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Designing Safety Policies to Meet Evolving Needs: iGEM as a Testbed for Proactive and Adaptive Risk Management

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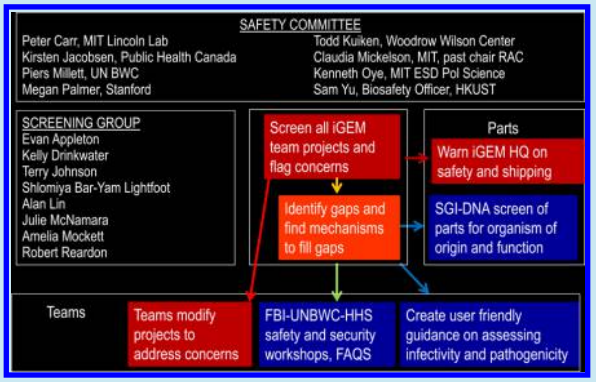
ABSTRACT: iGEM has spent the past decade encouraging teams to push their projects to the frontiers of synthetic biology. However, as project complexity increases, so too does the level of assumed risk. In the absence of a coherent international framework for evaluating these risks in synthetic biology, iGEM has recently engaged with the MIT Program on Emerging Technologies to develop a progressive approach for handling questions of safety and security. These two groups have worked together to create a rigorous screening program, acknowledging that a strengthened set of iGEM safety policies ultimately serves to expand, not contract, the universe of acceptable projects. This paper reports on the policy process evolution thus far, screening findings from the 2013 competition, and expectations for future policy evolution.



Much like synthetic biology as a whole, iGEM has exploded in size, geographic scope, and technical capabilities over the past ten years. While this growth is beneficial, it also means that advancements have at times outpaced regulations. iGEM has reckoned with this mismatch most directly on issues of biosafety and biosecurity. However, rather than limiting projects' scope to remain conservative in the face of uncertainty, iGEM has engaged directly with safety challenges. Working with the Massachusetts Institute of Technology (MIT) Program on Emerging Technologies (PoET), iGEM Headquarters has begun a multiyear process of developing progressive safety policies. This paper considers the motivations behind these changes, highlights the growth of key partnerships and collaborations, summarizes the 2013 safety screening findings, and looks ahead at opportunities for continued policy evolution.

BACKGROUND

In 2011 and 2012, iGEM implemented a standardized screening system for teams' safety forms. Prior to 2011, there was not a systematic review process in place. The new form consisted of questions prompting teams to (1) consider possible environmental, health, and safety implications of their projects and (2) provide sufficient information about their projects and procedures so that the Safety Committee could identify potential concerns. Before regionals, the MIT PoET group reviewed the forms, and projects that raised concerns were examined by the iGEM Safety Committee. Screening thresholds were set with a deliberate bias toward generating false positives as opposed to false negatives. Completion of the safety form was a requirement for participation.

Comprehensive project screening revealed a series of near misses in the 2011 and 2012 seasons. In iGEM, these apparent near misses were a consequence of inaccurate reporting. For example, one team improperly understood their project, reporting that they were using biological parts from an organism of concern in an insufficiently protective laboratory environment. On further review, the Safety Committee determined that the team had misclassified the biological parts with which they were working, and that the laboratory was appropriate for the true level of risk associated with their project. Near misses can serve as valuable sources of information for tracking potential weaknesses in a system, such as here where the team had clearly been insufficiently informed as to how to differentiate between safe and unsafe work.

The MIT PoET group used the results of two years of project screenings to propose changes to the 2013 process. These revisions were the product of discussions with the Safety Committee, faculty advisors, and iGEM Headquarters. The revisions aimed to shift the point of intervention closer to the time when actual laboratory work was being performed, such that potential hazards could be detected and prevented prior to a harmful event, rather than after the high-risk work had already been completed (Figure 1).

In 2013, teams submitted forms describing safety procedures and project implications, and also listed the chassis and parts used in their projects. If any parts or chassis were derived from mammals or organisms above risk group level one, teams also

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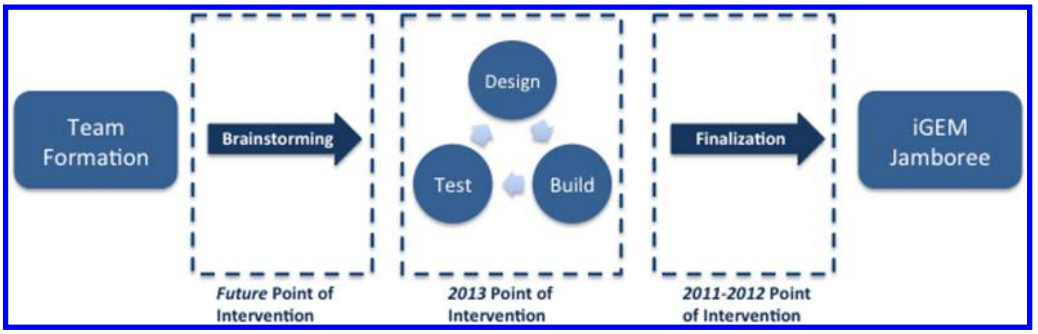

Figure 1. Advancing the point of intervention. In 2011 and 2012, the safety process was limited to screening after projects had been completed (right); in 2013, the screening shifted closer to intervening during the design-build-test cycle (middle). Future iterations aim to move intervention further up the chain to maximize safety (left).

completed more detailed forms addressing areas of potential concern. Here, "chassis" refers to a host organism, such as *Escherichia coli* or *Bacillus subtilis*, into which a synthetic device is placed, while a genetic "part" is a component of the device, such as a promoter or terminator. Risk group assignments are based on the relative risk of the originating organism, as assigned by organizations such as the World Health Organization[1] and the U.S. National Institutes of Health Recombinant DNA Guidelines.[2] Assignment of organism-level risk group to its component parts is a conservative approach, but currently a necessary starting point due to the limited state of regulations. Developing an expedited screening protocol based on part functionality rather than organism of origin is a near-term goal.

Deadlines were earlier than in previous years and forms were required to be updated to reflect project changes, which facilitated intervention prior to teams conducting potentially dangerous work. However, the 2013 update did not make the screening occur early enough, as the majority of the process still took place beyond the point of maximum utility. This is a policy priority for future years. The program succeeded more significantly on other fronts, though, such as by instituting standardized data entry, requiring updated forms for relevant project changes, and increasing the emphasis placed on consideration of parts' functional properties. The program also strived for increased participant engagement with safety concerns and saw gains in the areas of more in-depth form reporting, team-driven shifts in project scope due to safety concerns, and active participation with the Safety listserve, suggesting a desire to improve understanding rather than solely ticking check boxes.

Because of the process changes, participants had to be educated on risk group levels, changes in risk due to genetic modifications, the relationship of part functions to risk group assignments, and laboratory biosafety levels. However, as iGEM's new policies outpaced many international biosafety efforts, appropriate supporting educational documents had yet to also evolve. Multiple stakeholders assisted iGEM in providing guidance. One primary contributor was Public Health Canada, which aided in the development of the updated screening criteria. Additionally, J. Christopher Anderson and Terry Johnson of the University of California-Berkeley provided video instruction on traditional biological risk assessments, as well as on understanding and defining responsible conduct in synthetic biology.

2013 also marked the beginning of a collaboration between MIT PoET and iGEM with Synthetic Genomics, Inc. (SGI). This partnership resulted in SGI applying its proprietary screening tool, Archetype, to the entire iGEM Parts Registry. Archetype, which screens at a higher level of detail than the International Gene Synthesis Consortium (IGSC) standards require, validated previous screening efforts by revealing no concerns that the Safety Committee had not already flagged. The results of this screening were also used to set terms of access to iGEM parts, and are providing an empirical basis for evaluating national regulations and international agreements governing parts' safety and security. Continuation of this partnership through an annual screening of all newly submitted parts would institutionalize a vital secondary check within the overall safety system.

2013 FINDINGS

The 2013 collegiate-level safety screening involved the review of 184 wet-lab teams before the regional jamborees. In a continuation of recent trends, the 2013 competition again witnessed increased project complexity and higher possible risk exposure. Here, the primary factors of safety concern—chassis risk group and part risk group—are characterized by region and overall. Comments regarding laboratory biosafety levels are also included.

Chassis. The safety screen recorded the highest reported risk group level of chassis used per project. For any efforts involving an organism above risk group level one, a Secondary Form was also required. The vast majority of iGEM teams used chassis from the lowest risk group level; across all competitors, 90% employed no higher than a risk group level one chassis (Table 1).

Parts. The 2013 iGEM safety screen also required information on any new or modified coding regions that teams were using in their projects. A Secondary Safety Form

Table 1. Chassis and Part Risk Assignment[a]

	chassis				part			
risk group level	1	2	3	other	1	2	3	other
North America	92%	6%	0%	2%	56%	37%	0%	8%
Europe	86%	12%	0%	2%	59%	27%	2%	12%
Asia	90%	8%	0%	2%	52%	31%	3%	15%
Latin America	91%	9%	0%	0%	55%	27%	0%	18%
total	90%	9%	0%	2%	55%	31%	2%	12%

[a]Highest chassis and part risk group level per team, presented by region and in sum. "Other" refers to areas of unresolvable assignment uncertainties.

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was required for any part sourced from a risk group two or higher organism, or from a mammal. Parts from the 2013 Distribution Kit were exempted from review. Overall, 55% of iGEM teams reported no use of parts from higher than a risk group level one organism (Table 1). A further 31% reported use of parts from risk group level two organisms.

Teams' detailed reporting in the Basic and Secondary Forms allowed for intervention on all serious concerns prior to the Jamborees. Though not every safety concern was fully resolved, there were no last-minute surprises in 2013. The quality of reporting was mixed, with some teams providing exemplary responses and demonstrating deep consideration of the relevant issues, while others were either cursory in their efforts, or were uninformed about their universities' or countries' biosafety regulations.

The most troubling mistake found across multiple forms was teams incorrectly asserting that their universities had no Institutional Biosafety Committee or equivalent group. Teams' home universities hold the key responsibility for ensuring sound laboratory practices, so a lack of understanding of these resources and requirements is cause for concern, and should be a target for future educational efforts. The importance of home institutions serving as the safety backbone of iGEM is reinforced by the self-reporting nature of the safety policies. While standardized forms requesting specific data helped to improve reporting, there remain no ready means for iGEM to ensure the veracity of statements provided. Therefore, emphasizing compliance and consultation with home institutional biosafety entities, which do have access to laboratories for verification purposes, helps to reduce the uncertainty around responses provided. Further, planned improvements to guidance documents will include better explanations of the intentions of various questions in the coming year, and thus, the safety process should expect more informed responses.

FUTURE CONSIDERATIONS

Changes made to the 2013 screening process marked an important step in the overall evolution of safety policies within iGEM. However, improving safety at iGEM is an iterative process, and lessons learned from 2013 will necessarily inform changes to the 2014 effort. Of these modifications, the following are of top priority:

1. *Preapproval of projects exceeding certain risk thresholds.* iGEM is striving to attain points of intervention that optimize participant safety while maintaining project flexibility (Figure 1). By requiring advance approval of plans to use organisms or parts more likely to present hazards, iGEM aims to prevent situations such as those in 2011−2013, in which teams worked with dangerous components before the safety screeners were made aware of their plans and had an opportunity to act.
2. *Improved clarity and guidance.* Much remains unknown about how to assess risk when organisms are broken down to component pieces. iGEM and collaborators have attempted to provide guidance; however, significant room for improvement remains. Guidance documents must be produced concomitant with policy evolution in order to provide clarity in this area.
3. *Increased advisor involvement.* The iGEM safety process relies on teams' home universities, and thus, active advisor involvement is vital. The 2014 process will continue to work on facilitating communication and engagement with the overseeing parties.

A strengthened set of iGEM safety policies ultimately serves to *expand* the universe of acceptable projects. By understanding areas of concern, and knowing how to address them responsibly, teams are capable of working safely along the technology frontier. Safety policies are evolving in pursuit of this goal, and with this aim, safety at iGEM is pointing toward the future.

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Author Contributions

All authors contributed to the development and implementation of the iGEM safety program and to researching, writing, and editing this article.

Notes

The authors declare no competing financial interest.

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