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Office of the Deputy Director for Advanced Technologies and Strategic Partnerships
National Cancer Institute
National Institutes of Health
31 Center Drive
Room 10A03
Bethesda MD, 20892

RE: First-Generation Guidelines

June 29, 2006

Dear Dr. Compton:

This letter responds to the *First Generation Guidelines for NCI-Supported Biorepositories* as they appeared in the *Federal Register* on April 28, 2006 (71 Fed. Reg. 25184-25203) ("Guidelines"). It was prepared by the Data Sharing and Intellectual Capital Workspace (DSIC WS) of the cancer Biomedical Informatics Grid (caBIG™) initiative with input from the caBIG Tissue Banks and Pathology Tools and Strategic Planning Workspaces.

caBIG™ is a voluntary network or grid connecting individuals and institutions to enable the sharing of data and tools, creating a World Wide Web of cancer research. The goal is to speed the delivery of innovative approaches for the prevention and treatment of cancer. caBIG™'s Data Sharing and Intellectual Capital Workspace (DSIC WS) seeks to enable data sharing between and among caBIG™ participants by addressing legal, regulatory, and proprietary barriers to data exchange. Among these issues are the privacy and security of data exchanged, the nature of agreements among the centers, and the requirements of abiding by federal law and regulations, such as the Common Rule for Human Subjects Research, the FDA Regulations on Human Subjects, the Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rules, and state, local, and institutional requirements. DSIC WS contains about twenty regular participants, and an additional twenty to thirty ad hoc participants. Participants include intellectually property and regulatory lawyers, patient advocates, policy specialists, biomedical researchers, bioethicists, bioinformaticists, experts in technology transfer, and others. More information is

available on the DSIC WS Web site at https://cabig.nci.nih.gov/working_groups/DSIC_SLWG/index_html. We strongly applaud this attempt to develop guidelines in this complex and fragmented area and note with approval many of the proposed provisions therein, notably the requirements:

- that SOPs be "printed in a manual that is readily available to all laboratory personnel" (Section III.1.C.3, *Guidelines Overview-Technical and Operational Guidelines* at 71 Fed. Reg. 25185-86);
- that a facility disaster plan include appropriate measures to protect personnel (Section III.1.C.6,*Guidelines Overview-Technical and Operational Guidelines at* 71 Fed. Reg. 25186);
- that staff review new and revised policies and procedures prior to implementation, and that documentation of staff review and any associated training be recorded (Section 1.C.4, *Guidelines Details–Technical and Operational Guidelines: Quality Assurance/Quality Control: SOPs Manual* at 71 Fed. Reg. 25191);
- that an honest broker-guided procedure be used to protect research participants' privacy for samples and data (Section 1.E, *Guidelines Details-Biorepository Informatics: Data Management and Inventory Control and Tracking: Ethical Legal Issues,* ¶1 at 71 Fed. Reg. 25193);
- that access to personal information be restricted to "only those" that need it, and limited to the "number of personnel" with such access (Section 2.B.4,*Guidelines Details–Ethical, Legal and Policy Guidelines: Access to Biospecimens* at 71 Fed. Reg. 25195); and
- for formal tissue disposal/destruction procedures and disclosures of conflicts of interest (Sections 2.D.2 and 2.D.3, *Guidelines Details–Ethical, Legal and Policy Guidelines; Custodianship at* 71 Fed. Reg. 25196).

These items and others reflect on the security and integrity of tissues and information, a topic of interest to DSIC WS, and are components of a comprehensive, well-thought out security program.

Substantive comments and requests for clarification are laid out on the following pages. We have also proposed a number of organizational and editorial revisions, which will be forwarded separately as a red-lined version of the Guidelines.

As an initial matter, our readers found the document difficult to navigate and analyze. A Table of Contents, with each section and subsection designated with a number or letter, would vastly improve the ability to review, analyze and implement the document. Also, many sections of the document seem to address similar, if not identical, issues. Some text passages are repeated verbatim in multiple sections of the document. The document may have been organized in

this fashion to provide a general statement of principles, followed by more detailed specifications. However, the document would be much easier to read, analyze and implement if these sections were organized thematically. Consolidating the general and detailed sections would have the added benefit of simplifying the process of updating the Guidelines and ensuring that language is exactly consistent and non-repetitive for each issue addressed. Should NCI determine not to adopt this approach, we recommend the frequent use of cross-references in the "Overview" and "Details" sections.

SUBSTANTIVE COMMENTS

1. **Economic Impact. Section II - Background,** paragraph 3, at 71 Fed. Reg. 25185 states that the Guidelines "…will be distributed to managers of all NCI-supported intramural and extramural biorepositories, who will be initially asked to conform to them on a voluntary basis." Members of DSIC WS have expressed concern that this sentence implies an intent to work towards mandatory standards or regulations for NCI-supported biorepositories. First, the economic burden of not only achieving compliance, but establishing mechanisms to demonstrate and report such compliance can be substantial. These administrative burdens will require significant reallocation of funding and resources. Second, future technology and laws will certainly drive changes in best practices, and the Guidelines would therefore need to be revised periodically to reflect these changes. Institutions may not be able to react as quickly to such changes if they are required to wait for the Guidelines to be redrafted and finalized. Finally, research institutions will already have ample incentive to adopt best practices, as it is in their best interest to ensure the integrity and usability of the tissues they store and the information that can be derived from those tissues. Therefore, DSIC WS recommends that the Guidelines remain voluntary best practices that can be implemented in a manner fully appropriate to the size, scope, function, and resources of each institution and that certification of specific practices and capabilities not become conditions of receiving NCI funding.

2. **References to ISBER Best Practices**. Section III.1.A.18, *Guidelines Overview-Technical and Operational Guidelines: Biospecimen Collection, Processing, Storage, Retrieval and Dissemination* at 71 Fed. Reg. 25185, refers to the ISBER Best Practices, available at http://www.isber.org/ibc.html. DSIC WS is uncertain of the degree of overlap between the Guidelines and the ISBER Best Practices, and whether it would be possible to incorporate the latter document by reference. Some readers found the Guidelines inconsistent in scope in some areas, providing very general guidelines on some topics and very specific standards in others (e.g., the sections on "Biospecimens Storage" and "Biospecimens Shipping" read as if they were

excerpted from existing protocols such as the ISBER Best Practices). Incorporating the ISBER Best Practices (or similar community-vetted documents of similar granularity) may assist in achieving a consistent scope by leaving this document high-level and allowing the more technical ISBER Best Practices to provide more specific standards.

3. **Direction of Biospecimen Collection and Processing**. Section III.1.A. 7, *Guidelines Overview-Technical and Operational Guidelines: Biospecimen Collection, Processing, Storage, Retrieval and Dissemination* at 71 Fed. Reg. 25185, states that biorepositories must ensure that a pathologist directs the collecting and processing of surgical and autopsy biospecimens. In practice, this is not always necessary. For example, the collection of post-surgical, completely anonymized tissues that would otherwise be destroyed can be collected with no risk to patients. A physician may extract the tissue, but the researcher who requests and receives the tissue (who has appropriate IRB approval to do so) would not need to be a physician, merely qualified to collect and process the sample in such a way as to protect its integrity and usability. We recommend broadening this passage such that physicians are required only for tissue extraction, and that qualified personnel direct the collecting and processing of surgical and autopsy biospecimens.

4. Security Policy and Procedures for Biorepositories.

a. Development of Biorepository Security Policy. Section 2.C.3, *Guidelines Details-Ethical, Legal and Policy Guidelines: Privacy Protection* at 71 Fed. Reg. 25195, states that "[t]he level of security should be appropriate to the type of biorepository." It is well established that a number of factors must be considered in developing security policies and procedures, including the type of personal information stored with the collected biospecimen in the biorepository, potential harms that may result from inadvertent disclosures of data related to the specimen, the type of biohazards associated with the specimen, and any other factors that would have negative safety, financial, or other impacts. For a comprehensive consideration of security risk assessment factors, it would be useful to consult published guidance from the National Institute of Standards and Technology (NIST). See, e.g., NIST Special Publication 800-30, *Risk Management Guide for Information Technology Systems* (July 2002).

b. Written Policies for Biorepository Security Systems. Section III.1.C.4, *Guidelines Overview-Technical and Operational Guidelines: Quality Assurance/Quality Control* at 71 Fed. Reg. 25186, requires organizations maintaining biorepositories to establish security systems, including equipment monitoring and alarm systems. We strongly recommend that this

section also require biorepositories to maintain a *written* set of security policies and procedures that address management, operational, and technical security. Virtually all computer security authorities specify the criticality of written documentation. See, e.g., *NIST Special Publication 800-53 (Revision 1), Recommended Security Controls for Federal Information Systems* (March 2006), p. 12 (documenting the agreed-upon set of security controls in the system security plan is "paramount to an effective information security program"), and the HIPAA Security Rule, 45 CFR § 164.316 (b)(1), Documentation, requiring maintaining policies and procedures implemented to comply with the HIPAA Security Rule and all actions, activities and assessments conducted pursuant to requirements of the HIPAA Security Rule.

c. SOPs for Security. Section 1.C, *Guidelines Details–Technical and Operational Guidelines: Quality Assurance/Quality Control: SOPs Manual* at 71 Fed. Reg. 25191, lists a number of topics that must be addressed by SOPs. We strongly recommend the addition of a bullet in this section that specifically requires SOPs on administrative, technical and physical security; the additional bullet could note that SOPs for HIPAA-covered entities should be designed to comply with the requirements of the HIPAA Security Rule. We also note that this section requires rewriting SOPs every two years. We recommend changing the wording to "no less often than once every two years, and whenever significant changes in practices, procedures, technology, law or regulation necessitate an update."

5. **Allocation of Liability**. Section III.1.D.6, *Guidelines Overview–Technical and Operational Guidelines: Biosafety* at 71 Fed. Reg. 25186, requires biorepositories to establish indemnification agreements with users of biospecimens except where prohibited by law. While the DSIC WS understands that materials transfer agreements must address issues of liability, we do not agree that all agreements should require indemnification as a default condition of transfer. The general practice in this area is to allocate liability but often through an assumption of responsibility rather than an agreement to indemnify. Therefore, we recommend that this section be rewritten to advise biorepositories to enter into agreements that provide for the allocation of liability, but not to mandate a particular approach.

6. **Criteria for Access to Biospecimens**. *Guidelines Details–Ethical, Legal and Policy Guidelines: Access to Biospecimens and Data,* Section 2.B.2, second bullet at 71 Fed. Reg. 25195, states that one criterion for obtaining access should be the use of a "standardized, validated research biomarker assay methodology." DSIC WS notes that the criterion for access to repositories of "standardized, validated" technology could preclude the use of novel technologies with specimens distributed by biorepositories seeking to comply

with the Guidelines. We suggest changing the criterion to "Research methodologies that are standardized, validated, or otherwise evaluated as scientifically sound."

7. **References to Informed Consent Template**. Section III.2.A.1, *Guidelines Overview–Ethical, Legal and Policy Guidelines: Informed Consent,* at 71 Fed. Reg. 25186, states that "[t]he NCI will provide all of its repositories with a sample consent template, which should be reviewed and adapted by the relevant IRB." Further, *Guidelines Overview-Technical and Operational Guidelines: Biorepository Informatics: Data Management and Inventory Tracking and Control,* Section III.1.E.2 at 71 Fed. Reg. 25194, describes an "NCI Infrastructure to Support These Guidelines" and states that "The NCI will provide biorepositories with a *sample consent template*, for example, the NCI Sample Consent Form for Use of Tissue for Research (Appendix 1) ("NCI Sample Consent Form"). DSIC WS recommends that the Guidelines include more information about the history and use of the NCI Sample Consent Form, such as how long it has been in use; how feedback from users is received and implemented; and how often such feedback is received. This information could provide users of the Guidelines with greater confidence that the NCI Sample Consent Form can be used to provide clear and comprehensive notice to human subjects. DSIC WS notes that feedback received on the *Guidelines* represents one such opportunity to collect such feedback and ensure that it is incorporated into the NCI Sample Consent Form if appropriate.

   To that end, DSIC WS notes that the NCI Sample Consent Form does not address the specific question of whether genetic information (e.g., the sequencing of genes or even larger sequences) may be made generally available, e.g., in open-access research repositories or on the World Wide Web. We recommend that this issue receive further examination, which may perhaps be coordinated with approaches taken by other NCI programs.

SUGGESTED CLARIFICATIONS

1. **References to Donor Patient Privacy.** Section III.1.A. 3, *Guidelines Overview-Technical and Operational Guidelines: Biospecimen Collection, Processing, Storage, Retrieval and Dissemination,* at 71 Fed. Reg. 25185, refers to "donor patient privacy." It is worth noting that not all specimens will derive from patients as of the time of collection or redistribution. Some materials come from decedents, organ donors, relatives of patients, research participants, or others. We recommend using the phrase "tissue donor privacy."

2. **Position vs. Location.** *Guidelines Overview-Technical and Operational Guidelines: Biospecimen Collection, Processing, Storage, Retrieval and*

Dissemination, Section III.1.A.4 at 71 Fed. Reg. 25185, refers to identifying the "position" of every stored aliquot. DSIC WS recommends the word "position" be changed to "location." Some storage protocols enable the researcher to locate containers of 1-200 samples, and researchers are able to select the sample of interest with a minimum disturbance to other samples. Most do not have storage practices that indicate the exact position of each individual sample. In addition to addressing a potential burden on individual biorepositories, this issue has a connection to patient privacy. As a best practice, records that contain information on individuals—even records of the location of de-identified samples—should contain the minimum amount of information necessary to achieve their purpose. Under current practices, many biorepositories are able to function fully without identifying the position of each sample.

3. **Definition of "Unique Identifier".** Section III.1.A.4, *Guidelines Overview-Technical and Operational Guidelines: Biospecimen Collection, Processing, Storage, Retrieval and Dissemination*, at 71 Fed. Reg. 25185, uses the term "unique identifier" for each storage container. We assume that this usage refers to the container of each aliquot or sample, rather than a freezer, cabinet, liquid nitrogen tank, or other multiple-sample repository. Use of this term can be further clarified by providing a definition of "unique identifier" in the *Guidelines Glossary* (71 Fed. Reg. 25200-203) that makes clear that it refers to an identifying number, code, or other retrieval element for each specimen or aliquot in each repository. We further recommend that the definition of "unique identifier" specify that such identifiers should not include or be obviously derived from elements of protected health information (PHI) (defined in the *Guidelines Glossary* at 71 Fed. Reg. 25202) though the researcher may wish to use an honest broker service or process to enable re-identification of the sample if needed. Again, this issue is relevant both to the burden on individual repositories as well as meeting the "minimum necessary" best practice.

4. **Reference to "Universal Clinical Data Set."** Section III.1.B.1, *Guidelines Overview-Technical and Operational Guidelines: Collecting and Managing Clinical Data* at 71 Fed. Reg. 25185 states that "[t]he NCI will establish a minimal 'universal' clinical data set." We are not certain what the term "universal clinical data set" means. We suspect it refers to a minimal set of CDEs associated with each biospecimen and utilized by any NCI-supported biorepository. We recommend that this usage be clarified by adding a definition of "universal clinical data set" to the *Guidelines Glossary*.

5. **Purposes of Biospecimen Storage.** Two references are made to the purposes of biospecimen storage. Section III.2.B.7, *Guidelines Overview–Ethical, Legal*

and Policy Guidelines: Access to Biospecimens and Data at 71 Fed. Reg. 25187 states, "Store human biospecimens only for research purposes according to approved protocols, not to serve individual research participants' needs or wishes." Very similar language appears at Section 2.B.5, *Guidelines Details-Access to Biospecimens and Data,* at 71 Fed. Reg. 25195. We are not certain what condition or irregular practice this statement is intended to address. We believe it refers to discouraging the practice of storing private specimens for participants, to be used at the participant's sole discretion. However, the phrase could also be interpreted to forbid individual researchers from maintaining unapproved, undocumented biorepositories. We note that our misunderstanding might be addressed by defining "participant" in this context and/or by describing the unsuitable practice the statement discourages.

6. **Scope of Potential Recipients.** Section III.2.A.3, *Guidelines Overview–Ethical, Legal and Policy Guidelines: Informed Consent* at 71 Fed. Reg. 25186, recommends "[d]ocumenting clear policies for biospecimen and data access." It is unclear whether this recommendation refers to access on the part of human subjects, researchers, tissue sample providers, or other stakeholders. We suggest expanding this section to make clear that policies should establish rules for providing (or restricting) access for all of these stakeholders.

7. **Approval for Shipping Biospecimens.** Section 1.A, *Guidelines Details–Technical and Operational Guidelines: Biospecimen Collection, Processing, Storage, Retrieval and Dissemination: Shipping Biospecimens*, ¶1, at 71 Fed. Reg. 25189, states that requests for transfer need to receive approval from "the appropriate committee." We suggest clarifying that this recommendation refers to any institutionally defined review process, such as a materials transfer committee, IRB, legal staff, or other reviewing office or body as defined by the biorepository's institutional policy and procedures.

8. **Curation of Validation Process.** Section 1.B, *Guidelines Details-Technical and Operational Guidelines: Collecting and Managing Clinical Data: Longitudinal Clinical Data*, ¶5, 71 Fed. Reg. at 25191, requires dedicated and trained personnel to "curate the validation process." We are not certain what this phrase means. We recommend rewording the phrase to clarify.

9. **Definition of "Universal Precautions."** Section 1.D., *Guidelines Details-Technical and Operational Guidelines: Biosafety: Biohazard Precautions,* ¶ 2, 71 Fed. Reg. at 25192, uses the term "universal precautions." We are uncertain if this is a term of art with specific meaning (such as that provided at 29 CFR Part 1910.1030(b), *Definitions* ("Universal Precautions"). We recommend that the term be included in the *Guidelines Glossary* with appropriate references.

10. **PHI and Audit Logs.** Section 1.E, *Guidelines Details-Biorepository Informatics: Assessing Biorepository Informatics System,* ¶ 3 at 71 Fed. Reg. 25192, refers to "audit logs of all access to protected health information in the database." This requirement uses the same definition of "protected health information" as the HIPAA Security Rule. In effect, this requirement would only apply to HIPAA Covered Entities, and to data that meets the narrow definition of PHI within those biorepositories. We recommend using a different, broader term (such as "data" or "information related to biological samples") to be sure that the auditability requirement is implemented as a best practice, which would also allow interoperability between HIPAA covered entities and other potential business partners.

11. **Fees and Cost Recovery.** Section 1.E, *Guidelines Details-Biorepository Informatics: Ethical and Legal Issues,* ¶ 3 at 71 Fed. Reg. 25193, states that "[d]ata about biospecimens should be provided on terms that are not exorbitant . . . [and] are otherwise not unduly onerous." The DSIC WS is unclear how the terms "exorbitant" and "onerous" are defined, and whether they should be distinguished. A related issue is the cost recovery charges repositories charge for transferring biospecimens. Some repositories calculate such charges on the basis of the cost of storing each sample (marginal cost), versus the cost of overhead divided by the number of transfers requested each year (full cost). We would be interested in the NCI's perspective on this issue and whether it can be addressed in future iterations of the *Guidelines.*

Thank you very much for considering these comments. We would be very happy to discuss any and all of these with you, and to provide additional assistance to future versions of the Guidelines. Contact information for the DSIC WS leadership is provided at the bottom of this document.

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