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The quiet death of the Recombinant DNA Advisory Committee (RAC)

By **Edward Hammond**

In changes little noticed outside of US scientific circles, the US National Institutes of Health (NIH) has eliminated the Recombinant DNA Advisory Committee, or RAC, the national-level review body that has been the centrepiece of the US scientific "self-regulation" system for genetic engineering since 1975. The RAC was formally replaced in December 2019, when the first meeting of a successor committee was held.

Review of proposed biotech experiments by the RAC – a committee of safety experts primarily drawn from universities – had for decades been the highest level of consideration in the US for genetic engineering experiments in contained use, especially those posing novel risk. The RAC also considered and recommended changes to the NIH Guidelines on Recombinant DNA Research, which set national standards for laboratory biosafety with genetic engineering used not only by health, but also by agriculture, defence and other biotech research institutions.[1]

With the RAC's disbanding by NIH, the US is left with an even more decentralized and *laissez faire* system for oversight of biotechnology experiments. With limited exceptions (explained below), there is now no national body to review proposed experiments, and the

1 The NIH Guidelines, while promulgated by the US health ministry, apply to and are used across many US government agencies, including the ministries of defence, energy (which has extensive biotech programmes) and agriculture. Thus, the Guidelines apply not just to biomedical, but also agricultural, industrial and other research, including many greenhouse and even some 'contained' outdoor experiments with genetically modified organisms.

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local institutional biosafety committees (IBCs) that are the first line of defence against biotech accidents are now effectively also the last.

Changes and their implications

Two new federal-level entities are emerging in the wake of the RAC, though neither serves the same role as its predecessor. The first is named the Novel and Exceptional Technology and Research Advisory Committee, or NExTRAC, and the second is the Potential Pandemic Pathogen Care and Oversight, or P3CO, committee.

While NExTRAC is described by NIH as the RAC's direct successor, it does not serve the same functions as the RAC did. NExTRAC's charge is to review a broad range of biomedical technologies with significant societal implications – not just recombinant DNA – and make general recommendations about oversight of those technologies to the NIH Director. Thus, NExTRAC is considering everything from human germline modification to what are essentially electromechanical discoveries in neuroscience; it does not review the safety of specific experiments.

The result is that the IBCs are now the first and only review bodies for genetic engineering experiments in practically every case, and there is no space for an "appeal" afforded to any dissenting IBC member(s) concerned about the risks of an experiment. IBCs exist at universities, institutes and companies that accept public research funding that includes genetic engineering experiments and are typically almost entirely composed of professors from the same institution whose research they are reviewing.[2]

In the past, an IBC that was uncertain about an experiment could seek public review by the RAC, and the RAC was available to review – and publicly pass judgement on – experiments gone awry. Now, this higher and more institutionally detached oversight, a source of potential restraint and more independent risk review, is gone.

The second committee, the P3CO, is a secretive internal US government group. This committee is the only major exception to the devolution of genetic engineering experiment review and approval authority to the local IBCs.[3] But the scope of the P3CO's work is very limited. It is to review research that is proposed for funding by the US government that could result in the creation of novel and more dangerous potentially pandemic pathogens. It does not cover any other type of biotech experiment, for example, potentially dangerous gene drives or agricultural experiments that could lead to the escape of harmful plant or insect transgenes.

Membership in the P3CO is limited to US government officials, and not even the committee's roster has been made public. Indeed, it is unclear if any substantive information about this committee will ever be made public, including its methods for assessing proposed research, the protocols it reviews, and information on its decisions.

Notably, the P3CO is limited to research that is being considered for funding by the US government. Privately conducted experiments fall outside its authority. And there is no national registration system or other means in the US for the government to necessarily learn of privately funded research before it is conducted or published. US critics of the P3CO say the severity of this limitation is demonstrated by controversial Canadian experiments to synthesize and recreate horsepox, a potentially dangerous relative of smallpox virus thought to be extinct in the wild,[4] that were performed with private funding.

2 IBCs need to have a small number of "public members", ostensibly offering a foothold for the broader community in project review, but universities and other institutions quickly found ways to ensure compliant "public" members who do not represent divergent perspectives. For example, retired bioscience professors from the same institution – unlikely to challenge their still-working peers – are perhaps the most frequently appointed "public" members of IBCs.

3 There is another exception, "deliberate transfer of a drug resistance trait to a microorganism when such resistance could compromise the ability to control the disease agent in humans, veterinary medicine, or agriculture," which requires approval of the NIH Director (if conducted with US government funding, otherwise it is unregulated). This exception in practice is likely to overlap with the P3CO committee's remit.

4 Reportedly, a remaining sample is kept at the US Centers for Disease Control, and laboratories in the former Soviet Union may hold samples. (Naturally occurring cases of horsepox were recorded in Mongolia into the 1970s.)

The role of IBCs is also linked to US government funding, and IBCs are not required in the US at companies and other research institutions that don't receive US public genetic engineering research funds. This means that those entities are free to devise their own biosafety strategies, whether or not they are consistent with widely accepted practice, unless those entities handle pathogens on a short list of "select agents" maintained by the US Centers for Disease Control and Department of Agriculture, in which case (ironically) compliance with the voluntary NIH Guidelines on recombinant DNA is theoretically made mandatory.

While it is not new that privately funded genetically engineering research can escape the US oversight system, with the RAC's demise, fears about poor local decision-making are heightened.

The RAC's role in biosafety was real, but it was also a longstanding source of "propaganda" value for biotechnology proponents, who cited the RAC as being an effective tool to control biotechnology risk in the absence of comprehensive safety legislation. Born in 1975 following the Asilomar Conference at the dawn of genetic engineering, for decades the RAC had been promoted by scientists and the US government as being the capstone of the US "self-regulation" approach:

> "*The original guidelines of the Asilomar Conference played a crucial role in the development of biotechnology… Public confidence in biotechnology was also enhanced by the creation of the RAC within the NIH (essentially as recommended at Asilomar). The RAC proved to be an effective forum for the discussion of any new experiments.*"
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> – (Former US Vice President) Al Gore, in *Yale Law & Policy Review*, 1985

Dismissing those who question the safety of genetic engineering, not only in medical but also in agricultural and industrial applications, the "self-regulation" system's supporters argued that the RAC demonstrated the mettle of the US system by its regular public meetings and in-depth reviews. Its authority in biosafety matters was a guarantor of safety, supporters of the system argued, despite the general absence of binding biosafety law in the United States.

> "*The National Institutes of Health has probably shaped global biotechnology regulation more strongly than any other agency. In the absence of explicit statutory enforcement powers of its own, NIH achieved this distinction by developing a successful – and widely copied – approach that permitted rDNA research to proceed, without harming workers or the environment.*"
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> – from *Biotechnology and the Environment: International Regulation* (Macmillan, 1987)

The RAC's disbanding is thus somewhat surprising considering its history as the public showpiece of the loose biotech oversight system promoted by the United States internationally (and sold to its own citizens as being effective). And with the RAC's demise, NIH appears to be saying that biotechnology research does not even need a public and relatively neutral national safety forum for consideration of novel or particularly risky research.

Ostensibly the most important change that prompted NIH to first reduce the power (2016) and finally disband the RAC (2019) was a decision by the US Food and Drug Administration (FDA) to step up its oversight of human gene therapy (HGT) experiments. Because the RAC's workload had, over time, included oversight of more and more HGT experiments, the FDA's decision, NIH argued, created unnecessary "duplication" between the governmental bodies, and even though the approach of the two groups was notably different, NIH leadership was eager to cede an oversight role to the FDA.

In 2018, NIH published a public notice that misleadingly described the process that eventually killed the RAC as one to "modify the Committee's roles and responsibilities". In fact, the "modification" was to eliminate any continuing place for the RAC in the NIH Guidelines on Recombinant DNA Research. Many comments were submitted to NIH expressing support for the RAC, and these noted its ongoing value in review of HGT experiments, as well as other functions in biosafety more generally, particularly as a

public forum for discussing biosafety risks. NIH killed the RAC anyway, formalizing the proposal made in its public notice, in April 2019. By December 2019, the RAC was formally replaced with the first meeting of NExTRAC, the "successor" in name that actually has no function in relation to the NIH Guidelines.

The upshot of the recent changes in US oversight of biotechnology experiments is that with very narrow exceptions related to specific types of experiments with particularly dangerous pathogens, essentially all responsibility for biosafety review and approval of genetic engineering experiments has been renounced by the federal government and passed to local IBCs, committees whose transparency and proper functioning has in the past come under fire.[5] And while these committees in theory must comply with the NIH Guidelines (if the institution receives public research funding), the Guidelines are essentially limited to assigning a biosafety level to experiments. In almost all cases, IBCs do not meet in public or offer any forum for community discussion. Indeed, many IBCs are so deferential to the potential commercial interests of their professors and institutions that little substantive information about their processes and decisions is available. Nor are IBCs seriously monitored by national authorities.[6]

While backers of the US system would claim that it has a generally good track record, and that this record warranted the disbandment of the RAC, critics would cite the regular occurrence of accidents[7] with potential to cause human and environmental harm. For example, the father of Jesse Gelsinger, an American teenager who died in a poorly conducted human gene therapy experiment, lobbied NIH not to remove the RAC oversight of HGT experiments.[8] He was ignored. And, despite being forced to rely on limited data because accidents are often not publicly reported, Harvard epidemiologist Marc Lipsitch has made alarming estimates of the probability of lethal lab accidents involving potentially pandemic pathogens.[9]

Conclusions and recommendations

With the exception of a few narrowly bounded types of research involving especially dangerous disease agents, oversight for genetic engineering experiments in the US has been devolved to local committees composed of institutional insiders. And in those few cases where review is conducted at a national level, it is to be done in nearly complete secrecy – despite the fact that these by-definition highly risky experiments arguably pose the greatest societal threat.

The loosening of safety oversight of biotechnology in the US leaves it more vulnerable than ever to a laboratory disaster. A significant relaxation of safety reviews has been undertaken despite new and potentially quite dangerous biotechnologies that are emerging, such as gene drives, which cannot be adequately dealt with through an advisory and unfocused approach like NExTRAC. As practical barriers to conduct of ill-advised experiments fall lower through the dissemination of techniques like CRISPR combined with cheap DNA synthesis, instead of beefing up oversight, the US NIH is deliberately eroding its own ability to oversee such research.

In the present US political context (mid-2020), it is difficult to be optimistic that policy officials will seek any biotechnology policy changes that would encounter significant resistance from the biotechnology industry and academic institutions, both of whom wield tremendous influence over policy and share the goal of debilitating federal government oversight.

5 Race MS and E Hammond 2008. An evaluation of the role and effectiveness of institutional biosafety committees in providing oversight and security at biocontainment laboratories. *Biosecurity and Bioterrorism* v6 n1. March 2008.

6 NIH can request information from IBCs, but reporting is usually limited to simply providing a roster of members to NIH. Accidents with rDNA are theoretically reportable to NIH, but the requirement to report does not carry the weight of law, and sanctions have never been imposed by NIH on any entity that failed to report accidents.

7 For example, Lynn Klotz provides, in the *Bulletin of the Atomic Scientists*, analysis of the significance of 128 containment breaches in the US involving recombinant DNA that were reported to the US NIH from 2004 to 2017. See: Klotz L 2019. Human error in high-biocontainment labs: a likely pandemic threat. *Bulletin of the Atomic Scientists*. February. https://thebulletin.org/2019/02/human-error-in-high-biocontainment-labs-a-likely-pandemic-threat/

8 Public comments received by NIH in response to its 26 April 2019 Federal Register notice, page 3. See: http://osp.od.nih.gov/wp-content/uploads/Aug162018_AllComments_r508.pdf

9 Lipsitch M and T Inglesby 2014. Moratorium on Research Intended to Create Novel Potential Pandemic Pathogens. *mBio* v5 n6. December 2014.

But administrations change, and factors that stimulate policy change – perhaps, for example, new attention to lab safety provoked by concerns emerging in the course of the COVID-19 pandemic – can appear unexpectedly. While industry and research institutions can be expected to seek to firmly shut any opening in the policy window, steps that could be taken to substantially improve the US oversight system include the seven recommendations below.

Notably, these changes would not replace the current system of local committees, but correct the system's flaws by changing the structures that connect local committees to federal entities, incorporating privately funded research, and making compliance mandatory. As a result, instead of working independently and mostly beyond effective oversight, IBCs would operate in an environment where palpable legal consequences existed for failure to perform (the stick) and IBCs were encouraged, in some cases required, to avail themselves of higher national-level review for difficult or novel safety situations that would bring in additional expertise and ensure a more thorough and more public consideration (the carrot).

1. *Extend to privately funded research*

Until the US extends biosafety rules to cover privately funded research, this enormous and unjustifiable loophole will remain the Achilles heel of the US system. The need to cover privately funded research is becoming more acute as the economic barriers to entry to genetic engineering fall, and access to powerful and dangerous technologies increases. This problem is exemplified not only by the privately funded recreation of horsepox virus, but also by so-called "biohackers" who are attempting to formulate biotech biological drugs, vaccines and genetic "enhancements" in *ad hoc* facilities, inject themselves with the result, and then circulate in the general population, with potential implications not only for themselves but for the health of others.

2. *Place oversight with an independent federal agency*

One of the greatest problems in the US regulatory system for genetic engineering research in the lab is that the federal agency that oversees it, the National Institutes of Health, is also a major funder of genetic engineering research, creating a plethora of conflicts of interest. NIH is reluctant to impose penalties on the entities that it funds and the researchers with whom it has decades-long relationships. Doing so would, in a sense, be a self-condemnation that brings NIH's funding judgement into question. And the experts it appoints to oversight bodies like the RAC (and, to a large extent, NExTRAC) are its fundees, persons who are financially dependent or whose institutions are financially dependent on NIH. This frequently extends even to bioethicists and social scientists NIH appoints. These "experts" are ostensibly detached observers of the scientific ecosystem, yet very frequently they too are compromised by financial links to federally funded genetic engineering projects. For instance, at least two social scientists appointed to NExTRAC are recipients of government funding to participate in the "social component" of projects with the goal of developing and releasing gene drives.

Placing oversight of genetic engineering research in the hands of an independent federal agency would remove many of the conflicts inherent in its placement with NIH. An independent federal oversight agency would be unencumbered by decades of mutual dependence linked to research funding, and could approach its job with far clearer vision and far fewer compromising relationships with the entities and scientists it oversees. Further, it is obvious that genetic engineering research has many applications outside the field of human health, especially in agriculture and manufacturing, as well as (in the US and some other countries) defence. An independent agency would be able to balance oversight of the different sectors in a superior manner to what NIH is able to accomplish, given the limitations of its scope.

3. *Re-establish a transparent national review body, merged with the P3CO*

The absence of a national review body for novel and risky research proposals creates confusion and a decision-making vacuum that thrusts too much responsibility onto local IBCs which may lack core competences to review

some research types, particularly cutting-edge techniques whose variables and implications are not fully understood even by practitioners.

At the same time, the wall of secrecy being erected around the P3CO is damaging to the public reputation of infectious disease research and erodes confidence in the intentions and safety of activities by researchers. Moreover, the secrecy denies safety reviews the benefit of a wide airing, which could bring in different perspectives, considerations and observations about proposed research. And with the P3CO, there is also the question of responsibility to the public, which could find itself the victim of such research – think of a lab accident with a genetically engineered pathogen – without ever having had even the possibility of gaining knowledge of and commenting on the research before it was conducted.

The national review body could operate in ways not entirely dissimilar to the RAC. It could receive research proposals referred from local committees, be charged with reviewing any proposal that triggers criteria established by the independent federal agency (e.g., proposals that might alter a pathogen in ways that could render it more difficult to treat or eradicate), and it could review the operations of local committees, calling them to task when errors are made.

4. *Mandatory compliance*

The myriad conflicts that debilitate NIH oversight of the labs and researchers it funds can be clearly discerned in the history of poorly functioning IBCs and the near-total absence of enforcement actions in cases of non-compliance. Indeed, the only powerful tool at NIH's disposal to punish non-compliant institutions is termination of rDNA funding, a penalty that it has never imposed, despite many recorded instances of severe non-compliance with the NIH Guidelines (e.g., IBCs not meeting for years on end, despite the institution conducting federally funded rDNA research, including with dangerous pathogens).

Fear of the possible imposition of a loss of funding, a power that NIH has never used in over 40 years, is closer to a joke than a threat for research institutions which enjoy strong funding relationships with NIH and which have their professors and other representatives deployed on key federal advisory committees. The serious problems of this toothless oversight need to be resolved. To do that, compliance with federal rDNA biosafety rules must be made a matter of direct regulation, that is, made a legal obligation on all labs using genetic engineering.[10] By making compliance with safety rules an obligation, the federal government would not only capture the ability to oversee private labs and biohackers, it would regain leverage over the universities and other research institutions that know they have little to fear from NIH if they screw up, as NIH will not even bare the few teeth it has, much less use them.

5. *Routine application of penalties*

The culture of US rDNA research oversight has become one of all carrot and no stick. While many institutions operate lower-risk research programmes that are competently locally overseen, there are ongoing problems of non-compliance and a broadening of risk associated with technological changes. For example, despite years of NIH efforts, including many individual contacts and the issuance of federal guidance documents, many IBCs do not maintain proper records of their actions and routinely violate provisions of the Guidelines on public access to local committees.

In the hands of an independent agency, a federal response to non-compliance that included the actual imposition of penalties – even symbolic small fines or short suspensions of projects – would have a sea-change effect on biosafety oversight of labs. For the first time, non-compliance would have real legal consequences. The federal agency needn't entirely nor even in the majority rely on imposing penalties, but by concretely showing its willingness to do so, it would gain safety leverage over potentially dangerous research that NIH has never been able to obtain, creating a more evenly incentivized and safer set of

10 Although there is confusing variation between federal agencies, none of whom (including NIH) actually enforce the Guidelines, as a general statement, compliance with the NIH Guidelines is not a legal requirement for labs but rather a term / condition included in the contracts between NIH and recipients of its funding.

balances between researchers, local committees and government.

6. *Licensure for particular types of activities*

To better ensure proper training and responsibility of scientists and institutions, an independent federal oversight agency for rDNA safety should implement a licensing programme for particular types of activities. Satisfying the requirements of licensure for specific kinds of especially risky activities could have several beneficial effects by creating obligations for enhanced training, reporting, safety practices and penalties for non-compliance in particularly dangerous types of research. At present, three types of research are obvious candidates to potentially require licensure: 1) research that could lead to the creation of gene drive organisms that, if released, have any potential to survive in the outside environment, 2) research to heritably modify a human being, and 3) research with a human, animal or plant pathogen that may modify the pathogen such that it would be more difficult to control or eradicate if it escaped the laboratory.

7. *Enhanced transparency*

Beginning with the anthrax letters of 2001 (the product of a US laboratory), followed by controversies over "dual use" research, including gain-of-function experiments with human pathogens, the US government and committees that advise it have been locked in spirals of security-oriented discussion about biological research. One of the effects of these discussions has been an erosion of transparency in US research as institutions, which infer from federal authorities that some of their biological research might have national security implications, have reacted with amateurish and ineffective "security" measures that inhibit public knowledge and discussion while doing nothing to achieve their purported ends.[11] And the most recent US government "solution" to the problem of how to manage especially dangerous research review, the extremely secretive P3CO, will only exacerbate alienation of the public and, indeed, a wider community of scientific practitioners and related specialists – e.g., epidemiologists, doctors and ecologists – from awareness and engagement in the oversight of especially dangerous rDNA research.

Thus, all the previous steps should be undertaken with a new commitment to transparency, something that – at least rhetorically – is part of the scientific ethos of publication and sharing. For example: Penalties will have no broader beneficial effect if their application is not made publicly known, public identification of licence holders will enhance motivation for personal and institutional responsibility, and review of especially dangerous research will suffer from limited inputs if conducted in secrecy.

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11 A common misdeed by research institutions is to remove all reference to especially dangerous infectious diseases from their websites and to black out the names of people and all details of such research in publicly available documents. Yet a professor will still publish his or her paper on, for example, anthrax, and thereby publicly identify the labs and individuals conducting such research. Such "security" would only thwart the least intelligent and least capable would-be security threat, yet it exacts a toll on public awareness of research risks.

“Oversight” that overlooks – How many genetic engineering experiments escape mandatory safety review in the US