HARVARD T.H. CHAN | SCHOOL OF PUBLIC HEALTH

Enhanced PPPs, DURC, and a unified framework

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Speaking in academic/personal capacity

CENTER *for* COMMUNICABLE DISEASE DYNAMICS

P3CO and DURC

- Comments on the draft modifications to P3CO policy
- Issues for consideration related to combining policies

Draft Findings and Recommendations of the P3CO Working Group

- I support Findings 1-6 (but some concerns about 7) and all Recommendations 1-4 (but argue that Recommendation 5 is inadequate).
- In particular, Findings/Recommendations 1 and 2 on definitions and exclusions are most welcome

Key Points Missing from the WG draft

1. **Regulating the reasonably anticipated result, not the starting point.**

The ePPP Framework is unclear as to whether it governs research that (i) is reasonably anticipated to enhance an existing potential pandemic pathogen (PPP) vs. (ii) is reasonably anticipated to enhance virulence or transmissibility of any pathogen to make it become an ePPP, irrespective of whether the starting pathogen meets the criteria of transmissibility and virulence for a PPP.

Interpretation (i) makes little sense as a policy but is probably the more natural interpretation of existing language. This needs to be clarified.

Key Points Missing from the WG draft

2. Transparency language is weak and nonspecific

Recommendations are nonspecific adoption of an implementation plan and to "consider sharing a summary of key determinants and decisions of USG review."

*Actual transparency requires sharing such a summary, including dissenting views and a complete list of proposals reviewed. For example, the experiments described in **Science** this week by Dr. Moss should be reviewed under the policy, and the public should know if they have been or not. The recommendations may not accomplish this.* They should be made far more specific.

Key Points Missing from the WG draft

3a. The benefit side of risk-benefit analysis remains undefined

Many ePPP experiments have been asserted to enhance vaccine or surveillance efforts, without a rigorous assessment of that claim. For experiments involving population-level risk, generic claims that all knowledge is valuable are not compelling, and many assertions of the public health value of ePPP experiments may not withstand careful scrutiny. The only way to know is to insist that they receive it, and this should be specified in the framework.

Key Points Missing from the WG draft

3b. The risk of incorrect generalizations from ePPP experiments, leading to poor decisions about surveillance or countermeasures, should be explicitly considered.

Some proponents of the 2013 H5N1 enhancement studies argued that mutations obtained conferred ferret transmissibility but not necessarily human transmissibility. This effectively untestable claim, if true, would render the experiments potentially misleading if used to prioritize variants for surveillance or vaccine development. Framework should specify that this risk should be explicitly considered in risk-benefit evaluations.

Key Points Missing from the WG draft

4. Information hazards are not addressed.

The ePPP framework focuses on biosafety and physical biosecurity risks, without addressing the information hazards of publishing methods or sequences to create ePPPs. This omission should be corrected.

Key Points Missing from the WG draft

A complete list of outstanding concerns is being submitted to the NSABB by Drs. Inglesby, Relman, and myself with multiple cosignatories.

Considerations for unifying DURC/ePPP frameworks

Pro: Would potentially simplify for investigators, one flowchart and set of considerations, not two.

Pro: Would enhance clarity by encouraging HHS to define each and explicitly clarify the distinctions and common features.

Pro: Potential sharing of best practices, such as:

- Dr. Sever's proposal to link preprint server scrutiny to acceptability of the server to funders.
- Methods for dealing with unexpected results and possible rereview
- Risk assessment and mitigation

Considerations for unifying DURC/ePPP frameworks

Pro: Systematically consider the biosafety and biosecurity issues of each kind of work

Con: Risks shifting focus too fully to biosecurity. ePPP is technically a subset of DURC, but it raises biosafety issues that are not typical.

Table 1 Matrix of biosafety and biosecurity concerns

		Biosafety concerns about harm from accidents in the conduct of research		
		No	Yes-occupational health	Yes-public health
Biosecurity concerns about harm from research for malevolent use	No	Most scientific research	Laboratory studies of dangerous pathogens not considered suitable for malevolent (eg, *Streptococcus* spp.)	?
	Yes	IL4 mousepox	Studies of anthrax and other 'weaponisable' but non-transmissible pathogens	PPP experiments

PPP, potential pandemic pathogen

Evans Lipsitch Levinson *J Med Eth* 2015

Considerations for unifying DURC/ePPP frameworks

- **Resolution:** unify frameworks but with specific considerations (biosafety) for ePPP, in addition to biosecurity considerations that ePPP shares with all DURC

Lists vs. criteria

- As noted on slide 4, criteria seem the only sensible approach to PPP regulation. “Reasonably anticipated to result in….” language is well-suited.
- Lists seem guaranteed to be incomplete, risk obsolescence, and encourage gaming

Engineering safer alternatives: support for Dr. Wegrzyn's hypothesis

Table 1. Prior Studies That Identified Mutations of Concern That Were Later Identified in GOFROC Studies, And Exceptions to The Idea That They Are Associated With Increased Risks

Mutation Identified to Prompt Enhanced Concern That Was Derived From GOFROC Studies [8, 9]	Prior Studies Not Involving PPP Creation That Identified These Mutation	Exception
Hemagglutinin (HA) Q222L (influenza A[H5N1] virus)	[12–18]	Context dependence: changes do not quantitatively shift receptor binding in related H5 influenza virus strains [18]
HA S133A, S135N, S123P, S155N	[14, 19]	. . .
HA T156A, Q222L (influenza A[H7N9] virus)	[20, 21]	. . .
Polymerase B2 subunit PB2 E627K, D701N	[22]	Misleading inference: both absent in 2009 pandemic influenza A(H1N1) virus [23]; could have led to its misclassification as low risk

Abbreviations: GOFROC, gain-of-function research of concern; PPP, potential pandemic pathogen.

Thank you!

Questions and discussion!