

BIORISK MANAGEMENT CASE STUDY: US DEPARTMENT OF ENERGY JOINT GENOME INSTITUTE



Last Updated: September 26, 2022

SUMMARY

The U.S. Department of Energy (DOE) Joint Genome Institute (JGI) is a user facility that offers a variety of capabilities to the scientific community, including DNA sequencing, single cell genomics, metabolomics, and DNA synthesis/engineering biology approaches. Since 2013, synthetic biology proposals submitted to the JGI have been assessed for the broader aspects and implications of the research, beyond technical feasibility and scientific merit. It uses a qualitative approach to evaluate the broader aspects of proposals:

- Proposers submit **written qualitative responses** to a short set of open-ended questions as part of their application.
- The JGI takes steps to ensure the **active engagement of project proposers**.
- Following a review of scientific potential, proposals are evaluated by small diverse **teams of three external reviewers**.
- Reviewers are asked to consider a range of potential issues, including **biosafety, biosecurity, ethical, legal, social, and environmental concerns**.
- So far, proposals have never been rejected on broader-aspects grounds, but **proposers are sometimes asked to provide more information or even modify their project**.

DISCLAIMER

Biosafety and biosecurity risk management practices can change over time. This case study represents one point in time and is a sample of an evolving set of risk management practices. For additional information on current practices please contact the organization directly.

THE VISIBILITY INITIATIVE FOR RESPONSIBLE SCIENCE (VIRS)

The goal of the Visibility Initiative for Responsible Science (VIRS) is to share information about the value of biorisk management and how life science stakeholder organizations approach the issue. VIRS was conceived by a multi-stakeholder group during an April 2019 working group meeting of the Biosecurity Innovation and Risk Reduction Initiative (BIRRI) program of NTI Global Biological Policy & Programs. With support from NTI, Stanford University Bio Policy & Leadership in Society VIRS produced a set of Case Studies in biorisk management, and The Biorisk Management Casebook that provides cross-cutting insights into contemporary practices.

THE BIORISK MANAGEMENT CASE STUDIES

The Biorisk Management Case Studies describes biorisk management processes for a diverse set of life science research stakeholders. The collection serves to evaluate the feasibility and value of knowledge sharing among both organizations that have similar roles and those that have different roles in managing research. Case studies were developed in consultation with organizations through a combination of research based on public sources, interviews, and providing a template with guiding questions for organizations to complete directly. Additional analysis can be found in The Biorisk Management Casebook: Insights into Contemporary Practices¹ in this collection. Project Directors: Megan Palmer, Stanford University; Sam Weiss Evans, Harvard University.

Cite as: Hillson, N., Harmon-Smith, M., Simirenko, L., Greene, D., and Brink, K. (2023). Biorisk Management Case Study: US Department of Energy Joint Genome Institute. Stanford Digital Repository. Available at <https://purl.stanford.edu/rr427mq4842>. <https://doi.org/10.25740/rr427mq4842>.

CONTRIBUTORS

- Nathan Hillson Ph.D., Senior Staff Scientist, Lawrence Berkeley National Lab
- Miranda Harmon-Smith, Senior Scientific Project Manager, Lawrence Berkeley National Lab
- Lisa Simirenko, Senior Software Engineer, Lawrence Berkeley National Lab
- Daniel Greene, Stanford University
- Kathryn Brink, Stanford University

ORGANIZATION BACKGROUND

The U.S. Department of Energy (DOE) Joint Genome Institute (JGI) is a user facility that offers a variety of capabilities to the scientific community, including DNA sequencing, single cell genomics, metabolomics, and DNA synthesis/engineering biology approaches. Since 2013, synthetic biology proposals submitted to the JGI have been assessed for the broader aspects and implications of the research, beyond technical feasibility and scientific merit. These broader aspects are often not addressed by life scientists who apply without prompting from JGI.

The JGI began its broader aspects review to demonstrate to its peer community and the broader public that research is being conducted in a responsible manner. Years ago, a previous JGI Director was giving a keynote presentation at a DOE meeting, describing a project to modify a bacterium in such a way that, among other putative objectives, could make it more resistant to phage infections known to severely disrupt industrial fermentation processes. Following the presentation, an audience member asked what might happen to this organism in the environment in the absence of phage predation. This question prompted the Director, familiar with Internal Review Boards (IRBs) for animal research, to implement an analogous process for the JGI's Synthetic Biology program.

The origin of the JGI's broader-aspects review process, then, was a top-down directive with full institutional leadership support. At that time of origin, program managers at DOE, who play a role in overseeing work at the JGI, were also very supportive of these efforts. To this day, through JGI leadership and DOE program management changes, there has remained strong support of this review process, and this support has been critical to the establishment and ongoing implementation of the JGI's review process.

PROCESS

Scope of risks considered

The JGI's broader aspects review is intentionally quite expansive. Reviewers evaluate proposals along the following dimensions: General, Biosafety, Biosecurity, Ethical, Legal, Social, and Environmental. While more emphasis is placed on the Biosafety, Biosecurity, and Environmental aspects, other dimensions are also considered. It is also important that the expertise of each reviewer varies (e.g., a specialization in public policy) and is generally different from scientific/technical reviewers. This expertise influences the areas of emphasis on a reviewer cohort basis.

Overall sequence of steps

First, proposers fill out an application to the JGI that includes questions about broader impacts. One important component of the broader-aspects review is a section which describes the project in accessible language for the general public.

A team of three reviewers is formed on an ad hoc basis to review a set of 3-4 proposals at a time. There is an effort to integrate diverse reviewer experience, so the reviewer team composition is not often exactly repeated. This also allows the more familiar reviewers to impart their experience without revealing any specifics about any one past proposal.

Technical feasibility and scientific merit reviews are performed first and only then are selected applications advanced to the broader aspects review. These limits broader-aspects reviews to those proposals likely to be awarded, which conserves external reviewer efforts.

The JGI SynBio program manager sometimes preemptively asks for changes to proposal submissions, anticipating reasons for modification frequently requested by the review committee, so as to minimize proposer and reviewer effort and to accelerate the review process.

The JGI finds it critical to give proposers an opportunity to modify their proposals based on reviewer feedback, even if it delays the approval process. The goal is not always to substantially change the proposal, but often to increase the proposer's awareness of the broader impacts of its work.

Currently, there is no follow-up review after proposals are approved. However, the JGI is considering following up with investigators in the future, for example, to see how their views on the broader aspects and implications of their work have changed as the project has progressed over the years.

Risk assessment

The proposal sections dedicated to the JGI broader-aspects review are not intended to be deep, rigorous, standardized, or over-structured. They are also not intended to be onerous for proposers or require an undue time burden to complete.

The JGI emphasizes the importance of avoiding an overly detailed and cumbersome review process, which tends to push proposers and reviewers to mindlessly respond to concerns as line items, rather than engaging in a holistic assessment of a proposal's broader aspects.

Reviewers also learn to recognize patterns in responses that can raise concern, such as an attitude of dismissiveness about risks or lack of awareness of some dimension of the broader aspects review. These patterns tend to trigger follow-up conversations with proposers.

Risk mitigation

After discussion, reviewers can elect to approve proposals, request proposal modifications, or reject proposals. Research has never yet been outright rejected, but changes to projects have been requested. Reviewers do not expect proposers to solve or anticipate all possible concerns in advance, but they are expected to provide a process for how they will address concerns as they arise. Prospective check-ins with the investigators, as mentioned above, will be important for the JGI's assessment of how well this proposed process was followed and what the outcomes and impacts were.

The JGI provided three examples of risk mitigation efforts:

- A research team submitted a proposal to study ways that a rice plant recognizes the presence of a pathogen (e.g., through physical contact). It proposed engineering a version of the pathogen that did not emit a chemical signal that was suspected to trigger a response from the rice plant. However, the team did not consider that in the process, it might create a more virulent, stealthier version of the pathogen that could harm a staple crop used worldwide. The team even checked a box to indicate it was not producing an agent that was more infectious, suggesting that self-report checkboxes can be untrustworthy. However, after the risk of its work was pointed out, the team modified its proposal to more accurately reflect risks, and confirmed it would have the necessary facilities and permits to handle the agents it was creating. The team did not need to change its work plan because it already was capable of appropriate levels

of biosafety and biosecurity. Rather, it was being asked to demonstrate it was aware of risks and able and willing to manage them.

- A research team proposed synthesizing a novel metabolite and claimed it was not toxic, but reviewers noted the team had no way of knowing its toxicity if it had never been made before. The team was asked to scale down its experiment and provide appropriately cautious containment protocols for the metabolite.
- A research team proposed creating a biosensor using olfactory receptor systems whose genetic material was sourced, in part, from humans. Reviewers expressed ethical concerns about “humanizing” the yeast chassis that was being used and asked the research team to change to a different source genome.

Expertise required

According to the JGI, the broader-aspects review does not take much time, but access to expertise is a limiting factor. JGI identifies reviewers primarily through personal contact networks. There is a limited supply of reviewers with relevant expertise, and they are often busy with many other projects, so recruitment can be a challenge. The JGI does not pay reviewers; payment may help improve recruitment.

Training reviewers is also a challenge. Reviewers might not have a sense for appropriate local norms of review. For example, they might not know how much detail to expect in a proposal, or how much to expect consensus across the review team. A related issue is that proposals and reviews are typically only seen by reviewers and are not available for retrospective study. In the absence of visibility into past proposals, the JGI believes it is important to give reviewers access to experts who have completed reviews in the past. As noted above, the JGI varies the composition of reviewer teams so that more experienced reviewers can share their expertise without revealing any specifics about specific past proposals.

Finally, proposers themselves also need “training” to understand what information they need to supply for a broader-aspects review. In the JGI's experience, research proposers (typically academic life scientists) are not trained to think about the broader biosafety, biosecurity, or other ethical aspects of their work. One possible solution to this problem is to provide proposers with examples of “good” proposals. The problem with this approach is that if examples are too prescriptive, they become a blinder to critical thinking, and if not prescriptive enough, they are not

helpful teaching tools. The JGI tends to avoid this dilemma by having conversations with proposers to understand more about the project and communicate their expectations in a more organic manner.

FEEDBACK & IMPACT

As of December 2021, 153 proposals had been reviewed by a set of 28 reviewers, who made 636 comments across all categories of evaluation. Roughly 61% of proposals were approved without further discussion, 9% were approved after discussion, and 30% were approved after modification. The process has not rejected any proposal to date.

The process has proven to be very valuable to JGI, in that it serves as a time-stamped paper trail of external reviewer concerns expressed over proposed research that JGI has (or will) enable. The JGI has found it useful to refer to this process when communicating to the broader public that research is being conducted in a responsible manner and it has also added significant value to downstream biosecurity screening processes (e.g., those implementing the U.S. Department of Health and Human Services guidelines for providers of synthetic double stranded DNA).² For example, in the rice plant pathogen project described above, the broader aspects and implications review process, beyond the scientific proposal itself, drew out additional information not only about potential risks and concerns, but also content concerning the contextual mitigations, permits, and facility appropriateness for the proposed research.

The JGI described the broader-aspects review process as moderately difficult at first, but much easier starting the second time. If proposers already have experience writing a response to the broader-aspects question, then modifications and follow-up are not necessary, and the evaluation process only takes 10 or 15 minutes. However, follow-up engagements with proposers can cause delays and proposers are sometimes impatient to begin research and fail to see the value of the broader-aspects review.

Similarly, while the scientific and operational leads of the JGI Synthetic Biology program have always felt that having the broader-aspects review process was the right thing to do, concerns have been raised about the resource-intensiveness of the activity (both for the JGI internally as well as for external reviewers) and about the delay it can impose on the initiation of scientific or technical research work. At times, these concerns have led to doubts and critical sentiments towards the broader-aspects review process. In the JGI's

experience, an effective means of calming these doubts and fostering positive sentiments toward the review process has been to share positive feedback the JGI has received about this process from the community. This includes feedback from local community outreach/communication events and from scientific advisory committee meetings, where participants have underscored the importance, merit, and value of performing a broader-aspects review in spite of the effort required to perform it.

SHARING

While the JGI has publicly described its broader aspects and implications review process, both in written documents (e.g., a conference proceeding paper,³ online JGI website materials⁴) and in conference presentations, beyond non-attributed case-study high-level exemplars such as those mentioned above, the JGI does not share any specific research proposal or broader aspects and implications reviews beyond those people that need to know (e.g., reviewers, JGI staff performing the work).

The JGI proactively shares its experiences in the assessment of the broader aspects and implications of synthetic biology / engineering biology research, as it is a public demonstration of its values, and may help other institutions and organizations better decide if they would like to do something similar, and if so, to make it easier for them to stand up and operate their own analogous processes.

As mentioned above, the sharing of specific past broader aspects and implications reviews is limited to those anecdotal non-attributed normative experiences each reviewer brings to their new review cohort, and what JGI support staff may offer them as appropriate. These limitations are important to protect the sensitive nature of the proposer's pre-publication ideas and intellectual property.

REFLECTIONS

The JGI emphasized the importance of proposers taking the broader-aspects review seriously, and the importance of designing a process that draws out reflection on the part of the proposers—even to the extent of requiring them to submit a modified proposal. Proposers may at times be defensive of their work or dismissive of concerns about the broader aspects of their work. Dismissiveness is a warning sign that proposers are not being reflective. Reviewers look for signs that proposers have been thoughtful, are aware of the broader aspects of the proposed work, and if needed, have connections to outside experts to discuss these aspects as the work progresses.

While it is a relatively light obligation, the broader-aspects review creates additional work for proposers and might deter some from submitting proposals. There is some concern that proposals will be taken to a different organization that does not have a similar barrier, though the JGI does not have data to support or challenge this idea. Organizations interested in implementing a process like the broader-aspects review may need to accept some risk of deterring some applicants.

The JGI also recommends asking proposers to provide a closing document at the conclusion of the project with updated information on the broader aspects of their work. This can provide a feedback mechanism to validate the review process. However, once a project has concluded, proposers have little formal incentive to provide a closing document, so it can be difficult for organizations like the JGI to acquire them. According to the JGI, the idea of strongly punishing proposers for non-compliance is not generally popular among funders.

REFERENCES

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APPENDIX A: JGI SYNTHETIC BIOLOGY INTERNAL REVIEW SYSTEM REVIEWER GUIDELINES

Purpose of this document

This document provides guidance for Reviewers as they participate in the Synthetic Biology Internal Review process. For a tutorial and information concerning how-to use the Synthetic Biology Internal Review System software, please refer to: http://jgi-sbirs.jgi-psf.org/SBIRS/docs/SBIRS_Reviewer_Tutorial.pdf

Background

Synthetic biology has the potential to accelerate science and bolster economic growth. However, like any new technology, synthetic biology could be misapplied or result in unintended consequences. Serious concerns have been raised over the potential for intentional use of synthetic biology approaches to engineer pathogenic organisms as well as the possible accidental environmental release of genetically engineered organisms. Scientists pursuing synthetic biology research must diligently consider issues such as these.

Overview of the JGI Synthetic Biology Internal Review Process

The JGI Synthetic Biology Internal Review process seeks to assess, beyond technical and scientific merit, certain broader aspects (e.g., environmental, biocontainment, biosafety, or biosecurity) of the research proposals associated with the JGI's DNA synthesis program. The purpose of this internal review process is two-fold: 1) to assess the broader aspects of the research, request proposal modifications if issues of concern are not sufficiently addressed in the proposal, reject research proposals where issues of concern are not or cannot be satisfactorily addressed, and output a paper-trail audit of the review process; and 2) to encourage and educate researchers to more extensively consider the broader aspects of their research, including beyond the immediate research itself.

All JGI DNA synthesis proposals (including those from the JGI Community Science Program and from the DOE Bioenergy Research Centers) contain a broader implications section dedicated to a brief discussion of these broader aspects. This broader implications statement should address not merely the possible rewards but also a considered statement of the risks associated with the work. These

statements serve as a useful tool to protect not only the public, but the Investigators (and their institutions), as well as JGI itself. These statements are proof of consideration and deliberation - proof of the responsible application of science. As members of the research community, we must consider risks, and be able to show our consideration of those risks - even if they are demonstrably small.

After a synthetic biology research proposal has successfully passed technical feasibility and scientific merit review, the proposal enters the JGI's Synthetic Biology Internal Review process. A JGI system administrator uploads the proposal to the Synthetic Biology Internal Review System (SBIRS) and assigns a minimum of 3 Reviewers to it. Each Reviewer reads the full proposal, makes comments on the proposal in the SBIRS, and votes in the SBIRS to either approve the proposal or to discuss it further with the other assigned Reviewers. If not unanimously approved, the assigned Reviewers discuss the proposal in person or via telephone, and decide to approve or reject the proposal, or to require that modifications be made to the proposal to address the Reviewers' concerns. The Reviewers email the decision to a system administrator (jgi-sbirc-admin@lists.lbl.gov), who records the decision in the SBIRS. If the Reviewers decide to approve the proposal after discussion, a JGI Director is required to approve the proposal before work begins. A JGI Director can reject any proposal and can require that additional modifications be made to any proposal. The entire Synthetic Biology Internal Review process should take three weeks or less (unless modifications are requested, which could delay the process by an additional three weeks or more).

Guidelines for Reviewers

Reviewers should assess whether Investigators are actively thinking about the broader implications of their research, and whether the Investigators have mitigation strategies in place to address outstanding issues of concern. Note that Investigators are not expected to provide an in-depth analysis (e.g., full socio-economic analysis) of their early-stage research, but Investigators should demonstrate that they are currently considering the implications of their research, and that more in-depth analyses can and will be pursued as their research matures. Reviewers should request proposal modifications if issues of concern are not

sufficiently addressed in the proposal, and reject research proposals where issues of concern are not or cannot be satisfactorily addressed.

Reviewers should be especially diligent in explicitly identifying if the proposed research would:

1. Demonstrate how to make a vaccine ineffective
2. Confer resistance to antibiotics or antiviral agents
3. Enhance a pathogen's virulence or make a non-virulent microbe virulent
4. Increase transmissibility of a pathogen
5. Alter the host range of a pathogen
6. Enable a pathogen's ability to evade diagnostic or detection modalities
7. Enable the weaponization of a biological agent or toxin

Here are a couple of illustrative scenarios that may assist Reviewers as they think about the broader aspects of the proposed research:

- A. A plant lab is seeking to better understand plant/pathogen interactions. As part of the research plan, the researchers will develop a plant pathogen strain that no longer stimulates a response in the plant. What are the concerns around an unintentional and/or intentional uncontrolled release of this engineered pathogen? What could and should the plant lab itself do to address these concerns, and who else could and should it collaborate with along these lines?
- B. A microbiology lab is seeking to develop a more robust microbe that can break down cell walls of a wider variety of feedstocks, some of which may contain components that can impair cell growth and replication. To this end, the researchers will add exogenous catabolic and solvent-tolerance genes to a non-pathogenic microbe for the purpose of more effectively deconstructing the feedstock biomass. What consequences could result from such work if this engineered organism were to be unintentionally released from the lab? What could and should the microbiology lab itself do to address these concerns, and who else could and should it collaborate with along these lines?

Note that these two illustrative examples are by no means the only issues to consider. It is up to the Reviewers (and the Investigators) to determine the broader aspects of the proposed research.

Reviewers are requested to ignore the incidental spelling and grammar mistakes they find in proposals. When composing comments and preparing documentation notes as to how the Reviewers came to their decision, Reviewers should be as constructive as possible (without “rewriting” the proposal) and to refrain from using inflammatory or defamatory language, which is not conducive to a productive review process. Moreover, Reviewers should make their remarks so as to refer to “the proposal” rather than to the “PI”, where possible, and should not use non-neutral gender pronouns such as “he” or “she”. Note that after the Reviewers have submitted their decision, but before the review report is sent to the Investigator, an Internal Review process administrator may edit comments or decision documentation notes for inflammatory/defamatory language or references to the “PI” or “he”/ “she”.

Requesting and Evaluating Proposal Modifications from Researchers

As mentioned above, one possible outcome of the Internal Review process is that the Reviewers may require modifications be made to a proposal before it can be approved. When modifications are required, the Internal Review decision report that the Researcher receives will contain a section entitled “Review Committee Decision Notes” as well as a section entitled “Reviewer Comments”. Reviewers should be sure to list the specific modifications required in their Reviewer decision notes summary statement, and evaluate the revised proposal based on how well it addresses the points of concerns listed therein. While Researchers may also respond to any of the individual comments in the “Reviewer Comments” section in their revised proposals, the Reviewers should not adversely evaluate the revised proposal based on responses (or lack thereof) to individual comments that do not also appear in the Reviewer decision notes summary statement. It should be noted that, as described above, Reviewers individually comment on each proposal before discussing proposals together. During group discussion, Reviewers may collectively determine if any of the individual comments must be responded to, and if so, the Reviewers should include these points of concern in their decision notes.

Summary

Reviewers should assess whether Investigators are thinking broadly about the aspects of the proposed research, request proposal modifications if issues of concern are not sufficiently addressed in the proposal, and reject research proposals where issues of concern are not or cannot be satisfactorily addressed.