Soliciting Stakeholder Input for a Revision of Biosafety in Microbiological and Biomedical Laboratories (BMBL): Proceedings of a Workshop

DETAILS

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The National Academies of
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COMMITTEE ON SOLICITING STAKEHOLDER INPUT FOR A REVISION OF "BIOSAFETY IN MICROBIOLOGICAL AND BIOMEDICAL LABORATORIES": A WORKSHOP AND VIRTUAL TOWN HALL[1]

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[1]The committee members were not involved in the writing of the proceedings of the workshop.

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This proceedings of a workshop has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published proceedings as sound as possible and to ensure that the proceedings meets institutional standards for objectivity, evidence, and responsiveness to the study charge. We wish to thank the following individuals for their review of this proceedings:

Kenneth Berns, University of Florida (emeritus)
Sherry Bohn, University of Maryland
Maureen Ellis, International Federation of Biosafety Associations
Robert Ellis, Colorado State University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse, nor did they see, the final draft of the proceedings before its release. The review of the proceedings was overseen by Ron Atlas of the University of Louisville, he was responsible for making certain that an independent examination of the proceedings was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the proceedings of a workshop rests entirely with the author and the National Academies of Sciences, Engineering, and Medicine.

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INTRODUCTION

Since its publication by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) in 1984, Biosafety in Microbiological and Biomedical Laboratories (BMBL) has become the cornerstone of the practice of biosafety in the United States and in many countries around the world. The BMBL has been revised periodically over the past three decades to refine the guidance it provides based on new knowledge and experiences—allowing it to remain a relevant, valuable, and authoritative reference for the microbiological and biomedical community.

Seven years after the release of the BMBL 5th Edition, NIH and CDC are considering a revision based on the comments of a broader set of stakeholders. At the request of NIH, the National Academies of Sciences, Engineering and Medicine conducted a virtual town hall meeting from 4 April to 20 May 2016 to allow BMBL users to share their thoughts on the BMBL in general and its individual sections and appendices. Specifically, users were asked to indicate what information they think should be added, revised, or deleted. Major themes from the virtual town hall meeting were further discussed in a workshop held on 12 May 2016 in Washington, DC. The workshop was also webcast live. A steering committee was appointed by the National Academies of Sciences, Engineering, and Medicine to lead and moderate the workshop discussion. This document encapsulates the discussion of the major comments on the BMBL that were posted on the virtual town hall (http://nas-sites.org/bmbl/) prior to 12 May 2016 and the various BMBL comments and issues related to biosafety that were raised during the workshop by participants who attended the meeting in Washington DC and those who listened to the live webcast.

A total of 257 comments were posted on the virtual town hall from 4 April to 20 May. The majority of the comments pertained to Section VIII (112) and there were 41 general comments. The total number of comments for the rest of the BMBL sections and appendices are as follows: Section I (4); Section II (15); Section III (6); Section IV (22); Section V (10); Section VI (3); Section VII (3); Appendix A (11); Appendix B (9); Appendix C (4); Appendix D (2); Appendix E (4); Appendix F (3); Appendix H (1); Appendix I (2); Appendix J (4) and Appendix K (1). There were no comments on Appendix G and L on the virtual town hall. The comments on the virtual town hall were from individuals affiliated with the following type of institutions: university lab (36); animal facility (11); government lab (23); public health lab (120); private lab (27); clinical lab (3); and other (37). A total of 71 miscellaneous comments were sent in by the online workshop participants. Not all the comments from the virtual town hall and the online workshop participants were discussed during the workshop, only the major comments; these are presented in bold and italic font in this document. Comments posted on the virtual town hall after the workshop are not included in this workshop summary but they may be viewed at the virtual town hall website. The workshop had a total of 115 attendees, 22 attended in person and 95 viewed the webcast. A copy of all comments posted on the virtual town hall and those that were sent in during the workshop have been provided to NIH and CDC.

This document was prepared by Camilla Y. Ables as a factual summary of the discussion that occurred during the workshop. The role of the steering committee was to review the comments posted on the virtual town hall prior to the workshop, share the major comments from the online workshop participants, and lead/moderate the discussion of these comments as well as the issues brought up by those who attended the workshop in person. The statements contained herein are those of the author and the virtual town hall meeting and workshop participants and do not necessarily represent the views of all users of the BMBL who may or may not have posted comments on the virtual town hall, the workshop participants, the steering committee, and the National Academies of Sciences, Engineering, and Medicine.

WORKSHOP DISCUSSION

Soliciting Stakeholder Input — Opening Remarks by NIH and CDC

According to Deborah Wilson (NIH; one of the editors of the forthcoming BMBL 6th Edition), the BMBL 5th Edition was completed with input from over 200 scientists, biosafety professionals, and subject matter experts—yet, despite the participation of numerous individuals in the previous BMBL revision, there were criticisms that the scientific and biomedical communities were not given the opportunity to provide input. She said for the next BMBL revision, a more open and transparent process will be employed, with input from users of the BMBL (obtained via the virtual town hall meeting and workshop).

Wilson said she is interested in hearing comments about a couple of areas, most importantly, she said she hopes the following questions will be addressed:[1]

- **Should the BMBL remain performance based or should it be more prescriptive, be more regulatory in nature**?
- **To what degree should the BMBL be revised—is a major revision needed or only a minor one?**
- **Should there be editorial and technical updates?**
- **What new information or special topics should be included in the BMBL?**
- **What new agent summary statements should be included in the 6th Edition of the BMBL?**
- **Are the agent summary statements adequate; are they useful, what information should be added to these statements?**

The BMBL as a Guidance Document

Paul Meechan (CDC; co-editor of the BMBL 6th Edition) reiterated that the BMBL has been historically a guidance document. He added that although it has been used internationally, as the basis of international guidance and regulations, it remains as a guidance document in the United States—it is not based on regulations and is centered on thoughtful risk assessment. Meechan said all the comments received (via the virtual town hall and the workshop) will be looked at and considered and international partners will be consulted for harmonization.

Q&A Session with NIH and CDC

After the introductory remarks from Wilson and Meechan, the chair of the steering committee, Bob Ellis (Colorado State University) opened the floor for questions from the workshop participants (those attending in person and those viewing the live webcast). Robin Schoen (National Academies of Sciences, Engineering, and Medicine) asked if a bit more information could be provided about the revision process—to answer such questions as: How is the team assembled? Does the document go through review? Will it be published in the Federal Register?

Wilson said there is an executive BMBL steering committee,[2] composed of federal employees, and an editorial board that is also composed of federal employees from different agencies and mission partners. She clarified that the BMBL is not a regulatory document and hence will not go through public comment and review. She noted that the BMBL has historically been performance based and has served as the standard for similar documents around the world but there have been suggestions to make it a regulatory document, hence, they (BMBL editors) want to know if users think it should be more prescriptive. Wilson added that for each section of the BMBL there will be a lead (a federal employee) as well as subject matter experts, who will be recruited from all over the country and the world (not federal employees). Tom Ksiazek (University of Texas Medical Branch [UTMB]; member of the steering committee) explained that the pressure to make the BMBL more prescriptive or more regulatory is due to the current regime of select agents; but not everyone handles select agents, so this document serves a larger audience. He said he thinks the BMBL should remain performance based.

[1]The virtual town hall commenters were not asked to specifically address these questions.

[2]This executive BMBL steering committee is not the same as the steering committee, which was appointed by the National Academies of Sciences, Engineering, and Medicine to lead and moderate the workshop discussion.

Jim Welch (Elizabeth R. Griffin Foundation) commented on the use of the word "should" in the BMBL text about occupational medicine/health being cognizant of risks. He suggested that the text be worded more strongly to encourage researchers to be aware of the risks. His concern is that the use of "should," which some people interpret as something one has the option to not follow, is part of the reason why occupational health does not learn many of the risks that workers face until exposure has occurred.

Wilson was then asked to clarify the intent of the BMBL—who is the audience? She explained that it was meant to provide performance-based guidance to biomedical and life sciences laboratories and clinical laboratories, although there have been other guidance documents for clinical labs. She said it was meant for use in the academia, industry, and government but it has been used broadly, i.e., as basis for many other guidelines and even regulations in other countries. Wilson added that, since NIH and CDC do not have regulatory authority, the BMBL should not be considered as a regulatory document. Meechan noted that a number of institutions and agencies have taken general performance-based recommendations from the BMBL to craft more prescriptive guidance specifically suited to their institute or field, such as clinical laboratories. He said he doesn't see a problem with this and thinks that clinical labs have done a good job in tailoring BMBL recommendations to their specific needs. He asked if the BMBL should be expanded to have additional appendices for a series of greater or narrower fields and added that although this might not be to their best interest, the editors are open to discussing this.

David Harbourt (USAMRIID[3]) inquired about the plans to have a clinical-specific BMBL (supplementary document) and an agricultural-specific BMBL. Wilson said they have asked the USDA to look at and revise the BMBL Appendix D (which USDA created). She said USDA is also developing a companion document that will address agricultural needs; however, USDA plans to refer to the BMBL where laboratory guidance is needed. Ellis mentioned that CDC published a document a few years ago about human clinical labs and veterinary diagnostic labs, particularly about the unique challenges with biosafety and containment of unknowns that come to the labs daily in large volumes. He said this document set some baselines but did not go into the details that are contained in the BMBL; it is a good supplement but the BMBL remains the basis for most of the work that is being done. Debra Hunt (Duke University; member of the steering committee) said clinical labs have also developed their own standard through the CLSI,[4] which addresses clinical microbiology and gets into specific procedures and safety issues and is revised every now and then. However, she noted, the BMBL still has the biggest impact on microbiology labs and clinical microbiology labs. Joe Kozlovac (USDA-ARS) said that USDA has, since 2013, planned to come up with guidance on agricultural biocontainment as a co-document of the BMBL. He said the addition of Appendix D to the BMBL 5th Edition was the first time that agricultural biocontainment was addressed in the BMBL; Appendix D will also be in the 6th Edition because the USDA guidance on agricultural biocontainment will not be done by the time this edition comes out (the guidance will take 5 to 6 years to finish). It will probably not be in the BMBL 7th Edition because the USDA guidance will have replaced Appendix D when this edition is released, he said.

Brit Hart (Association of Public Health Laboratories[5]) said APHL members are interested in having guidance on emergent pathogens or high-consequence pathogens. For example, when the recent Ebola outbreak occurred, not having the proper guidance became a problem, he added.

Ellis shared a comment on Section VIII that was received via the virtual town hall. The comment was about ***how updates on agent risk level can be expediently shared with the public, without waiting until the next edition of BMBL is released.*** He explained that if research has shown that it is perfectly safe to work with an agent at BSL[6]-2 instead of BSL-3, then the risk group is lowered from 3 to 2 but some entities will not recognize this change unless it is published in the BMBL. Wilson said this is an issue that has been discussed before and still has not been resolved,

[3]U.S. Army Medical Research Institute of Infectious Diseases.

[4]Clinical Laboratory Standards Institute.

[5]APHL and ASM (American Society for Microbiology) also sent the following recommendations in a letter dated 25 May 2016: 1) Inclusion of clinical and public health representatives on the BMBL steering committee and BMBL editorial board; 2) Inclusion in the text of the need for rigorous risk assessment prior to assignment of biosafety level; 3) Addition of recommendations for working with unknown clinical samples; 4) Addition of guidelines for pathogen inactivation; and 5) Addition of clinical guidance for all agent summary statements.

[6]Biosafety level.

but it is one of their primary interests. She said the BMBL editors have consulted the SALS[7] and other subject matter experts and written letters to help in situations where institutions felt they didn't have the authority or the wherewithal to make risk-based decisions—but the editors don't want to do this on a regular basis. She said the BMBL has to be more of a living document, posted in an electronic format that is easier to use and can be readily updated as science evolves and as public and global health situations change. Ksiazek said having the BMBL 5th Edition available only in digital form for a couple of years (no printed copies) was not ideal from the viewpoint of some users; it cannot be too much of a living document. Meechan said this is something that will not be done again.

Meechan said having 6 or 7 years between revisions leaves gaps and there were instances when people requested that NIH/CDC get the word out about working on an agent in reduced containment to encourage research. However, he said, NIH/CDC cannot simply share information that has not been fully vetted; there has to be a formalized process to make the BMBL a living document—there needs to be more formal interactions with organizations like SALS so when issues arise, there is a conduit for consulting with experts, and a decision can be obtained and published. Ksiazek, who is currently the chair of SALS said the process needs some work; SALS is willing to review and provide documentation, and has done so before but it is not within SALS's power to change the process. He said a process that parallels that for select agents probably makes the most sense.

Patricia Delarosa (NIH) said she thinks the greatest area of confusion is with the risk assessment, across the board, both in the public health and lab sector but more so in the public health sector. She also commented that the BMBL does a good job of telling users when to increase the BSL for special procedures but provides very little instruction on when BSL can be decreased. Citing the incident where a nurse was infected with Ebola as an example (the hospital PPE[8] was not adapted), she asked if there could be something added in the risk assessment section that gives BMBL users a better idea about increasing or decreasing BSL to address certain risks. Ksiazek said risk assessment is a formal science but experience counts as well; sometimes one is presented with a new situation for which there is no experience—and a practical approach is needed to deal with it, not just assign this to BSL-4. Meechan said that hospitals are different from labs, the BMBL cannot advocate for humans to be put in level 4 containment because hospitals are not able to do this. Delarosa said it would be very helpful if the BMBL could better communicate risk to people, as this is an important component of risk assessment.

General Comments on the BMBL

Ellis went over the following major comments that were posted on the virtual town hall:

Appendix F addressed emergency responses, which appears in the BMBL 4th Edition, but it is not found in the BMBL 5th Edition. Ellis said that while he agrees that each lab should have appropriate emergency response plans, it would be difficult to lay out specific emergency response plans in the BMBL—because different labs deal with different types of pathogens with different emergency response requirements. He suggested that for the next edition, the editors consider telling BMBL users to work with their institution, which would have their own plans, in crafting emergency response plans for their labs.

The terms "risk group" and "biosafety level" are used interchangeably, which should not be the case.[9] Ellis said risk groups are not changed without a deliberative process; biosafety levels should be determined based on proper risk assessments—this needs to be communicated in the BMBL.

Perhaps the BMBL could address containment and biosafety in relation to gain of function, dual-use research, and CRISPR[10]/Cas9[11]. Ellis said a discussion of these fairly new topics (perhaps in the introduction part) seems

[7]Subcommittee on Arbovirus Laboratory Safety; SALS is under the American Committee on Arthropod-borne Viruses (ACAV), which is under the American Society for Tropical Medicine and Hygiene.

[8]Personal protective equipment.

[9]A risk group is a classification based on the relative hazard of an infective microorganism. A biosafety level is a designation based on a composite of the design features, construction, containment facilities, equipment, practices and operational procedures required for working with agents from various risk groups (WHO. 2004. Laboratory Biosafety Manual, 3rd Edition. Available online at http://www.who.int/csr/resources/publications/biosafety/Biosafety7.pdf?ua=1. Accessed July 14, 2014).

[10]Clustered regularly interspaced short palindromic repeats.

[11]CRISPR associated protein 9.

appropriate. References could be made to the actual documents published by agencies that handle concerns particular to these topics, he added.

Fieldwork is probably beyond the scope of the BMBL, would this be covered by the document that USDA is working on? Joe Kozlovac said the USDA document has a section on fieldwork.

Should there be an easy-to-understand flow chart for certain things like how to clean up a spill?

Add a section on the importance of hiring credentialed biosafety professionals. Ellis said the BMBL is currently geared more towards providing guidance to PIs[12] and lab directors on how to safely conduct research but biosafety professionals should also be involved in making decisions on procedures.

Ksiazek said the approval of the use of an organism or a protocol is done by the IBC[13] in some institutions; the IBC also reviews notices of use and notices of intent, however, sometimes these are just reviewed by a safety officer or by the PI. This process is somewhat nebulous and ought to be clarified, he added.

There should be a section on the importance of developing a strong safety culture. Ellis suggested that instead of a stand-alone chapter, this could just be added to the introduction.

Ellis said there was also a comment about the recently released GAO[14] report on high-containment labs, particularly ***the six elements in the GAO report and ways of having bio-risk management standards***. He said he thinks these are important issues but is not sure where they should be addressed and how much detail should be included in the BMBL.

The BMBL should have an online version that can be updated as new information becomes available. Ellis commented that as changes arise, how can the BMBL be updated without having to rewrite and republish the full document? There needs to be a mechanism for relaying changes to BMBL users in a timely manner, he said.

Consider rearrangement of chapters. Ellis said most BMBL users are now accustomed to how the chapters are arranged; if they are rearranged then users have to get used to a different arrangement.

The concepts in the BMBL don't necessarily translate into low-resource environments. Ellis said he agrees with this comment but he also recognizes that the BMBL is primarily a U.S. document. Wilson commented that NIH and CDC are not going forward with the BMBL revision with the intent that it would be used as an international document.

Harbourt said he appreciates the need to hire credentialed biosafety professionals when possible but care should be taken so as not to close the avenue through which new biosafety professionals enter the profession, i.e., by initially holding entry-level positions to gain experience to eventually obtain credentials. Welch commented that business owners are required to have certified public accountants (CPAs) perform audits; similarly, there are certain research activities that require credentialed biosafety professionals. He added that although the BMBL is a U.S. document, the U.S. biosafety community is also trying to build up biosafety expertise around the world, and the only way this can be done is through certain types of credentialing programs that somehow measure competency to work at certain (biosafety) levels**.** He said it is an essential element of bio-risk management to have credentials that indicate a certain level of expertise. Meechan asked Welch to clarify if he is suggesting that the level of certification required be tiered or based on risk. Welch said there are labs, because of the type of research they perform, that do not necessarily require certified biosafety professionals. However, for institutions like CDC, NIH, Duke, Colorado State, and UTMB, he expects a certain level of expertise. He said verbiage that totally eliminates a need or a desire for credentialing will do damage. As a follow up on Welch's CPA analogy, Wilson said there are business schools and professional programs for advanced accounting but there are currently none for biosafety and this is why she supports

[12]Principal investigators.
[13]Institutional Biosafety Committee.
[14]Government Accountability Office.

Harbourt' s remark—because a more flexible approach is needed. However, she said she also believes in having certified biosafety professionals.

Sherry Bohn (University of Maryland) said stating that biosafety professionals need continual professional development would be helpful because biosafety is such a broad field and it is not static; it's important to get the word out to people who could assist in supporting and funding professional development. Kristie Yeakle (DAIG[15]) mentioned the difficulty of getting the training and still being expected to do their jobs. Hunt said the need for biosafety professionals should be emphasized to elevate the status of this professional category.

Meechan asked if the steering committee is suggesting that there be, in the BMBL introduction, language that says what the institution's role is in overseeing biosafety, which includes the development of professionals who perform biosafety roles that are commensurate with the obligations of the institution. Hunt clarified that the steering committee is not giving recommendations; its members are just making comments as BMBL users. Hunt said developing a strong safety culture could also be an institutional issue. Delarosa mentioned that the Trans-Federal Task Force Report[16] Section 1.2 has recommendations for governance that would support a biosafety program; it also suggested having a laboratory biosafety specialist and other upper level management positions. She suggested dovetailing those recommended positions with the BMBL guidelines on good governance.

Ksiazek said applied biosafety research is lacking and safety officers use anecdotal evidence because of lack of data. He said there should be a way to hire people to do experiments that address issues that lab workers have to deal with. He noted that some experiments have been done in the 60s and 70s and very little has been published recently. However, he wondered if the BMBL is the right place for a discussion of this issue but it needs to be raised. Meechan agreed that the BMBL is not the right venue. He said this issue was mentioned in the 2009 Trans-Federal Task Force report; it needs to be brought back to the fore—without funding, it won't happen. Wilson said there are several ongoing federal activities that would have an impact on the BMBL. She asked Theresa Lawrence (HHS[17]) to go over these activities.

Lawrence said there are federal activities under the offices of the White House, the Office of Science and Technology, and the National Security Council. She mentioned that a memo requesting that agencies develop an implementation plan to address specific activities for strengthening biosafety and biosecurity in the United States was released last October. She also said an implementation plan that addresses the culture of responsibility and biosafety/biosecurity governance[18] was developed and two reports were issued, one written by the Federal Experts Security Advisory Panel, which contains recommendations to strengthen biosafety and biosecurity and one written by the Fast Track Action Committee on Select Agent Regulations, which focuses on select agent regulations. She added that they have taken concrete actions to implement measures to enhance biosafety and biosecurity and address some of the issues being discussed today and that they will be engaging stakeholders in their activities.

As a follow up on the issue on the lack of applied biosafety research, Kozlovac said he thinks biosafety professionals will not be the ones who would actually conduct the research. He said researchers are needed who will be funded to do this, and the only way this can be done is by having applied biosafety research programs. He mentioned that he made this point in the Trans-Federal Task Force report and there are working groups on this that he and Theresa Lawrence are leading.

Hunt mentioned these general comments from the online workshop participants:

The BMBL should remain a guidance document, but much debate remains about the basis of its implementation. Hunt said the comment included a suggestion to ***add language that strengthens the intent of the BMBL and clarifies the use of the term "guidance".***

[15]Department of the Army Inspector General.

[16]Available online at http://www.ars.usda.gov/is/br/bbotaskforce/biosafety-FINAL-REPORT-092009.pdf. Accessed June 13, 2016.

[17]United States Department of Health and Human Services.

[18]Available online at the S3 website http://www.phe.gov/s3/Pages/default.aspx. Accessed June 14, 2016.

The discussion of risk assessment was a little dismissive. Ellis said the comment included a suggestion to ***add a small guide to tools for risk reduction, hierarchy of controls, risk assessment methods, and risk reduction methods and metrics to the BMBL***.

Comments on BMBL Section I – Introduction

Hunt noted that not too many comments were received on Section I. She shared the following comments that were posted on the virtual town hall:

Providing guidance on dual-use research of concern and gain of function.

Adding information on controlling hazards using the OSHA[19] model and work practices that are consistent with OSHA.

Updating laboratory acquired infections (LAI) data. April Shea (USAMRIID) said she agrees with the suggestion to include current LAI data but wonders if there is enough information on the causes of LAIs. Wilson pointed out that while there had been recommendations from many taskforces and workgroups to have LAI data collected and kept in a central repository, this central repository does not currently exist. She added that CDC and NIH, for practical reasons, will not wait for LAI data to accrue before proceeding with the BMBL revision. Ksiazek said there are occasional clinical reports that could be incorporated. Hunt said editors of agent summaries could be encouraged to include updates on LAIs that have been reported in literature. Bohn commented that the current working environment has changed drastically from the time when some of the LAI data were collected; many of the reported LAIs happened before biosafety containment became common practice. Wilson said many things have changed for the better; she agreed that this is worth mentioning in the BMBL. Bohn said it would be worthwhile to have this discussion especially if it shows that administrative controls, safety practices, use of PPE, and engineering controls help reduce LAIs. Wilson said the discussion would only be qualitative due to lack of data.

Reynolds (Ren) Salerno (CDC) said the inability to know what is going on and to make evidence-based biosafety decisions is due to the current culture, which does not encourage reporting; the practice of trying to find a single root cause of an accident and penalizing the individual who made the mistake prevents the reporting of LAIs, accidents, and near-misses. He said it would be helpful if the BMBL could articulate the concept of a culture that does not penalize those who made mistakes and instead encourages people to have regular discussions of laboratory incidents, whether good or bad, and to provide feedback without fear of retribution. Ksiazek mentioned an NRC[20] report that said there has to be an environment where people can report incidents without fear of retribution. He said he isn't sure that such an environment currently exists because in a lot of instances, somebody (e.g., Congress) wants to hold somebody responsible. Lawrence said that, as part of the implementation plan of the Federal Experts Security Panel, they are working on addressing the culture of responsibility as well as the issue of incident reporting by developing a nonpunitive voluntary incident reporting system. Kozlovac commented that not everyone gets penalized for reporting and that agencies/labs should come forward and make this a norm, regardless of the press, because there will be a shift eventually. Shea clarified that determining the root cause would be more for writing modern and accurate risk assessments.

Comments on BMBL Section II – Biological Risk Assessment

Hunt said the following suggestions were posted on the virtual town hall meeting:

Adding a little bit more risk assessment information on toxins.

Explicitly noting that the aerosol route of transmission must also be considered by anyone referencing the BMBL as part of the risk assessment process.

[19]Occupational Health and Safety Administration.

[20]National Research Council. 2014. Safe Science: Promoting a Culture of Safety in Academic Chemical Research. Washington, DC: The National Academies Press. Available online at http://www.nap.edu/catalog/18706/safe-science-promoting-a-culture-of-safety-in-academic-chemical. Accessed July 9, 2016.

Replacing "infective dose" with "infectious dose" (editorial change).

Moving information on the transmissibility of select agents in cage mates to the respective agent summary statements in Appendix D. Harbourt said adding information on cage mate transmissibility would be valuable; he suggested that a caveat be included: that transmissibility is also dependent on the work practices of the husbandry staff.

Emphasizing that droplets, not just aerosols, contaminate the environment and might also be part of the covert exposure that might be experienced.

Salerno said the concept of risk assessment, i.e., asking what could go wrong and having a way of prioritizing the risks, was not well described in this section. He requested clarifying this concept better. Delarosa suggested adding, in the risk assessment chapter, the use of risk assessment for defining SOPs[21] that are used in lab biosafety manuals and biosafety manuals for specific facilities. Ksiazek said one of the issues is who reviews a risk assessment. He said the IBC is a mandated committee that reviews essentially all biosafety protocols that involve recombinant agents or materials and in some institutions the IBC reviews other biosafety protocols, but the BMBL does not fully address or mandate a formal mechanism for having documents reviewed by the IBC. Meechan said the risk assessment process mentioned in the BMBL does refer to the assessment being reviewed by the IBC. Hunt said there was a comment that ***not all IBCs review assessments***.

Comments on BMBL Section III – Principles of Biosafety

Ellis said there were several comments made on this section in the virtual town hall, including the comment that ***the BMBL lacks information on good microbiological practices and techniques, how people should be trained and proficient in these practices/techniques***. He said there were also comments about ***the concept of tertiary barriers being addressed in the BMBL*** and ***risk assessment of recombinant or synthetic nucleic acids;*** Ellis said recombinant or synthetic nucleic acids are now being actively studied and somehow need to be addressed. He added that NIH guidelines address recombinant or synthetic nucleic acids to a certain extent but some of the actual safety mechanisms that can be built into the local lab area should also be discussed. He said there were also comments about the ***HTML version of the BMBL, i.e., adding links to other references that can be very useful, and adding various mechanisms for transfecting cells***.

Meechan said the BMBL editors need input on the right terms to use, other than "shall" and "should", to tell BMBL users what's important. He further commented that even if the BMBL says something is mandatory, CDC and NIH are not in a position to enforce what the BMBL says should be done. Wilson said one idea is to define what "should" or "may" means in the context of the BMBL so that guidelines are not taken out of context by people who don't understand them or by other regulatory agencies, etc. She added that aside from having the definition, how institutions can implement a guideline could also be discussed in the BMBL and if the guideline should be made mandatory for institutions. Bohn said that as an entity or institution adopts the BMBL guidelines as requirements, the entity or institution should say that it is the one requiring the guidelines to be followed—and the institution should find a way to enforce them. Welch commented that when a document says something "should" be done, it means that the person in charge of the laboratory has a duty of care, i.e., the responsibility to mitigate a risk. An online workshop participant said ***the Guide for the Care and Use of Laboratory Animals (8th Edition, page 8) defines the terms "must", "should", "shall", etc. in the context of the document and that having something like this in the BMBL would be incredibly useful and would help frame decisions and discussions with researchers***.

Comments on BMBL Section IV – BSL Criteria

Ellis said aside from requests for clarification, there were comments posted on the virtual town hall about the following topics:

Eye protection with or without contact lenses. Ellis said perhaps it should be more clearly stated that all people must have some sort of eye protection. He also said maybe a little bit of information could be added on what that eye protection could be. Wilson pointed out that there is already a variety of standards for eye protection out there, such

[21] Standard operating procedures.

as ANSI,[22] which could be referenced. She said providing definitions for types of protective eyewear would be somewhat counterproductive since there is already established guidance. Meechan said that perhaps they should just talk about eye protection and not focus on contact lenses.

It would be great to have some reference to what eye protection should be worn in a clinical diagnostic lab versus bench work versus biosafety work.

Directional airflow/reversal of airflow. Ellis mentioned that there were repercussions, especially in select agent-approved labs, from the BMBL 5th Edition guidance on directional airflow. He said the statement that there could be no reversal was taken to mean that there could be not one particle of smoke that could go a half inch out of the lab when exhaust systems were tested. He added that this guidance has been applied more practically through the years but asked the BMBL editors to take a look at the wording as they go through the BMBL.

The HVAC[23] system. Ellis said a discussion of how the HVAC system works would be pretty extensive but he thinks that lab personnel should understand how it works and know why they have to leave the lab when the HVAC system fails, and understand the basics of HVAC system re-start.

Ellis said one comment that was editorial in nature was ***about the use of "suit laboratory" and "cabinet laboratory"—there appears to be typos in this section.*** Wilson explained that the errors could be due to the redundancy in presenting information, which entailed a lot of copying and pasting. She explained the rationale for being redundant—people do not read the BMBL cover to cover; they only read parts of it or just print out certain sections of the manual. She asked the workshop participants if information in the BMBL should be consolidated and not presented repeatedly. Several workshop participants, including one online workshop participant said ***redundancy is helpful, do not consolidate the information.***

Ellis also mentioned the following comments from the online workshop participants:

If the intent of the BMBL is not to limit the applicability of its guidance to research labs, then it will help to have a remark to that effect. Meechan said they were not intentionally limiting the application of the BMBL to research labs, the BMBL says "microbiological and biomedical", it doesn't say "research laboratories". He added that they will make sure that the scope of the BMBL stays as wide as possible.

Include the term and concept of "duty of care". Could the definition include the criteria under which not following the guideline is expected or is acceptable? Wilson said if the BMBL editors decide to incorporate the term "duty of care", the Office of General Counsel has to be consulted because the term has legal connotation. Or there might be a way to come up with another term, she added.

Regarding the use of "should" and "shall", who takes the responsibility for enforcing compliance? It would be helpful if the BMBL stated that a best practice of biosafety is for the institution to put in place policies for everyone to follow when working with biological material. The policies will be informed by the BMBL, but the BMBL is not the policy. Most of the problems with wording arise when institutions don't have policies.

Bohn said she wonders if a performance standard could help in situations where what is required for biosafety conflicts severely with some of the GMP,[24] especially with startup companies.

Handwashing sinks (hands-free) should also be required in BSL-2 labs. Ellis said this requirement might be a burden to BSL-2 labs. He added that maybe adding procedures for proper exiting and handwashing and something about future consideration for having hands-free sinks, at least one at the exit area of the BSL-2 lab, would work.

Ellis said several edits were also suggested in this section and there were other comments, including one about ***increased stringency and justification that supports increasing level of precautions for BSL-1 agents.*** He also ex-

[22]American National Standards Institute.
[23]Heating, ventilation, and air conditioning.
[24]Good manufacturing practices.

plained that all comments received were or will be looked at and that even if the comments were not discussed during the workshop, they will be sent to the BMBL editors.

Wilson asked the workshop participants to comment on the signage and posting in BSL-1 labs. Ellis said signage in a BSL-1 lab is helpful because it would alert people who might be at risk (immunocompromised etc.); however, there is a point where people will stop reading signs, when there are too many of them. Melissa Morland (University of Maryland) made a comment about manufacturing attenuated vaccines in BSL-1 and requiring signage and then giving these vaccines to other people—what is the message we are sending out if we're warning people who manufacture them but we inject them into other people? Ellis commented that one aspect of this issue is the volume that the manufacturing side handles versus the volume being administered; this is about risk assessment and judgment call, he said. Welch said signs have impact on people who are new to the environment or who are foreign to it, such as maintenance workers or new employees, etc., not on people who work there. If there is a risk to people who are never or rarely at those BSL-1 labs then this is the reason why signage is needed, he added.

Requiring lab coats and eye protection when entering BSL-2 labs. Ellis said a problem with this requirement arises if there are common open areas in the lab where people have their desks; are these people required to wear lab coats and eye protection when they are at their desks or only when working at the lab bench? He said maybe a practical statement can be made about this. He also mentioned a comment about ***developing plans for dealing with spills of infectious materials;*** he said he agrees this information should be in the BMBL but it doesn't have to be a step-by-step spill clean-up protocol, this should be developed at the local level (lab).

Before closing the discussion of Section IV comments, Hunt mentioned the following comments from the online workshop participants:

Eye protection and determination about face shields or respirators should be based on risk assessment—this is not an absolute requirement as written in the BMBL.

Testing and certification of HEPA filters annually. Ellis said he thinks the standards are very well defined and understood by most people.

Hunt shared the following comments from the online workshop participants:

BSL-1 signage is helpful to define when biological materials can be used in a lab, to indicate that a sink is present, and when the lab is really only for nonviable materials and chemicals. Persons who use the lab rarely, such as clinical research coordinators, otherwise believe they can handle biological materials anywhere—having a sign reassures them that they are using the right lab.

Risk assessment is a judgment call, as was just noted. However those that use the BMBL as a guide for inspections rarely give credit to local risk assessments that are based on a comprehensive assessment of risk at the organization. It would be beneficial if the BMBL would include language that empowers organizational leadership to present a detailed risk assessment as a justification to not employ a recommended practice that is written in the BMBL. Ksiazek said if a protocol was developed that diverts from the recommendations it should be reviewed by the institution and should be supported by a documented formal risk assessment.

Comments on BMBL Section V – Vertebrate Animal BSL Criteria

Ksiazek said there was a comment about ***whether BSL-2 waste can be removed by simple surface decontamination and moving it to an area where it is autoclaved or in some instances, having it removed by a commercial medical waste company.*** He said he thought this approach is adequate. Wilson said she does not recall a requirement for treating BSL-2 waste before it leaves the animal room or the lab, this is only required for BSL-3. Ksiazek said the generally accepted procedure is not taking the waste to the dump; the formal procedure is to decontaminate it in an autoclave or to hand it over to commercial waste disposal companies. Hunt said there was a comment about ***a little disparity between BSL-2 and the animal section where it seems to suggest that waste needs to be autoclaved before being removed from the animal facility.***

Ksiazek shared another comment about ***animal work approvals—whether the protocol is reviewed by the IBC or the IACUC.***[25] He said sometimes the IACUC wants the protocol reviewed by the IBC before they will look at it, or vice versa. He thinks there is a way for getting it reviewed where both of them do their parts, he said. He added that he doesn't think that the IACUC is responsible for biosafety but sometimes, the IACUC thinks it is. This decision depends on the institution and what its historical perspective has been.

On the issue of occupational health and review, Ksiazek said this is an institutional issue that is addressed when working with select agents, which requires medical surveillance. He said he isn't sure if pre-employment evaluation is part of the requirement but if there are pre-existing conditions, they should certainly be considered in terms of the biohazard that is presented to the worker from an occupational standpoint. He noted that there were other comments on this section that were posted on the virtual town hall; he said these will be passed on to the BMBL editors.

Comments on BMBL Section VI – Principles of Laboratory Biosecurity

Ksiazek discussed two comments in this section that were posted on the virtual town hall. One was about ***inventories and how it is done***. He said an inventory is only mandated at the select agent level and there are no requirements for using specific means of keeping track of agents in one's inventory. He added that the important principle is to keep track of what you have, be able to present your inventory, and have a way of verifying that the inventory is accurate when select agents are involved. The other comment was about having ***a written security plan.*** Ksiazek said this is mandated as part of the select agent registration process. The BMBL is not necessarily the appropriate place for this, but this could be mentioned in the select agent section, he added.

Comments on BMBL Section VII – Occupational Health and Immunoprophylaxis

Ksiazek said in the previous BMBL editions, it came across that IND[26] vaccines are needed, e.g., in order to work with Venezuelan equine encephalitis, you need to be vaccinated. He also said that the Army Special Immunizations Program is an asset that has been discontinued and that accessing the USAMRIID IND vaccines has become almost impossible because they are practically not available. He added that there is no source of funds to support or broaden this program, but sometimes, when there's an outbreak, an arrangement can be made with USAMRIID to immunize a special group of people but this is ad hoc and it is not easily done. He said in terms of immunizations it should be made clear that IND vaccines are no longer available and risks should be addressed in other ways.

Ksiazek said the requirement for surveillance for infections, i.e., anybody who doesn't show up for work should report to their supervisors and be evaluated by competent medical authorities if they are showing clinical indications of infection, addresses occupational health and surveillance.

Wilson said the editors decided to remove the term "medical surveillance" in the previous BMBL edition because they wanted labs to have a more active program, i.e., a preventive program. She said they changed the term to "medical response plan" to make sure that people will put preventive measures in place.

Ellis mentioned a comment about ***obtaining the most current vaccination, revaccination, and timeline information***. He said he thinks that adding links to ACIP[27] and other bodies that would provide this information would probably be the best way to address this comment.

Comments on BMBL Section VIII – Agent Summary Statements

Ksiazek said there was a request to ***move the listing of all the arboviruses to an appendix***. He said he thinks it is in a relevant place now and moving it to another appendix would make it harder to track it down.

Ksiazek also mentioned a comment about ***the recommendation for HEPA Filtration on Lab Exhaust for O'nyong-nyong virus and the Ibaraki virus in the table***. He asked that the editors take a look at this.

[25]Institutional Animal Care and Use Committee.
[26]Investigational new drug.
[27]Advisory Committee on Immunization Practices.

Ksiazek also brought up another issue related to arboviruses: the process of changing the risk group level and biosafety level practices. He cited the case of the Oropouche virus, wherein SALS did the review and CDC/NIH provided the information to the investigator but the institutional biosafety officer wouldn't accept the risk level change and asked that it be upgraded in the BMBL table. He said that determining a way for getting these changes reviewed and publishing them for public consumption would make the process less burdensome.

Wilson asked if it would be a good idea to again reiterate in this section that institutions are empowered to change their containment levels and their practices based on individual expert's assessment. Ksiazek responded that this has always been the case. He cited two examples of risk level changes that were adopted at the local level: one was for the flu virus; the other was for the TBE (tick-borne encephalitis) virus. Wilson said it takes a while for the risk group level change to get to the point where it is published in the BMBL. Ksiazek asked what can be done to streamline the process; if there should be a reference in the BMBL to the online approved list of select agents, which gets updated more often than the BMBL.

Ksiazek said there was a comment posted on the virtual town hall that mentioned ***a clinical report published in January this year about four confirmed cases of HIV infections in nonclinical technicians***; he said the agent summary statement should be updated. He also mentioned a comment about ***reviewing occupational health support services on an annual basis;*** it doesn't have anything to do with a biosafety program but it has to do with prevention in the larger sense, he said. Wilson said she thinks the comment is not about reviewing this section in the BMBL annually but that occupational health programs or medical response programs need to be reviewed annually based on the portfolio. Ksiazek said that in general, institutions should have a document that lists what they have in order to care for individuals if they become ill. He noted that most of the other comments posted on the virtual town hall are for the subject matter experts, he said the group that will review this section should take a look at *Francisella tularensis*.

Wilson asked the workshop participants to comment on the usefulness and the format of the agent summary statements. Hart said some members of his organization (APHL) like the Health Canada MSDS[28] style because it is very clear and concise. He said the agent summary statements are great in terms of how they are written and that they provide a lot of information, but they are not always consistent with each other, whereas the MSDS have a very consistent format. Bohn said it would be nice to have an online version that can be easily printed out and easily updated if necessary, one that is compartmentalized. Salerno agreed that making the agent summaries available online, with references to online resources might be more advantageous than trying to collect everything and putting them in a book that becomes out of date.

Salerno commented that those who have been in the biosafety community for a long time interpret the agent summaries differently than someone who is relatively new. He said that a lot of diagnostic labs all over the country are now staffed by relatively naïve biosafety professionals who may have the perception that the inherent characteristics of an agent define the biosafety level. Because of this, he said, there is a need to further emphasize the importance of risk assessments and that the agent summary statements only define the inherent biochemical properties of agents, the risk is dependent on how these agents are used in the lab. The institution's responsibility to conduct risk assessments—make the judgment and take responsibility—has to be explained. It would be helpful to emphasize what the agent summary statements are for and how the risk assessments use them but don't exclusively rely on them, he added.

Wilson said the current agent summary statements are written in a way that they provide additional information to assist people in conducting risk assessments; they are perhaps more difficult to use than MSDS because they need to be interpreted. She asked if the format should be retained or if the MSDS format should be used. The MSDS are clear and concise, which make them easier to read—but, she asked, are they really useful in terms of providing data needed for risk assessments? Ellis said his lab personnel use these two documents for different purposes: agent summary statements are used for risk assessments in individual lab situations and MSDS (or Agent SDS) are used for emergency medical response. Hunt said two comments from the online workshop participants were ***in support of the MSDS format for the summary statements***; she said one commenter also ***prefers the MSDS style*** and wanted ***decontamination methods to be included, especially for agents that are resistant to disinfection.***

[28]Material Safety Data Sheet.

Ellis said there were requests posted on the virtual town hall for ***additions to this section, i.e., other agents such as MERS;*** this and all other requested additions will be forwarded to the BMBL editors. Ellis also said there were several comments on ***updating LAI information***, which are useful for risk assessments. He also commented that he finds the agent summary statements to be more useful than the Canadian Public Health Lab summary sheets for doing risk assessments. Michelle McKinney (CDC) cautioned against trying to make the BMBL everything for everyone. She said the agent summary statements are a perfect example—is there a need to model them after the Canadian MSDS, and is there a benefit in replicating those documents that already exist? She noted that there are lots of resources out there for conducting risk assessments aside from the BMBL agent summary statements; these include the Canadian MSDS and the Manual of Critical Microbiology. She said a review of the agent summary statements is welcome but she would not advocate for mimicking other existing documents. Ellis, Hunt, and Ksiazek agreed with McKinney's suggestion.

Hunt mentioned the following comments from the online workshop participants:

The agent summary statements should only provide known facts about an agent, not unknown information.

The MSDS format is preferred.

The current format of the summary statements discourages local risk assessment.

Reconsider the overall writing format, mention setting and staffing vary from lab to lab, and encourage institutional risk assessments.

Adding an appendix on how to write a lab-specific manual or SOP would be helpful.

Comments on BMBL Appendix A – Primary Containment for Biohazards

Ellis said there were several comments posted on the virtual town hall that pertain to this appendix and these will be handed over to the BMBL editors. He noted that there is one really long and valuable comment that he thinks should be looked at by the editors; he suggested that the editors work with the person who submitted this comment to ensure accuracy throughout this appendix. He said the other notable comments include ***an incorrect vacuum diagram; the use of Bunsen burners or UV lamps in biosafety cabinets***; ***and training on the use of biosafety cabinets, i.e., how they function, how they can keep you safe and how they can be compromised.*** He said a statement about training and encouraging it would be very helpful and working with ANSI would help address these comments.

Ellis also mentioned a request to ***add information on recommended controls for cryostats and microtomes.*** He said he's not sure where this information should be addressed in the BMBL but it would be helpful to have better guidance on this topic.

Ksiazek said a comment that was repeated a couple of times was about ***the number of individuals that can work in a biosafety cabinet.*** He said the number obviously depends on the size of the biosafety cabinet, but two people should be able to work in a six foot cabinet, provided that they adhere to procedural rules etc. In some production and diagnostic labs it is almost a requirement that two people work in a biosafety cabinet, he added.

Harbourt asked if the BMBL editors would consider addressing the minimum performance criteria for downdraft tables because their use is currently in vogue, particularly for certain procedures in ABSL[29]-3 and ABSL-4 labs. He said NIH has guidance on local exhaust ventilation and asked if this guidance or parts of it could be incorporated in the BMBL. He also said it would be helpful to have some information about types of exhaust ventilation units and a discussion of when the use of downdraft tables has merit. Ellis said this is an excellent comment that was not posted on virtual town hall and that it would be good to address it. Ksiazek commented that having no ANSI standard for certification is an issue.

Harbourt also mentioned being forced to do all manipulations on any infected animals inside primary containment at ABSL-3 and having to use biosafety cabinets for some procedures when downdraft tables could not be procured

[29]Animal biosafety level.

immediately. He asked if the recommendation to handle infected animals and/or infected materials only within primary biocontainment can be looked at. Particularly, he asked if the BMBL could discuss when this practice should really be required—should this be a blanket requirement regardless of the experimental conditions. Wilson said when this recommendation was written in the BMBL no one expected it to be applied in a regulatory fashion, because there are procedures with animals that are dangerous when done in primary containment. She said out of necessity downdraft tables were being called primary containment, which they are not. Wilson thinks the BMBL editors should look at the recommendation to work on infected animals only in primary containment and refer to the use of local exhaust ventilation devices or slot hoods. She added that the language can be worked on to broaden the intent because there are procedures that are more dangerous when done in a biosafety cabinet than outside of it. Ellis asked if there might be a way to address this issue from a risk assessment standpoint.

Wilson said it's a shame that Rubbermaid boxes have to be used to move nonhuman primates in order to maintain primary containment. She thinks this should probably be addressed in the BMBL. Yeakle said that based on a risk assessment that her lab conducted, using Rubbermaid boxes to move nonhuman primates put their personnel at risk more than the animal. Yeakle reminded participants that engineering controls in the lab are intended to prevent an agent from contaminating the lab while moving animals; to avoid creating a hazard for the lab employees the lab needs to be decontaminated if the animal is not in some kind of a primary containment device. Harbourt said what can be done depends on institutional policy or the procedure itself; there are times when biosafety professionals have limited flexibility as to what containment equipment or devices they can work with.

Shea said she noticed some conflicting guidance in the BMBL concerning the use of PPE in lieu of primary containment in situations where primary containment is not feasible; there are sections that say this but other sections essentially say that all work will be done in primary containment—could a clarification be made as to which of these practices is considered best practice and could the contradiction be eliminated?

Hunt mentioned the following comments from the online workshop participants:

It seems that practices required or recommended for ABSL-3 in a BSL-3 enhanced space should be different from recommendations for ABSL-3 in other locations. Ellis and Wilson said there is no formal definition for "enhanced".

The NIH guidelines have just been updated to address containment for nonhuman primates at BSL-4.

Comments on BMBL Appendix B – Decontamination and Disinfection

Ellis said he thinks there should be a section that addresses the selection of inactivation methods, validation of inactivation, and safety testing of inactivation for removal of agents from a higher to a lower level of biosafety containment. He also mentioned the following comments from the virtual town hall:

Include some standardized approach for inactivation. Ellis said there have been failures and questions about inactivation so perhaps a format for developing inactivation procedures and validation methods for these procedures would be a good addition.

Add a recommendation on how often bleach mixtures should be made. Ellis said it would probably be best for this information to come from the manufacturer or the MSDS of different decontamination agents. He also said if a product will be used off label, studies should be conducted to confirm that it will work in the correct concentration and contact time.

Add a chapter on waste management. Ellis said he thinks the BMBL is not the place to have a lot of information on waste management and because local, state, and regulatory agencies will have their own regulations it will be difficult to have something in the BMBL about this that would be useful to everybody.

Hunt said an online workshop participant commented that ***a BSL-3 enhanced is a change-in and shower-out shower facility and a BSL-3 lab only requires a Tyvek suit***. Another comment she shared was ***BSL2+ is not a recognized level in the BMBL but it is used to refer to some labs.*** Ellis said there is no definition for BSL-3 enhanced or BSL-2+ that will satisfy everybody, because those are specific to whoever is using these labs; adding another mechanism of control,

containment, or protection should be based on a risk assessment. Salerno said he completely agrees with Ellis and would not suggest adding the definitions of these terms. Delarosa said the push for defining BSL-2+ and BSL-3 enhanced comes from management. It is for building or designing a facility and determining features, it is not about having enhanced practices. She suggested that instead of defining BSL-2+ and BSL-3 enhanced, maybe the alternatives can be discussed (e.g., cabinet labs being used in England and The Netherlands for higher level labs).

Salerno also commented that there seems to be a sense in the community that the BMBL is going to provide all the answers and all that needs to be done is follow what the BMBL says. It needs to be better explained that the BMBL only provides guideposts—what labs do has to be specific to their own risk assessment and activity. Hunt said an online workshop participant commented that ***it is the regulatory agencies that are using the BMBL as the bible and not recognizing subject matter experience and risk assessments.***

Comments on BMBL Appendix C – Transportation of Infectious Substances

Hunt said most of the comments received via the virtual town hall were about specific things and the DOT[30] and IATA[31] regulations; she said a lot of people asked for ***inclusion of IATA regulations on the transport of biologicals***. Ellis said he believes that because changes in regulations happen every year it would be better to refer to the IATA and DOT websites at the very beginning of this section and make it clear that BMBL users should access those websites to get the most up-to-date information.

Hunt also mentioned the following comments that were posted on the virtual town hall:

The person whose name appears on the declaration of dangerous goods should be familiar with what is being shipped because he/she will be called.

Make the section more user-friendly by listing the material to be imported or transported and the regulations that apply to it rather than listing the regulation and the types of shipment they would apply to.

Make sure that transport permits are up to date.

Transport of arthropods needs to be addressed in this section.

Ksiazek said he thinks we are getting dangerously close to losing our ability to ship some stuff and we need to do something about it—what can be done? He asked if federal agencies could do more to encourage FedEx to ship biological materials.

Comments on BMBL Appendix D – Agriculture Pathogen Biosafety

Ellis said there will be a standalone agricultural BMBL document in the future (as mentioned by Joe Kozlovac earlier); Appendix D will stay as it is, with updates, until the standalone document is released.

Comments on BMBL Appendix E – Arthropod Containment Guidelines

Ksiazek said there was a suggestion to ***cover insectaries in more detail***. He said the current version of the BMBL provides a link to ACME (American Committee on Medical Entomology) guidelines for insectaries that handle infectious agents. He said he agrees with this approach.

Comments on BMBL Appendix F – Select Agents and Toxins

Ellis said he agrees with the approach of referencing websites where CFRs[32] and updated regulations are found rather than discussing them further in the BMBL. He suggested providing an overview and then making references to these websites.

[30]Department of Transportation.
[31]International Air Transport Association.
[32]Code of federal regulations.

Comments on BMBL Appendix G – Integrated Pest Management

Hunt said no comments about this section were posted on the virtual town hall.

Comments on BMBL Appendix H – Working with Human, NHP and Other Mammalian Cells and Tissues

Hunt said there was a comment posted on the virtual town hall about ***text under Recommended Practices (page 383)***. She said the commenter is asking for ***clarification if it is all work or all aerosol-generating work that should be done in a BSC***[33]. She said an online workshop participant asked if any ***change is being planned in the BMBL with regard to the current effort in polio virus eradication.***

Meechan asked if Appendix H is useful and necessary, noting that these materials are mentioned in Section IV, under BSL-2 containment. Bohn said if these materials are put under BSL-2, then this appendix might not be needed; clearly explaining why these materials need containment and need to be worked on at BSL-2 would be important. Hunt said an online workshop participant commented that ***Appendix H is useful because it provides information that justifies how to work with these materials;*** she added that another online workshop participant wanted to see ***more emphasis on risk assessments in Appendix H.*** Ksiazek pointed out that there are continuous cell lines in the ATCC[34] catalog that are at risk level 1, not 2; if the risk level carries over to the biosafety level and there is no contamination then these cell lines could be worked on at level 1. Wilson said the possibility of contamination is an issue, i.e., contaminating a certified cell culture while working on it or receiving a "clean culture" from a manufacturer that is contaminated. She cited three incidents in their lab wherein a "clean culture" was found to be contaminated with HIV; this type of incident needs to be considered because it can and will happen, she added.

Hunt said an online workshop participant commented that ***the ATCC characterizations are just for shipping purposes***. Morland said the ATCC characterization of a material does not equate to how it should be handled and this is why Appendix H is useful to have. Hunt said an online workshop participant commented that ***well characterized cell lines are not always tested for adventitious agents that can be introduced in GMP environments and that contamination cannot always be controlled.***

Hunt said an online workshop participant asked ***if there will be more information on other aerosol-generating procedures—the published research is fairly old.*** Meechan commented that the information is old but it is still correct. Ellis said there may be new generators but Appendix H is not the place for this topic. Hunt said another online workshop participant said that ***this appendix is useful but could more emphasis be given to risk assessment here as well.***

Comments on BMBL Appendix I – Toxins of Biological Origin

Ellis said there were only a couple of comments on this appendix; one was about ***the definition of a biological toxin—is it a chemical or a biologic?*** He said the tables in this appendix are very useful but asked if information on common toxins, such as Diphtheria and Cholera toxins could be added. Ellis also said there was a question as to whether ***chemotherapy drugs and cobra venom could be considered as chemical toxins.*** Hunt said an online workshop participant commented that ***working with LPS***[35] ***is a challenge***.

Comments on BMBL Appendix J – NIH Oversight of Research Involving Recombinant Biosafety Issues

Hunt said one comment on the virtual town hall was about the inclusion of ***"Synthetic Nucleic Acid Molecules" to the appendix title and to update the definition on page 394***; she said this commenter also pointed out ***the omission that Section III-F experiments are exempt from IBC review and approval.*** She mentioned that there was a lengthy comment posted on the virtual town hall about ***dealing with the new realities of dangerous research, specifically the addition of a nongovernment committee of experts to the parties that review laboratory-created potential pan-***

[33]Biosafety cabinet.
[34]American Type Culture Collection.
[35]Lipopolysaccharides.

demic pathogens or research. She added that this comment also mentions dual-use research of concern (DURC), gain of function, and the NSABB[36]. Hunt suggested that updates be made.

Wilson said the comments about DURC, gain of function, and other attendant technologies will be discussed with the OSP[37] so these topics could be addressed in a way that the information does not become out of date prior to the completion of the next BMBL edition. Meechan mentioned saying something general about these technologies in the BMBL and not going into details that are too fluid. Bohn said she heard that DURC will be addressed in the recombinant section and in the select agent section and this worries her because DURC is not always a select agent or cross-recombinant. She asked if DURC could be addressed in the risk assessment section, i.e., say that as a risk assessment is performed, consider if the agent falls under DURC and then provide the resources that can be used for the risk assessment. She also asked if all upcoming technologies can be addressed in the risk assessment section. Ellis suggested that the BMBL editors refer to the most up-to-date guides, references, and regulations on DURC and other technologies. Wilson said the federal policy on DURC is very narrow right now, so they will take a narrow view. Meechan said the BMBL editors could mention DURC as part of risk assessment and then point to the section where DURC information is located—he guesses it will be in the recombinant section because it is under OSP. He added that they cannot go into the details of the current policies because they might be different by the time the next BMBL edition is published.

Hunt shared this comment from an online workshop participant: ***If the audience for the BMBL has changed since it was initially introduced, is it appropriate to keep its original scope? If it's a living document, we could and perhaps should change it with the changing times.*** Wilson said if the BMBL is being used in a way that it was not intended the editors would like to know about it and give it consideration. Hart said that while the BMBL was originally written more for academia and research, it is used by diagnostic labs and public health labs. He asked if it would be appropriate to add an appendix for their specific needs or to indicate the differences, in terms of risk assessment, between a public health lab, a clinical lab, and a research lab. Ellis mentioned that there is a CDC publication on clinical labs, human clinical labs, and veterinary diagnostic labs and asked if this document fills the gap. Hart said it is not the same and not as authoritative as the BMBL. Ellis said he thinks the document only covers day-to-day lab orientation and management and other topics that are not covered in the BMBL from a clinical and diagnostic lab standpoint.

Hunt said one other comment they received was that the ***bacterial agent summary statements include how specific organisms should be handled in the clinical lab versus the research lab but this is not the case with the viral agent summary statements***—so information should be added to the viral agent summary statements.

Welch pointed out that DIY[38] Bio are becoming popular nowadays and for those who use these home kits, the closest thing they have to safety guidelines is the BMBL. Could there be a reference to this, he asked. Salerno said the BMBL generally takes an agent-specific approach, which makes a lot of sense for research labs; however, often times in clinical labs the workers don't know what agent they have or they have a sample that could contain a variety of agents—this is when the agent-specific guidance becomes problematic. He mentioned hearing about a lot of confusion during the Ebola outbreak and now there is confusion with the Zika virus because of the Zika-Chik[39]-Dengue relationship and the listing of Chik as a BSL-3 agent; does this mean that any suspect Zika sample in a diagnostic lab has to be diagnosed in BSL-3? He said it would be worth clarifying this in the BMBL.

Ksiazek said it should be emphasized that a critical part of risk assessment is researching the topic, asking all the questions about risk, and looking at previous experience with the agent. There are allowances for handling an unknown sample in a clinical lab until you know what the sample is, he added. Hunt said there was a comment from an online workshop participant about ***including guidance for generic unknown samples (clinical and field samples) in the BMBL***.

[36]National Science Advisory Board for Biosecurity.
[37]Office of Science Policy.
[38]Do It Yourself.
[39]Chikungunya.

Comments on BMBL Appendix K – Resources

Ellis said the comment posted on the virtual town hall was to ***add NSF International as another resource***. Harbourt said the Department of Army reference is out of date.

Comments on BMBL Appendix L – Acronyms

There were no comments on this appendix.

Revising the BMBL: Final Thoughts

After the discussion of the BMBL sections and appendices, Wilson asked the workshop participants to address the following issues that she mentioned at the beginning of the workshop:

Should the BMBL remain performance based or should it be prescriptive?

Ellis said he agrees that it should remain performance based. Harbourt and Bohn said they prefer the BMBL to remain performance based. Harbourt said the current BMBL allows lab workers to accomplish their goals using different methodologies and making it prescriptive would take away their flexibility. Bohn said unfunded mandates would make it difficult for people to find workable solutions; having only one way to do something is scary.

Hunt said four online workshop participants commented that ***the BMBL should remain performance based***; she also shared the following comments from the online workshop participants:

More guidance is needed on the negative pressure differentials for BSL-2 (see Section IV BSL-2 D9). Documented support is needed for institutions and engineers to make changes. ***Guidance written in language that engineers are familiar with would promote changes, considering that engineers often make changes based on regulatory requirements rather than being convinced to do so by risk assessments.*** Wilson explained that negative or directional airflow for BSL-2 was recommended in order to address chemical odors, contaminant issues, and allergens that may be introduced to the lab when animals are brought in; there isn't a requirement for directional airflow at BSL-2.

There is no requirement but when it is needed, engineers take the minimal approach rather than having a differential that accomplishes the purpose.

Keep the BMBL performance based with emphasis on risk assessment.

Keep in mind that the BMBL is used as a basis for guidelines in other countries.

Consider if certain aspects should be prescriptive, such as minimum containment or facility design components, others should remain performance based.

Welch said if the true intent is to have a performance-based document, then the language in the BMBL should be performance based to avoid any confusion that it is a prescriptive document.

Hunt said an online workshop participant commented that ***it should definitely be performance based; with the multiplicity of public health and biosafety challenges and research avenues, and the accelerating rate of technological change in response to these challenges, any prescriptive approaches in the BMBL 6th Edition would most likely be obsolete upon publication; even real-time, web-based curation of the new edition would require constant updating of prescriptive procedures.***

To what extent should the BMBL be revised? What should be added to the 6th Edition, what should be deleted, what don't we need anymore?

Wilson said that based on the comments in the room she thinks the BMBL requires a few minor revisions. Delarosa said it has to be a living document. Harbourt and Bohn said it is an excellent reference but some areas need minor

revisions, and new items need to be added to them, such as up-to-date references—especially if it will be an online document; Bohn added that the BMBL editors should commit to updating it more frequently.

Should the BMBL be an online document, should it be a printed document, or both?

Yeakle said she thinks there is value in having both an online version and a hardcopy. Ellis said an online workshop participant also ***prefers having both a digital and a hardcopy***; the participant also said that ***the hardcopy would be good for those who may not have access to the online version, such as labs in developing countries***. Hunt said another online workshop participant commented that ***the online version would be essential for addressing the inevitable and needed amendments.***

Are the current agent summary statements adequate or should the content be changed?

Ellis said the earlier discussion was about the agent summary statements serving the purpose of the BMBL well and that some of them need to be updated or information should be added to them. Meechan and Wilson said they need to hear specific comments, i.e., what to add to these summary statements to make them more useful, but not requests to make them like the Canadian MSDS because doing that would result in having similar documents—this would be a waste of time and would not meet the purpose of the BMBL. Hunt said an online workshop participant commented that ***the agent summaries are good but they could be standardized as to content areas.***

Delarosa suggested having a modular BMBL, i.e., something that could be updated frequently and would allow users to only print out the sections they need, like the format that is available in developing countries.

Salerno requested that the editors consider adopting a management systems approach to safety. He said this means thinking about how developing metrics before putting a safety system into place can become a common practice; how to use risk assessments to set metrics; and how the effectiveness of the system can be continually evaluated so that the metrics are not simply LAIs or infections—so there is a way of tracking performance and evaluating, updating, and revising mitigation procedures based on data before accidents occur or major problems arise. Salerno also said that diagnostic and medical labs have relatively sophisticated quality management systems, which they are required to have, that embrace this approach. He said very few bioscience labs embrace a management systems approach to safety that diagnostic/medical labs require for quality, so this is worth considering.

Closing Remarks

Ellis thanked the BMBL editors, Deborah Wilson and Paul Meechan, and Jeff Potts (NIH) for giving the biosafety, research, and clinical community the opportunity to comment on the BMBL. Several online workshop participants also expressed their appreciation for the opportunity to give their input.

Appendix A

Biographical Sketches of Steering Committee

Dr. Robert Ellis is the Director of Biosafety at Colorado State University (CSU). He joined the faculty at CSU in January 1978, and is currently a professor in the Department of Microbiology, Immunology and Pathology. He was appointed to the CSU Biosafety Committee in 1978, and was Biosafety Officer from 1986 to 1989; He was reappointed to this position in 1997 and serves as a Biosafety Officer to this day. Dr. Ellis is a Certified Biological Safety Professional and a Diplomate of the American College of Veterinary Microbiologists (Honorary). He was elected to the American Biological Safety Association (ABSA) Council in October 2004 and served as ABSA President from October 2008 to October 2009. In addition to his CSU and ABSA activities, he served as Executive Director of the Conference of Research Workers in Animal Diseases (CRWAD) from 1987 to 2014, and was a member of the Scientific Advisory Board for the National Biosafety and Biocontainment Training Program (NBBTP) of the National Institute of Health (NIH) from 2006 to 2011. He currently serves on the Biosafety Committees for the National Renewable Energy Laboratory (NREL) and the National Wildlife Research Center (NWRC). Dr. Ellis is the founding Editor-in-Chief of Animal Health Research Reviews. He was the recipient of the Russian Academy of Agriculture Science, Division of Veterinary Medicine, Gold Medal of Achievement in the field of Veterinary Science in 2008 and the ABSA Everett Hanel, Jr. Presidential Award in 2015, which he earned for his outstanding contributions to ABSA. Dr. Ellis graduated from the University of Wyoming with a BS in Microbiology. He holds MS and PhD degrees from Purdue University, School of Veterinary Medicine.

Dr. Thomas Ksiazek is currently director of high containment laboratory operations for the Galveston National Laboratory at the University of Texas Medical Branch. He is also director of the National Biodefense Training Center and a world-renowned virus expert with 40 years of experience. Previously, Dr. Ksiazek was the chief of the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control, in Atlanta, Georgia. He had been in the Special Pathogens Branch at the CDC since 1991 after retiring from the U.S. Army as Lieutenant Colonel with 20 years of active duty service. Dr. Ksiazek is a member of the American Society of Tropical Medicine and Hygiene, American Society for Microbiology, American Association for the Advancement of Science, American Veterinary Medical Association, the Society of Tropical Veterinary Medicine, and is a member of the Phi Zeta Honor Society. He started his military career when he joined the U. S. Air Force in 1971, holding a position that year as Base Veterinarian at Sheppard Air Force Base, Texas. He then worked as Chief of Veterinary Services, Royal Air Force Chicksands, United Kingdom. Dr. Ksiazek earned his DVM from Kansas State in 1970, received a master's degree in virology in 1976 at the University of Wisconsin-Madison, and received a Ph.D. in epidemiology and virology in 1984 at the University of California, Berkeley.

Dr. Debra Long Hunt is currently Director of Biological Safety and an Assistant Professor in Community and Family Medicine at Duke University. She has also served as Assistant Director of Hospital Epidemiology, Manager of Infection Control, Infection Control Environmentalist of Environmental Safety and Hospital Epidemiology, Senior Medical Technologist of Clinical Microbiology Laboratory, and Medical Technologist of Clinical Microbiology Laboratory, all at Duke University Medical Center. Throughout her career, Dr. Hunt has been honored with several awards including the Duke University Presidential Meritorious Award, Becton-Dickinson Safety Recognition Award, and Arnold G. Wedum Distinguished Achievement Award from the American Biological Safety Association. Dr. Hunt is a certified Medical Technologist from the American Society of Clinical Pathologists and a Certified Biological Safety Professional from the American Biological Safety Association. She received her BA in Zoology from Duke University, Master of Public Health (MPH) at the University of North Carolina – Chapel Hill, and Doctor of Public Health (DPH) at the University of North Carolina – Chapel Hill.

Appendix B

Workshop Agenda

Soliciting Stakeholder Input for a Revision of "Biosafety in Microbiological and Biomedical Laboratories"

WORKSHOP

May 12, 2016

2101 Constitution Avenue, NW
Room 125, NAS Building
Washington, DC

AGENDA

9:00 Welcome, Introductions, Workshop Objectives, Agenda Overview, Discussion Format
Steering Committee

9:20 Remarks from NIH

9:35 Remarks from CDC

9:50 Q and A with NIH/CDC Reps

10:30 Morning Break

10:45 Discussion of Comments received via the THM (and any comments received during the workshop)

General Comments

Section I – *Introduction*
Section II – *Biological Risk Assessment*

Section III – *Principles of Biosafety*

Section IV – *Laboratory BSL Criteria*

Section V – *Vertebrate Animal BSL Criteria*

Section VI – *Principles of Laboratory Biosecurity*

Section VII – *Occupational Health and Immunoprophylaxis*

Section VIII – *Agent Summary Statements*

12:30 Lunch Break

1:30 Continuation of Discussion of Comments received via THM (and any comments received during workshop)

Appendix A – *Primary Containment for Biohazards*

Appendix B – *Decontamination and Disinfection*
Appendix C – *Transportation of Infectious Substances*

Appendix D – *Agriculture Pathogen Biosafety*

Appendix E – *Arthropod Containment Guidelines*

Appendix F – *Select Agents and Toxins*

Appendix G – *Integrated Pest Management*

Appendix H – *Working with Human, NHP & Mammalian Cells & Tissues*

Appendix I – *Guidelines for Work with Toxins of Biological Origin*

Appendix J – *NIH Oversight of Research Involving Recombinant Biosafety Issues*

Appendix K – *Resources*

Appendix L – *Acronyms*

3:00 Afternoon Break

3:15 Continuation of Discussion

4:50 Closing Remarks

5:00 Adjourn Workshop