2012).

Figure 2 provides a flowchart overview of TSCA regulation. For researchers, the more immediate need will be a TSCA Experimental Release Application (TERA) which must be submitted at least 60 days prior to the initiation of the research activity. Information that needs to be included in a TERA is outlined in §725.255. The EPA has prepared a "Points to Consider" document to help researchers prepare for a submission for intergeneric microorganisms. Another option is to schedule a pre-submission meeting with the EPA.

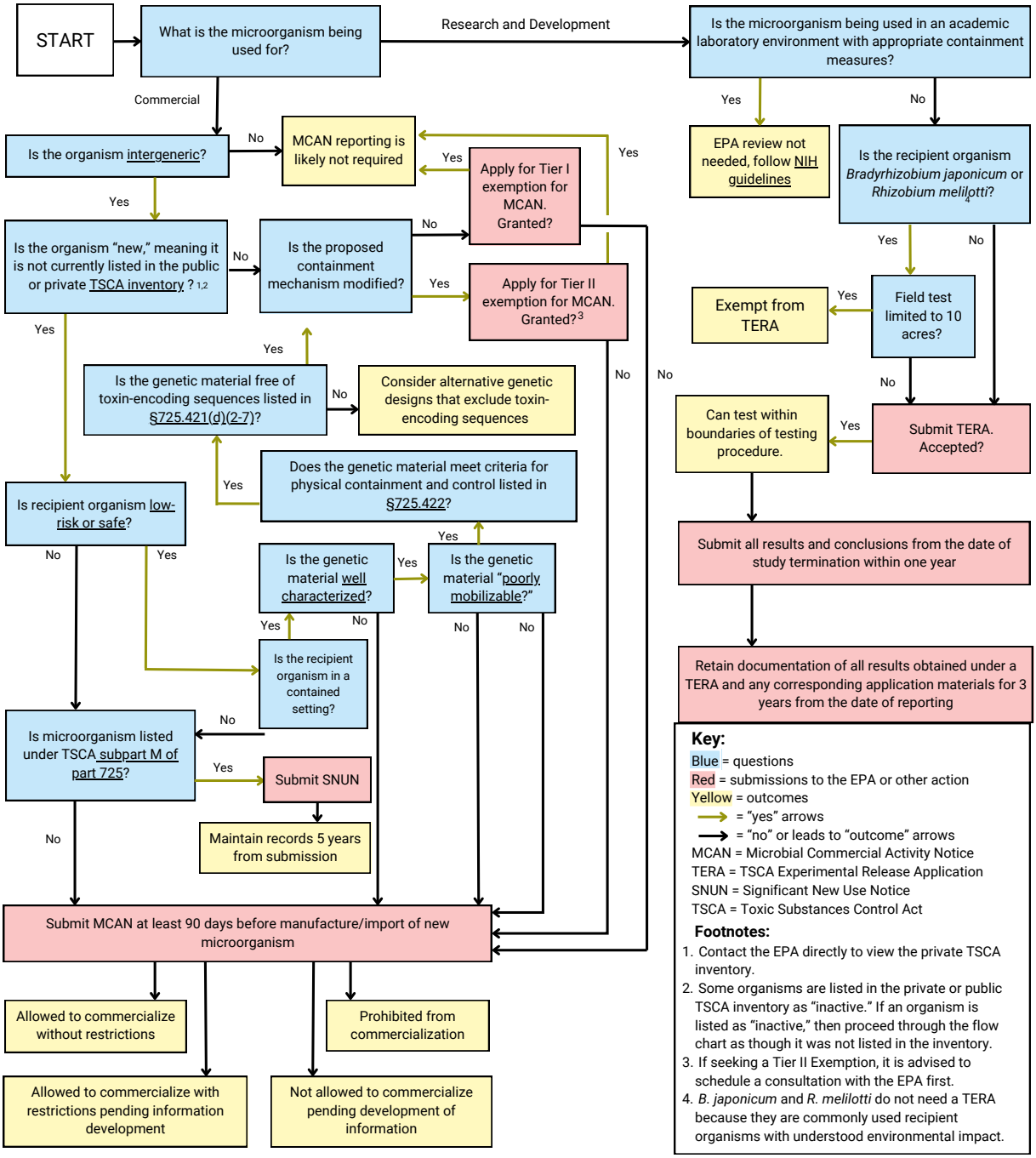
The submission of health and environmental effects data allows the EPA to be aware of any potential effects on human health or the environment of the new microorganism. The lack of environmental and health data on broader releases of engineered coupled with underdeveloped biocontainment mechanisms are a few reasons the EPA has not approved test releases of EMERs (Marken et al. 2024; Ezezika and Singer 2010). Researchers can submit their own data and use previously published data to fulfill this requirement. The data must cover the following topics: health effects, ecological effects, physical and chemical properties, environmental fate characteristics, and monitoring data and "other data related to human exposure to or environmental release of the new microorganism."

FDA Regulation of SynBio

The FDA, through the FDCA and PHSA, is the primary agency responsible for human SynBio applications including cellular and gene therapies (CGTs) under the US Department of Health and Human Services (HHS). The centers responsible for this regulation are the Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER).

The FDA also has regulatory authority over probiotics, including genetically engineered (GE) bacteria developed for therapeutic use in humans and for use as food additives. The regulatory pathway that probiotics fall into depends on its intended and marketed use. If the probiotic is marketed as helping or alleviating a broad, non-specific bodily function (e.g., "gut health" or "oral health"), then it would be classified as a supplement (Hoffman et al. 2014). Supplements are not required to undergo premarket approval processes but must follow good manufacturing practices. If a disease-specific claim is made for a probiotic (e.g., reducing inflammatory bowel disease), then this would trigger the investigational new drug (IND) process which would require clinical trials to determine efficacy and safety.

Figure 2 — EPA Regulation of Genetically-Engineered Microbes



Sources: Authors' analysis; 40 CFR Party 725; and Wozniak et al. 2012.
Note: EPA regulation consists of a series of questions (blue boxes) to determine when the EPA becomes involved (red boxes) and the different outcomes from EPA oversight (yellow boxes). Underlined text indicates a link that navigates to a section of the EPA Code of federal regulations.

The FDA's approach to regulating CGTs is still evolving due to the complexity of these therapies. For example, autologous and allogeneic therapies have different requirements due the differences in the donor for each therapy (i.e., self vs. an external donor that is a suitable match) (Jha et al. 2020). As a result, the FDA uses a variety of guidance documents to provide agency interpretations of policy and regulatory issues, especially for regulations of Human Cellular- and Tissue-based Products (HCT/Ps).

While guidance documents are non-binding and are not enforceable by law, they are critical to understanding how codified regulations are being implemented by the agency for CGTs. Regulatory statutes responsible for regulating CGTs include:

- 21 CFR Part 58 — Good Laboratory Practice for Nonclinical Laboratory Studies
- 21 CFR Parts 210 and 211 — Current Good Manufacturing Practices
- 21 CFR Part 1271 — Human Cells, Tissues, and Cellular and Tissue Based Products
- 21 CFR Part 312 — Investigational New Drug Application

The FDA has a process for developing these guidance documents and technical experts can use their knowledge to inform effective regulation and policies for cell therapies. Members of the public (e.g., researchers, industry officials, members of organizations, and advocacy groups) are invited to comment on draft documents. Public workshops or meetings are another avenue the FDA commonly uses to gather information. Documents open for comments and requests for information are posted in the Federal Register under "Current Issue." Researchers may also consider commenting on proposed rules and regulations using the US government's regulation website. These systems could change as HHS considers removing public comments from many HHS decisions.

Most genetically-engineered cell therapies will have to go through the IND process as they do not meet the requirement for minimal manipulation (Figure 3). The minimal manipulation exception, as the name implies, permits new innovations that do not substantially change a device, HCT/Ps, or technique nor introduces anything that could potentially increase risk for contamination (e.g., cells, enzymes, or solutions).

Researchers and sponsors are encouraged to contact the Office of Therapeutic Products (OTP) within CBER about setting up a Pre-IND or an Initial Targeted Engagement for Regulatory Advice on CBER/CDER Products (INTERACT) meeting. However, Pre-IND meetings only allow a maximum of 10 questions, so this time must be used wisely. Furthermore, a Pre-IND meeting is more appropriate if proof-of-concept and some preliminary toxicology studies have been completed. In contrast, an INTERACT meeting is more informal. It may occur earlier in research and development such as when preliminary proof-of-concept studies (with the intended clinical product) have been completed but toxicology studies have not yet been designed or conducted. Because the regulatory pathways can differ between each CGT product, these meetings

can help researchers identify what additional preclinical studies may be needed and/or whether planned studies are most appropriate.

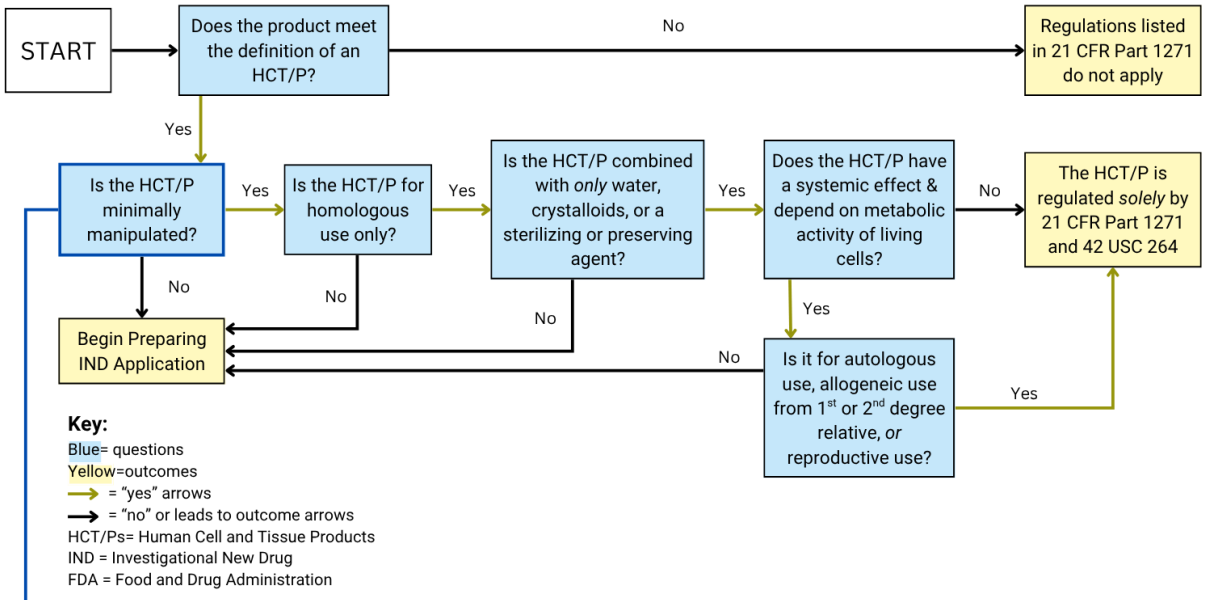
All INDs require preclinical studies that establish and confirm the potency, mechanism of action, long-term persistence, optimal dose selection, range, schedule, and route of administration, biochemical and physiological parameters (Table 2). There is no established set of experiments or studies to perform because CGTs are still relatively novel and vary in their applications, disease targets, and patient populations. These data provide a basis and rationale for patient eligibility criteria, clinical monitoring parameters, the dosage to give clinical trial patients, and identify potential safety risks (NIH SEED; Wensky 2019) provides a few examples of data that have been submitted within INDs for CAR-T cell therapy. The FDA also recommends that developers consider published preclinical or safety and risk data for the specific or similar CGT product in their study design.

To move into phase 1 human clinical trials, more extensive information on chemistry, manufacturing, and controls (CMC) are required. The type of information can slightly vary depending on whether the CGT uses microbial, human cells, or viral components. The main objectives of the CMC information are to ensure "product safety, identity, quality, purity, and strength of the investigational product" (Table 3).

Readers may notice that the terms drug substance (DS) and drug product (DP) are used. They are not to be used interchangeably. The DS refers to the "active pharmaceutical ingredient" that directly cures, mitigates, or treats the indicated disease (FDA 2020) that will be incorporated into the DP which is the "finished dosage form" (i.e. tablet, capsule, solution, etc.). Because of the difficulty to make a clear distinction between DS and DP, the FDA recommends that researchers and developers provide explanations for their designations of DSs and DPs in their IND application.

As with other therapeutics, HCT/Ps are required to go through three phases of clinical trials in humans to test safety and efficacy. These are negotiated with regulators and can be conducted in sequence, with some steps combined (such as conducting phase 1 and 2 trials concurrently), or steps can be repeated. Upon completion, FDA reassesses the data collected and a final decision is made regarding whether or not the therapeutic is ready for public distribution via a biologics license application (Umscheid, Margolis, and Grossman 2011).

Figure 3 — FDA Regulation of Biomedical SynBio



SynBio Products for Cell Therapies do not meet this Requirement. Why?

- **More-than-minimal manipulation vs. minimal manipulation.** The FDA interprets "more-than-minimal manipulation" to include cell expansion, encapsulation, activation, or genetic modification. Thus, most, if not all synthetic biology products are considered more-than-minimal manipulation
- **Homologous use?** The FDA defines homologous use as the HCT/P performing the same basic function(s) in the recipient as it does in the donor.
  - *Example of Minimal Manipulation + Homologous use* → Skin is processed by mechanical meshing, then cryopreserved to be packaged into sheets as meshed skin.
    - It is *homologous use* because the functions are similar in that skin is being used as a protective covering.
    - It is minimal manipulation because it only uses mechanical meshing and freezing.
- Because these fundamental requirements are not met, **almost all cell therapies developed using SynBio will have to proceed through the IND process** which is mostly discussed in FDA guidance documents (see section 2.2) of this document.

Sources: 21 CFR Part 1271; FDA, 2020.
Note: Most SynBio products would require an IND process since they have more than "minimal manipulation."

Table 2 — Recommendations for Preclinical Study Design for an IND

Study Design	Recommendations
Use of Animal Models	Describe limitations of the animal model: ○ Variability ○ Physiological and Physical Constraints ○ Differences between the animal model of disease and disease in humans
	Justify the choice of animal model: ○ Similarities of the disease model to humans ○ Effect of animal's disease status on the pharmacology of the CGT product ○ Establish long-term persistence & immune tolerance of the CGT product
	Standard Monitoring Parameters: ○ Body weight ○ Food and water consumption; environmental conditions ○ Clinical pathology (serum analysis, hematology, immunohistochemistry) ○ Clinical observation (health monitoring, clinical examination)
Proof-of-Concept (POC) Studies	Should investigate: ○ Effective dose range (minimal effective and optimal biological dose) ○ Optimization of the Route of Administration (ROA) ○ Optimization of timing the product administration ○ Optimization of the dosing schedule (i.e. one dose vs. multiple) ○ Characterize mechanism of action (MOA; in vitro studies are strongly encouraged for this)
Toxicology/Safety Studies	Study design should include: ○ Appropriate numbers of animals per sex ○ Adequate randomization (account for dosing, timing of administration) ○ Appropriate control groups (with justification for each group) ○ Multiple dose levels (POC study results should guide this) & corresponding justifications ○ A dosing schedule that reflects the intended clinical use ▪ Dose formulation procedure ▪ Sample collection ▪ ROA that mimics intended clinical administration ○ Multiple sacrifice timepoints to capture acute, chronic, or delayed-onset toxicity
	Investigation of safety aspects of the CGT product: ○ Humoral or cellular immune response ○ CT product fate ○ Behavioral testing ○ Presence of abnormal growths (hyperplasia or tumors) ○ Putative biomarkers ○ Imaging ○ Cardiac assessments ○ Assess biodistribution, persistence, & clearance in target & non-target tissues ○ Assess off-target effects on genome ○ Data evaluation and statistical analysis

Sources: 21 CFR Part 312; Preclinical Assessment of Investigational Cellular and Gene Therapy Products; Jha et al. 2020; Huang 2017; and Wensky 2019.
Note: POC studies inform toxicology studies; POC studies may include *in vitro* and *in vivo* systems as appropriate.

Table 3 — Overview of CMC Information Required for an IND

Topic	Required Information
Drug Substance (DS)	Name(s) used to identify the DS at all stages of development Structure of genetic sequence and/or cellular components: ○ Genetic sequence diagram including relevant regulatory elements ○ Information on sequences analysis and annotated sequence data ○ Defining physical and biochemical properties of the cell (if applicable) ○ Major and minor cell populations (for ex vivo modified cells) Biological Activity and Proposed mechanism of action
	Stability ○ Summary, conclusion, and protocols used to test stability ▪ describe storage container, formulation, storage conditions, testing frequency
	Manufacture ○ Name & address of each manufacturer involved that makes, tests, and stores the DS ○ Process and Process controls ▪ Cell collection, processing and culturing conditions (i.e., transductions, expansion, harvest(s), purification, filling, storing and shipping conditions) ▪ Vector production ▪ Donor screening and testing (if applicable) ○ Describe how each manufacturing run is numbered/labeled ○ List of all materials and reagents used in manufacturing ▪ Include documentation that materials meet standards appropriate for use ○ Description of cell and/or viral banking systems ▪master & working cell banks; master & working viral banks
Drug Product (DP)	Description of the DP and its composition dosage for: ○ Active & inactive components, function, quality standards for each component Stability summary, conclusion, protocols and results of stability studies
	Pharmaceutical Development ○ Overages (gene therapy product added in excess to account for degradation during manufacture, shipping, and storage) ○ Physicochemical & Biologic properties relevant to performance of the DP ▪ dosing, genotypic variation, infectivity, specific and immunological activities, etc. ○ Container closure system for storage, shipping, and use of the DP
	Manufacture ○ Name, addresses, and responsibilities of each manufacturer ○ Batch Formula ○ Description (flow diagrams and narrative) of manufacturing process and process controls with corresponding justifications ○ Control of critical steps and intermediates ○ Control of excipients (i.e. inactive substances) ○ Control of drug product (Describes testing plan and procedures that tests the physical, chemical, and biological properties of the DP to meet acceptable limits for identity, potency, quality, and purity) ○ Analytical procedures and their validation ○ Optimization of timing the product administration ○ Optimization of the dosing schedule (i.e. single dose vs. multiple) ○ Characterize mechanism of action (MOA; in vitro studies strongly encouraged) ○ Reference standards or materials

Sources: 21 CFR Part 312; FDA 2020 and 2008; and Jha et al. 2020.

USDA Regulation and SynBio

The USDA regulates biotechnologies through its Biotechnology Regulatory Services (BRS) office that is directed under the Animal and Plant Health Inspection Service (APHIS) (OSTP 1986). The Plant Protection Act (PPA) authorizes APHIS, through BRS, to review and authorize commercial deployments of genetically-engineered crops, imports of new plant products within the United States, and new developments of plant products (USDA 2014). The scope of regulation is focused primarily on the notion of plant pest risk, and that no new products deployed in the field should demonstrate an increased risk of harming native plants or established crop plants. APHIS reviews genetically engineered plant products based on an analysis of plant pest risk to determine if they are safe for use in sectors such as industrial crop production of ornamental plant agriculture (APHIS 2024). The USDA also invites comments from members of the public on developments within biotechnology, which is updated regularly on the is "Commenting Opportunities: Biotechnology" webpage.

APHIS has utilized several processes for assessing the plant pest risk of genetically engineered crops, ornamental plants, and forestry products in the United States. The flagship program, Petitions for Determination of Non-Regulated Status (PDNS), started back in the late 1980s/early 1990s. This procedure required developers or importers of engineered plant products to submit dossiers of information that describe the biological characteristics (especially the genetically engineered features) of their plant. Dossiers for PDNS are extensive, comprehensive documents that APHIS uses to analyze plant pest risk. Data collected via field trials was also required to demonstrate the product's level of plant pest risk and allow APHIS to evaluate the ecological characteristics of the product. If the evaluation determines that the product is not regulated, it is then authorized for commercial deployment in the United States.

Dossiers are relatively expensive and time consuming to construct. Many developers of genetically-engineered crops in the United States utilize plant pest strains in the transgenes inserted into crops (e.g. Bacillus thuringiensis genes) or in the vectors used to transform (transfer foreign DNA into a host) crops (e.g. Agrobacterium tumefaciens). These techniques have often required developers to go through the PDNS process. Over time, developers diversified their engineering techniques beyond bacterial vector-based transformation. For example, non-plant pest gene sequences may be used to achieve desired traits instead of genes from plant pests. To prevent developers from going through an onerous PDNS process, APHIS launched its "Am I Regulated?" (AIR) procedure in 2010 as an alternative to PDNS. Instead of building a comprehensive dossier of information, AIR asked developers to submit much smaller packages of information describing the nature of the genetic changes made to the engineered plant and its intended use. Based on this information, APHIS would send developers a letter informing them of whether or not their product might be regulated under the Coordinated Framework, and if they need to pursue a PDNS. The AIR procedure provided a pathway that saved money and time for developers whose products did not contain plant pest strains (George et al. 2022).

For SynBio researchers working on plant-based engineering, the PPA and the APHIS processes are important to be aware of and plan for. This is especially true for researchers planning to translate their research to commercialized products and/or build start-up companies. It is likely that novel engineering used to create products never before seen by the regulatory infrastructure will require more time, resources, and data to achieve an authorization for commercialization. Collecting field trial data early on in research processes before the spin-out phase may benefit products later on when pursuing a PDNS. In addition, researchers need to be aware of APHIS permitting and notification processes if they wish to conduct field trials or engage in importation or interstate movement of genetically-engineered crops (APHIS 2025). Open-release field trials may require a deliberate release permit which enforces certain criteria for conducting field trials such as size of trials, isolation distances, etc. Interstate movement may also require a specific permit or notification to APHIS depending on the nature of the product and its movement (APHIS 2025).

Conclusion

SynBio has made rapid advancements in the past decade and is poised to develop solutions for the environment, healthcare, and manufacturing. The positioning of SynBio as application-focused with the goal of solving societal issues suggests that many products will eventually enter a regulatory pathway prior to marketing or broad use. For EMERs with no agricultural applications, the EPA is likely to be the lead regulatory agency via TSCA. EPA focuses on regulating intergeneric organisms and designates a few microorganisms as generally recognized as safe (GRAS). With the advancements in DNA synthesis technology, EPA has offered guidance on synthetic genes. For CGTs, the FDA will be responsible for regulating these technologies. FDA regulatory statutes outline key guidelines for CGTs with guidance documents provided needed details for interpreting these statutes. USDA oversee development of genetically-engineered crops through the PPA and APHIS processes.

However, SynBio technologies have outpaced the US regulatory system as many statutes were developed prior to the existence of or at the beginning of genetic engineering techniques. Regulatory challenges arise from the decentralization of regulatory agency decision making processes and current statutes that do not cleanly address unique products resulting from SynBio. Prior failed attempts to use designated regulatory pathways to accommodate SynBio products demonstrate these problems (Maxon 2023).

There are calls to better streamline our regulatory system for SynBio products (NSCEB 2025). In the meantime, having an awareness of our current regulatory structures can help researchers and developers be more prepared to transition their products from the bench to commercialization. Furthermore, building research programs or designing experiments with these regulatory boundaries in mind can help researchers to best position their work for translation to real-world applications.

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