U.S. Regulatory Policy Workshop: Genome-Edited Microbial Products for Agricultural Use

Debrief

10/18/2022

Agenda

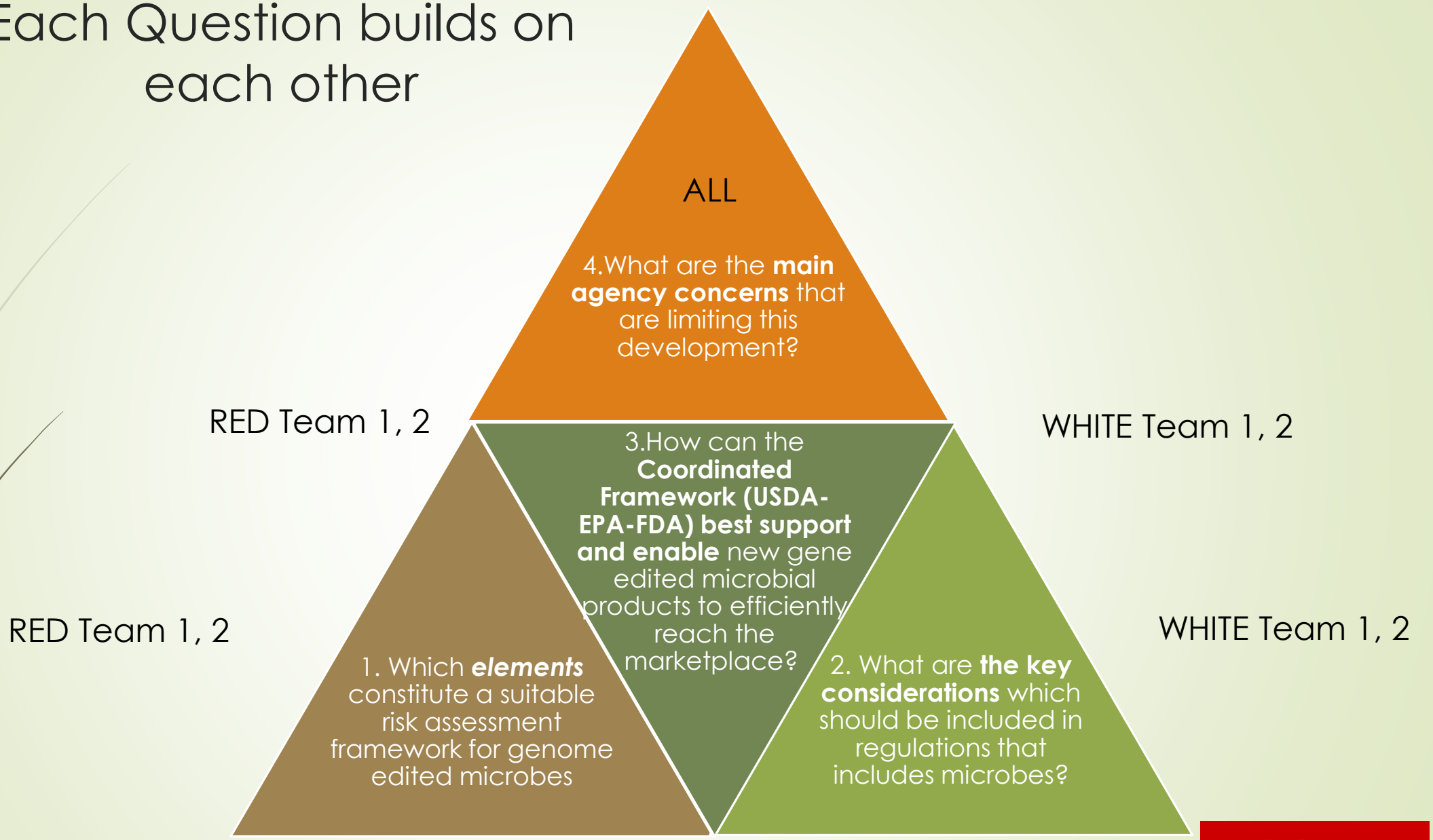
- Outcome, question and case study review
- Brief look at answers to each question
  - Most time spent on Rose/Bud/Thorn
- Consensus statement
- Walking questions
- Additional materials

Outcome

Collaborative understanding, development, and enhancement of risk-based regulatory framework for microbial genome editing

Using test case scenarios from day 1, we will answer 4 questions, to understand whether biotechnology regulations are helpful for microbial products

Each Question builds on each other



4 case studies (were modified by teams)

Red Team 1

- Endogenous CRISPR-Cas3
- Screening for prophage deletion
- GRAS organism
- Human probiotic already on the market to use in dairy products

White team 1

- Exogenous Cas9
- Single deletion of an antibiotic resistance gene
- GRAS organism
- Poultry feed

Red Team 2

- Exogenous Cas9 base editor
- Single base edit (C to T) in a non-coding region
- Species with Ag history of use, but novel strain
- Deployed for plan use (soil application)

White team 2

- Exogenous Cascade-Transposon
- Integration of a whole operon to generate a transgeneric enzyme
- In an industrial workhorse, but the enzyme (not the organism) is the product
- Spent medium will be used as a byproduct for the feed industry

1. Which elements constitute a suitable risk assessment framework for genome edited microbes?

Overall goal is predictable timelines for regulatory approval

- Endogenous CRISPR-Cas3
- Screening for prophage deletion
- GRAS organism
- Human probiotic already on the market to use in dairy products

Early product development

- focus on how product is different from existing products, not assessing all possible risks
- Pre-file opportunity using a class or family of constructs in one filing to reduce work needed on both the developer and regulatory sides
- "containment" – but there is a need for criteria or guidance on what that means.

- Exogenous Cas9 base editor
- Single base edit (C to T) in a non-coding region
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Late product development

- To assess residues, key data from applicant - historical data (bridging from parent strain)
- Persistence data
  - Consideration given to microbes with "kill switches"-sustainable tools that affect only GE microbe
- Effects on plant health
- Genomic data stability
- Spread and persistence
- Efficacy

2. What are **the key considerations** which should be included in regulations that includes microbes?

Goal is right-size operations/regulations to enable safe experimentation

- Exogenous Cas9
- Single deletion of an antibiotic resistance gene
- GRAS organism
- Poultry feed

- Is host/donor a plant pest—formerly there was a useful list of pests; would be extremely helpful to bring it back
- Take into account what we already know about safe microbes
  - Guidelines could be microbe specific
- Take a tiered approach to regulation, knowing early development phases
- Small trials need to move forward quickly
- Market based assurance program that is credible/workable/affordable.

- Exogenous Cascade-Transposon
- Integration of a whole operon to generate a transgeneric enzyme
- In an industrial workhorse, but the enzyme (not the organism) is the product
- Spent medium will be used as a byproduct for the feed industry

- History, legacy of use
  - Safety Data in poultry
  - Product formulation
  - Unintended consequences
- Risk/benefit analysis (EUA for Ag)
- single point of entry (provide visibility to other agencies);
- Microbe specific regulations
  - Harmonize regulations across agencies

3.How can the **Coordinated Framework (USDA-EPA-FDA) best support and enable** new gene edited microbial products to efficiently reach the marketplace?

- Develop regulatory guidance to enable self-government before new regulations are developed
- Since early stage development wants to fail fast, it's too expensive to prove 'completely safe" for this stage.
- Single point of entry for coordinated framework
- Harmonize requirements across agencies using EPA nomenclature of "tiered approach"
- maximize existing data (already done experiment, or someone else has); adding onto previous data – pointing out specifically what has already been approved/used
- Save time by using what is already known
  - Third party (NAS?) to assess risk of specific microbes and develop white paper

4. What are the **main agency concerns** that are limiting this development?
Summary discussion

messages that resonated and agree with.

1. Clear value of continued open discussion and dialogue among all workshop stakeholders
2. A tiered approach to regulation describing a commercial path
3. Bring back “the list” – Organisms that are known Plant Pests;
4. The coordinated framework is an international standard
5. Pre-filing on like groups(constructs, etc.) rather than filing each individual one is a better use of all resources

messages you wished were different

1. Path to commercialization not clear to companies
2. additional regulation
3. how do we receive guidance to self-govern first, before new regulations; technology is too early to show zero risk
4. Small changes become difficult to detect-how useful is persistence with respect to small changes?

What was missed? Opportunities to alter thorns?

1. Hold a cross-registrant conversation/agreement on persistence persistence vs. spread
   - Bar-coding as an opportunity
2. Unified website for biotechnology regulations website – can send an inquiry to all 3 agencies
3. Data package harmonization
4. Agility to evolve regulations based on what we know now
5. Opportunity to input into Farm Bill and Executive Order
6. Establish standardized data package from a 3rd party to be used in all submission packages
7. Is there a division of labor that helps drive efficiency among coordinated framework?

Consensus Statement from US Regulatory Policy workshop: Genome-Edited Microbial Products for Agricultural use

1.Genome edited microbes are needed for a sustainable agriculture system considering a changing climate with increasing pest pressures

2.We learned to be aware that the consumer has a role in developing the products, regulation, and creating trust.

3.We suggest, in the long run, developing a predictable regulatory path through commercialization that is specific for genome edited microbes; ultimately developing a tiered product development approach for uniform regulation

4.In the interim, we further suggest _Cross stakeholder conversations about uniform methods, consensus on risks to help agencies with response to opportunities such as the recent Executive Order the Bioeconomy and development of the 2023 Farm Bill.

5.Going forward, leverage the NAS to help in the development and formalization of collating and collecting unbiased, 3rd party baseline data related to microbial risk.

Walking Questions

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1. What are the immediate actions for regulators based on the recent executive order?
2. WHAT is the MOST Efficient Way to GET Input (NOT just Feedback) FROM The COORDINATED framework? (EPA + USDA + FDA)
3. How can industry help to communicate + educate the public on biotechnology and its safety?
4. why do developers generally not like Regulations?
5. Should APHIS-PPQ be included in future Workshops On this topic?
6. Are there microbe or microbe products. that fall in the gap w/in the coordinated framework (does not fall win one of the agencies)?
7. what future framework could best take advantage of intense scientific knowledge about unrelated microbes and products to expedite introduction to market?.
8. How can I keep engagement/progress in R&D microbe (GE) Space with an uncertain Reg environment or path to commercialization?
9. - How do you distinguish modified microbes from non-modified microbes in the field and their gene flow?
10. How much weight does GRAS hold with the USDA?
11. How do these 3 large federal agencies plan to coordinate various review streams: Risk assessment processes: timelines; data requests, etc?
12. As a non-scientist, with is the most important thing I should understand about the technology.
13. I couldn't attend yesterday, wo what was your "Ah ha!" moment yesterday?
14. How do you best reach the general public to educate them about GEMs?
15. How can I implement the major learnings from this workshop once I get back to my office
16. Are there other NGO groups aside from environmental groups, that should be engaged in these discussions?
17. How can we improve our pre-consultation meetings?
18. How does the EPA analyze horizontal gene transfer? (it was listed as something they do in their slides).
19. what are realistic timelines to clarify regulatory path-to-market with all 3 US agencies? (Workshop #3 is in 2024!)

Recommendations

- Share this deck with the entire workshop
- Share walking questions with entire workshop
- Opportunities for follow up for all stakeholders is captured in Rose/Thorn/Bud exercise
  - 7-12 opportunities. Need to prioritize

Additional materials

Pdf of flip charts: https://1drv.ms/b/s!AnY26JeKpnB9sCPYCZ2VvB6MAA8f?e=AMMmLI

Schedule, attendees, questions and use cases: https://1drv.ms/p/s!AnY26JeKpnB9sAUJUet92jRlDJe_?e=UdbYXs