June 14, 2016

The Honorable Sylvia Matthews Burwell  
Secretary  
U.S. Department of Health and Human Services  
Hubert Humphrey Building  
200 Independence Avenue, S.W.  
Washington, DC 20201

Dear Secretary Burwell:

On behalf of AdvaMedDx, we are writing as a follow-up to our comments (see enclosed AdvaMed comments to the docket submitted December 7, 2015) regarding the Notice of Proposed Rulemaking (NPRM) on the Common Rule on changes to federal policy on the protection of human subjects and its impact on the research and development of \textit{in vitro} diagnostics (IVDs). We appreciate the thoughtful discussions we have had with key Agency staff, in particular Dr. Kathy Hudson. Those discussions were helpful in understanding the intent of key elements of the NPRM given the complexity of the wide-reaching proposal.

AdvaMedDx member companies produce advanced, diagnostic (or IVD) tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted organization that deals exclusively with issues facing \textit{in vitro} diagnostic companies both in the United States and abroad. Our members work to provide the latest diagnostic innovations to support the public health. Our organization advocates for a legal, regulatory, and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology.

While AdvaMedDx believes the rule is well intended, the proposal is overly broad in scope and presents a myriad of issues that we believe will jeopardize the U.S. research enterprise – from early research and Food and Drug Administration (FDA) product submissions that support product safety and effectiveness to development of new targeted therapies to advancement of personalized medicine. Given the limitations of the NPRM as currently written, we believe that solutions can be found in a more tailored, flexible policy without the corresponding detrimental effect on diagnostics research and new test development for patients imposed by the NPRM.

Given the significant impact of the proposed change in the NPRM to require broad informed consent on the research and development of \textit{in vitro} diagnostics in the U.S., we wanted to take this opportunity to discuss some of our concerns with the NPRM proposal.
and to share our specific solution for your consideration that can be readily addressed in the Common Rule to help address issues and ensure access to innovation for U.S. patients.

**Clarification of Key Points in the NPRM**

In subsequent discussions with the Agency, it was clarified that once consent is provided in the initial broad informed consent, it continues indefinitely for all biospecimens collected from that patient over a 10-year period. Once 10 years have passed, new broad informed consent would be required for new biospecimens collected thereafter. We understand, however, that this does not apply to pediatric patients who provide broad informed consent prior to age 21. Once a pediatric patient turns 21, no matter when consent was obtained in the preceding 10-year period, new informed consent would be required. We believe this will hinder development of IVDs needed for pediatric subpopulations – populations for which it is already challenging to develop products and to achieve FDA clearance or approval.

We also appreciated the Agency’s intent to establish a simple broad informed consent template but would note this template was not included in the NPRM. However, we nonetheless continue to have concerns about the practical implications and impact of the broad informed consent requirement as discussed below. Given the complexity of the proposed rule, its impact on the maintenance of existing IVDs, the research and development of innovative, new IVDs and numerous other concerns, we also continue to believe the NPRM should be re-issued with revised regulatory language that is plain and understandable per the Plain Writing Act of 2010 and per President Obama’s Executive Order 13563, Improving Regulation and Regulatory Review.  

**Impact of the Proposal for Broad Informed Consent**

During our meeting with Agency staff, we shared a number of our concerns about how the NPRM requirement for broad informed consent will impact IVD manufacturers. We thought it would be useful to reiterate those and share several additional concerns illustrating the significance of the issues raised with the NPRM.

**Examples of Impact of NPRM on IVD Research, Development, Maintenance and Improvements**

It should be noted that in order to meet FDA requirements for test validation for premarket review (i.e., IVD clearance and approval) to support safety and effectiveness, many companies purchase de-identified samples from large repositories (which collect surplus or leftover biospecimens from clinician’s offices, community centers, hospitals or laboratories) or they collaborate with academic medical centers to obtain leftover biospecimens. These de-identified biospecimens are difficult to source and can cost millions of dollars to obtain and maintain and months to acquire. The systems necessary

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1 Executive Order 13563 states that “[our regulatory system] must ensure that regulations are accessible, consistent, written in plain language, and easy to understand.” 76 Fed. Reg. 3821 (Jan. 21, 2011).
to implement the NPRM requirement for broad informed consent are expected to be even more costly; given that, it is unclear whether any institutions will actually shoulder the responsibility, enormous costs and liability associated with such systems. If not, availability of these vital biospecimens will be substantially depleted.

Indeed, if institutions fail to develop these systems, or until multiple systems are in place to assure collection of the hundreds of thousands of diverse biospecimens needed to research, develop and continuously validate diagnostic tests, we anticipate significant negative impacts on companies’ ability to develop critically needed IVDs, which in turn impacts public health. AdvaMed companies shared the following examples and issues:

- Requiring informed consent for de-identified biospecimens would greatly hinder the development and the clearance or approval of urgently needed products that are critical to public health or needed in times of crisis, such as products that aid in the diagnosis of Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV), or the IVDs used to diagnosis the Ebola and Zika viruses. It is not clear patients will provide broad informed consent in a trackable database for diseases which may be viewed as stigmatizing (e.g., Ebola). De-identified biospecimens are essential to validation of assays that are critical to public health. In particular, assays used to aid in the diagnosis of the Ebola and Zika viruses used de-identified patient samples during development and analytical and clinical validation studies. In the case of the Zika virus, one manufacturer brought de-identified clinical samples into the United States from Latin America to carry out product validation. The costs and logistical aspects associated with obtaining informed consent for the samples in Latin America and then tracking that informed consent all the way through product testing in the United States would be significant. Such high cost and timing hurdles would decrease the motivation of manufacturers to provide these emergency use products to the market.

- Use of leftover biospecimens avoids the ethical challenges of drawing samples from chronically ill patients and assures access to rare cancer biospecimens. Tumor marker immunoassays to monitor for disease recurrence, disease progression or response to cancer therapies require longitudinal biospecimens collections for FDA clearance or approval. Each new assay, as well as significant changes to assays or instruments and analyzers requires access to longitudinal biospecimen collections. In addition, biospecimens are needed to assess test performance when other cancers or conditions are present. Some of the cancers are rare and biospecimens are frequently drawn from sick patients and the volumes needed could be taxing to patients. To preclude the use of leftover biospecimens and require collection under informed consent would

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2 To ensure IVD test performance and accuracy and the ability to detect mutagen pathogens, companies must conduct continuous surveillance with biospecimens.
subject these vulnerable patients to repeated and unnecessary blood draws and volumes that could be taxing to patients.

- In some cases, new and innovative tests for rare conditions simply will not be developed. Due to the requirement to obtain informed consent, obtaining rare and unique biospecimens from around the world will become more difficult, and it is likely companies will not be able to obtain the biospecimens needed. This will ultimately hinder new test development. In such cases, companies will not be able to sufficiently establish a statistically powered cohort to perform the required clinical studies for FDA clearance or approval.

- Using de-identified biospecimens for research studies has been essential for emerging companies’ innovation. De-identified biospecimens are an important resource, especially when establishing prototype feasibility and researching new applications. For example, de-identified biospecimens were critical for developing what became an innovative immunosequencing test for minimal residual disease (MRD) by a small startup company in the U.S.; the initial study used de-identified residual material from a Children Oncology Group (COG) trial to establish immunosequencing as a viable and sensitive method for measuring MRD in acute lymphoblastic leukemia (ALL). If the startup company had to re-enroll patients, the project would have been delayed months, if not years. These types of samples are used to enable continuous improvement of in-production assays; testing the impact of modifications on real clinical samples is critical. Changing this policy will enormously increase costs and delay the improvement cycle of IVDs. The change proposed by the NPRM will stifle innovation, especially for smaller companies with minimal resources.

- Requiring informed consent for de-identified biospecimens will impact development timelines, delaying the availability of innovative, new IVDs to patients. In considering the impact on new test development for patients, timelines associated with clinical studies requiring informed consent from patients are typically much longer than those using de-identified biospecimens. Protocols requiring informed consent frequently involve an extended Institutional Review Board (or IRB) approval process because it must go through a full board review. As a result, if informed consent is required, a typical two- to four-week IRB approval for a protocol relying on de-identified biospecimens could take up to 3 months for IRB approval of the same protocol. After IRB approval, additional time will be needed for an informed consent clinical study to recruit subjects that meet the inclusion criteria set forth in the study protocol and to ensure that the consenting process and approved procedures follow regulations. Additionally, for many informed consent clinical studies, subjects may not be able to consent themselves. In these situations, the informed consent process will take much more time and require additional resources to find and obtain informed consent from patients’ legally authorized representatives.
Increased costs associated with IVDs requiring informed consent will force manufacturers to choose between the products or product improvements they will develop or to delay bringing products to the U.S. market. Companies shared a number of specific examples of the expected costs associated with the NPRM proposal.

- A significant portion of innovative technology is initiated by small startup companies that are often at risk due to timelines and funding. The additional costs and increased timelines will put more of these companies at risk and could therefore prevent or slow the advent of new technologies that may be critical to patient health or wellbeing.

- A number of infectious disease tests require routine product updates due to disease mutation or to changes in the standard of medical care. Some manufacturers have estimated that the requirements of the NPRM will increase the cost of biospecimens for feasibility testing (excluding the costs for the pivotal clinical trial) from $250,000 to $2 million and lengthen the development timeline to two years for each product.

- For one innovator company who has developed over 20 IVD tests for the U.S. market, including tests for expanded or modified claims, all relied on de-identified leftover biospecimens. The cost increase associated with developing tests that rely on biospecimens with informed consent is estimated between 200 and 340 percent more and as a result at least one-third of their tests would never have been brought to market as the investment needed for prospective, informed consent biospecimens would have been prohibitive.

- Excluding the costs associated with development of sites and associated IRB approvals needed to obtain informed consent, it has been estimated that the differential between use of prospective samples with informed consent and use of de-identified biospecimens was nearly $300,000 to collect biospecimens for 4ml of serum for one study. This represents a substantial hurdle for U.S. innovators, whether small and emerging growth companies or larger companies, in discovery and new technology development for new cures and therapies.

- The sheer volume of biospecimens needed is already challenging for innovators. Thousands of de-identified biospecimens are needed to develop and validate new Class III IVD instruments and analyzers. One company has estimated that the clinical trial costs associated with just five Class III IVDs would cost in excess of $8 million dollars and would take over 10 months to collect biospecimens with informed consent, adding a full year to the development time assuming the availability of such specimens.
In short, redirection of money and resources to obtain informed consent will limit the number of IVDs companies that will be able to research, develop, maintain or improve tests in the U.S. at a time when new IVDs are needed to help identify and battle public health outbreaks such as Zika or E. coli resistant to the antibiotic colistin and to advance the President’s Precision Medicine Initiative. In addition, innovators will be unable to introduce novel markers and low prevalence infectious disease analytes to the U.S. due to the lack of availability of specimens as well as substantial research and development costs. This will likely widen the gap between the availability of innovative, beneficial tests for U.S. patients versus what is available to patients outside the U.S.

**Precision Medicine**

In President Obama’s January 2015 State of the Union address, he unveiled the Precision Medicine Initiative (PMI) and allocated $200 million to the National Institutes of Health (NIH) to build the related Cohort Program and program focus on oncology. The cohort program is intended to be highly diverse reflecting the U.S. population based on race, ethnicity and ancestral lineages; social, geographic and economic milieus; and age and health status. The program will target both common and rare diseases, and mental illnesses. Furthermore, the PMI also aims to support the development of new diagnostics and a modernized regulatory approach at FDA to support new safe and effective diagnostics, which are essential to advances in patient care from oncology to cardiac care. We also note that the recent Combating Antibiotic Resistant Bacteria (CARB) National Action Plan has highlighted the development of novel diagnostics.

This new philosophy of moving away from the one-size-fits-all paradigm to targeted, individualized treatment requires broad availability to de-identified biospecimens, yet the NPRM requirement for broad informed consent will result in precisely the opposite – access to fewer specimens at greater cost, greatly limiting the ability to develop precision IVDs. We would also note the irony that the federal government has in part excluded itself from this requirement (see for example, the proposed exclusions for “public health surveillance activities including the collection and testing of biospecimens … to investigate public health signals or the onset of a disease outbreak” and “… surveillance activities and related analyses, or the collection and use of biospecimens conducted … solely for authorized intelligence, homeland security, defense or other national security purposes” at §101(b)(1)(v) and (vi)). AdvaMed and its IVD companies have been called upon by the U.S. government to assist in public health surveillance in recent public health outbreaks (e.g., the West Nile virus and the H1N1 virus) and homeland security issues (e.g., bioterrorism use of anthrax bacterium).

**Other Concerns with the NPRM Proposal on Broad Informed Consent**

Although you may be familiar with many of the concerns expressed about the proposed requirement for broad informed consent, we briefly restate a number of them here. We would also like to highlight the recent comprehensive review and analysis conducted by the Council on Governmental Relations (COGR) with support from the Association of Public and Land-grant Universities (APLU) of the 2,186 public comments on the NPRM. According to COGR, APLU and the Association of American Universities (AAU), “the
analysis found that over 95 percent of patients and members of the research community were opposed to one or more of the major proposed changes.” They stated that “there is broad consensus that the proposed regulations regarding biospecimens, as written, would be damaging to science, medicine and human health and would not improve participant safety and autonomy.”

**NPRM Proposal Will Further Limit Underrepresented Subgroups in IVD Studies**

Both FDA and NIH are statutorily mandated to increase women, minorities and underrepresented demographic subgroups in clinical studies. Nonetheless, the proposed rule’s requirement for broad informed consent will have the effect of excluding diverse and underrepresented demographic subgroups from the research and development of IVDs as it is unlikely the clinicians and community health centers that serve underrepresented demographic subgroups will develop or participate in the sophisticated and costly informed consent tracking systems required under the NPRM. In addition, IVDs will be rapidly rendered less effective if they cannot detect all versions of a virus or pathogen circulating in diverse subpopulations. We fear this will further exacerbate inequalities and disparities in the U.S. health care system.

**The NPRM Broad Informed Consent Template Does Not Represent Meaningful Consent**

In order to ensure the legally effective informed consent of the human subject, the informed consent process under 21 CFR 50.20 and 45 CFR 46.116 at a minimum provides for a discussion between the human subject and the investigator covering key elements of the investigation. As stated in the regulations, “An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.” It is not clear that a short informed consent template that is, in effect, a pro forma document, represents meaningful consent or that it truly achieves the objectives of informed consent underlying the Common Rule. In fact, numerous healthcare organizations and research organizations have noted the great difficulty in implementation of such broad informed consent and expressed concerns that it would not be sufficient for purposes of informed consent and instead would raise a host of further legal and practical concerns.

**The NPRM Broad Informed Consent Proposal Increases Privacy Risks**

Currently, the fact that a biospecimen is de-identified is the best possible protection of a patient’s privacy. The tracking system or database required to implement the broad informed consent that links a particular biospecimen(s) to a human subject’s informed

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3 The NIH Revitalization Act of 1993, PL 103-43, directed the NIH to establish guidelines for inclusion of women and minorities in clinical research and the Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112–144, directed FDA to investigate how well demographic subgroups (sex, age, race and ethnicity) in applications for medical products – drugs, biologics and devices, submitted to the agency for marketing approval are included in trials and to provide recommendations for improving the lack of availability of such data.
consent and enables them to withdraw such consent will have the perverse effect of increasing human subjects’ privacy risk. It is also unclear whether patients will provide informed consent in a trackable database for diseases which may be viewed as stigmatizing (e.g., Ebola). Databases linking biospecimens to specific patients may either be misused or targeted in order to deliberately disclose sensitive private information about patients.

**Costs Associated with Infrastructure Required to Track Informed Consent**

As noted in our comments to the NPRM and in our meeting with you, we are very concerned about the significant costs that will be incurred by any institutions which agree to create the elaborate and sophisticated tracking systems or databases needed to house broad informed consent and to ensure that only the biospecimens of human subjects who provided consent are utilized for secondary research and to allow such subjects the right to withdraw consent for research use of their biospecimen(s). Any institutions who agree to develop such systems, along with accepting the associated liability, will inevitably expect to recoup those costs from those who utilize the specimens. As noted above, we would expect this to have a cascading and negative impact on the research and development of IVDs as companies will inevitably have to limit the number of IVDs they develop due to the limited availability and increased costs associated with obtaining biospecimens.

**The National Academies of Sciences, Engineering and Medicine Have Expressed Concern**

As you may know, the National Academies of Sciences, Engineering and Medicine issued Part 1 of a two-part report in 2015 titled *Optimizing the Nation’s Investment In Academic Research: A New Regulatory Framework*. Part 2 of the report is expected to be released in 2016. The Part 1 report findings state “requiring consent for all research involving biospecimens, as contemplated by the ANRPM, would substantially increase administrative burdens on investigators, research staff, and institutions, and would markedly hinder the conduct of critical science.” Further, the recommendations section states that: “1. The committee recommends that Congress direct federal agencies following the Common Rule to institute a risk-stratified system of human subject protections that substantially reduces regulatory burden on minimal-risk research while reserving more intensive regulatory oversight for higher-risk research.”

**Proposed AdvaMed Alternative**

If the rule is to move forward, AdvaMed proposes that HHS expand the proposed exclusion for secondary research use of biospecimens to include the criteria contained in FDA’s *Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using*  

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Leftover Human Specimens that are Not Individually Identifiable. The expanded exclusion would apply when:

- The investigation meets the IDE exemption criteria at 21 CFR 812.2(c) (3).

- The study uses leftover specimens, that is, remnants of specimens collected for routine clinical care or analysis that would have been discarded. The study may also use specimens obtained from specimen repositories or leftover specimens that were previously collected for other research purposes.

- The specimens are not individually identifiable, i.e., the identity of the subject is not known to and may not readily be ascertained by the investigator or any other individuals associated with the investigation, including the sponsor. If the specimen is coded, it will be considered to be not individually identifiable if neither the investigator(s) nor any other individuals associated with the investigation or the sponsor can link the specimen to the subject from whom the specimen was collected, either directly or indirectly through coding systems.

- The specimens may be accompanied by clinical information as long as this information does not make the specimen source identifiable to the investigator or any other individual associated with the investigation, including the sponsor.

- The individuals caring for the patients are different from and do not share information about the patient with those conducting the investigation.

- The specimens are provided to the investigator(s) without identifiers and the supplier of the specimens has established policies and procedures to prevent the release of personal information.

- The study has been reviewed by an IRB in accordance with 21 CFR Part 56 [to assure that the subject cannot be identified].

We believe our proposed approach – paired with strong civil and criminal penalties on institutions, investigators or others that intentionally re-identify biospecimens that are not individually identifiable – is an acceptable compromise which will harmonize the Common Rule with FDA requirements governing use of de-identified specimens. We believe it is preferable to alternatives that have been proposed to expand the current waiver at 45 CFR 46.116(d) because our proposed compromise underscores and emphasizes the privacy of human subjects. We further believe this proposal is consistent with the recommendation in the National Academies of Science, Engineering and Medicine report to introduce a risk-stratified system to reduce regulatory burden on

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5 FDA’s Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable. P. 7-8.
minimal-risk research. As we have stated previously, we believe that research use of identifiable biospecimens requires informed consent and in these cases subjects should be able to control the use of their specimens.

In closing, we appreciate this opportunity to elaborate on our concerns with the NPRM’s proposal for broad informed consent. Please do not hesitate to contact us if you have any questions.

Sincerely,

Andrew Fish
Executive Director
AdvaMedDx

Attachment
December 7, 2015

Jerry Menikoff, M.D., J.D.
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852


Dear Dr. Menikoff:

On behalf of the Advanced Medical Technology Association (“AdvaMed”), we are submitting major comments in response to the Notice of Proposed Rulemaking on Federal Policy for the Protection of Human Subjects (“NPRM”). As detailed below, AdvaMed members strenuously object to the proposed limitation on biospecimens that are not individually identifiable for research and development. We are extremely concerned that certain provisions of the NPRM mark a stark departure from current federal requirements on which the medical device industry has relied heavily to research, develop, and make available to healthcare professional and patients important medical innovations. While we fully share the federal government’s overall intent of the NPRM to strengthen and modernize human subject protections, to facilitate valuable clinical research, and to reduce burden, delay, and ambiguity for investigators, we conclude that certain provisions of the NPRM, if finalized in its current form, would not further those objectives and would, quite the opposite, impede, slow, and stifle certain important medical device research involving the use of human biospecimens and would do so without strengthening human subject protections. Therefore, AdvaMed respectfully encourages the signatories of the NPRM, as well as the Food and Drug Administration (FDA), to consider, in light of public input including AdvaMed’s comments described herein, the potentially significant adverse and deleterious consequences that the NPRM, if finalized in its current form, could cause for valuable medical device research and development.

AdvaMed is the world’s largest trade association, representing manufacturers of medical devices, in vitro diagnostic (“IVD”), and health information systems. AdvaMed's member companies develop and

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2 The following federal departments and agencies are signatories to the Notice of Proposed Rulemaking: Department of Homeland Security, Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Commerce, Social Security Administration, Agency for International Development, Department of Justice, Department of Labor, Department of Defense, Department of Education, Department of Veterans Affairs, Environmental Protection Agency, National Science Foundation, and Department of Transportation.
3 The NPRM states that, “FDA intends to modify its regulations in light of this NPRM, to the extent appropriate, considering its unique statutory framework and regulatory mission.” 80 Fed. Reg. at 53981.
produce the medical innovations that are transforming health care through earlier disease detection, less invasive medical procedures, and more effective treatments for diseases and conditions. AdvaMed has more than 400 member companies, ranging from the smallest to the largest medical technology innovators and companies. AdvaMed advocates for a legal, regulatory, and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. AdvaMed promotes public policies that foster the highest ethical standards, earlier access to safe and effective medical products, appropriate reimbursement, and broad access to international markets.

AdvaMed has carefully reviewed the NPRM and evaluated its potential regulatory, scientific, public health, economic, resource, and legal effects on medical device research. AdvaMed concludes that the NPRM, if finalized in its current form, would substantially impair the development and limit the availability of new in vitro diagnostics (“IVDs”) for the accurate and reliable detection of existing and emerging diseases and conditions. The NPRM would significantly affect AdvaMed’s members because, while medical device innovators and manufacturers may not conduct research supported by Common Rule department or agency funding, our members: (1) conduct “clinical trials” not otherwise subject to FDA regulation at U.S. institutions that do receive federal funding; (2) conduct clinical investigations subject to FDA jurisdiction; and (3) receive biospecimens collected during federally funded research or “clinical trials” as defined by the NPRM. The NPRM explains that FDA intends to adopt harmonized regulations, to the extent permissible under FDA law and consistent with its regulatory mission; this has merited special attention from AdvaMed and its members, as any adverse effects of the NPRM, if implemented in its current form, could be replicated in regard to FDA-regulated human research.

AdvaMed believes that many of the NPRM proposals, especially the new requirement to obtain informed consent for the storage, maintenance, and secondary research use of biospecimens that are “not individually identifiable,” would be starkly inconsistent with FDA’s statutory and regulatory mission of promoting public health and ensuring that medical devices provide a reasonable assurance of safety and effectiveness. By rendering unavailable millions of existing biospecimens that are not individually identifiable, and imposing unrealistic regulatory requirements for the collection and research use of future biospecimens, FDA, if it were to adopt this policy, would (i) increase risks to subjects, as described below, and (ii) impede and stifle research and the development of safer, more effective, and novel medical diagnostics and treatments. Thus, AdvaMed strongly opposes harmonization of FDA regulations with the NPRM in its current form.

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4 FDA defines “not individually identifiable” to be “the identity of the subject is not known to and may not readily be ascertained by the investigator or any other individuals associated with the investigation, including the sponsor.” FDA Guidance, "Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable" (2006) (“Leftover Specimens guidance”). For purposes of this document, AdvaMed uses “not individually identifiable” to encompass both de-identified and coded biospecimens that fall within the scope of the Leftover Specimens guidance.

The existing policy is consistent with FDA’s efforts to encourage companies to conduct clinical trials in the U.S. rather than elsewhere in the world. The NPRM however, if finalized in its current form, would establish new and onerous restrictions that likely would lead to more companies executing their clinical trials elsewhere.

Below, AdvaMed identifies and describes the most potentially adverse NPRM proposals.

I. **Requiring Consent for the Collection, Storage, and Secondary Research Use of Biospecimens That Are Not Individually Identifiable (§§.102(e) and.116(c))**

A. **Current Diagnostic Assay and System Development Process**

AdvaMed’s members conduct research on and develop *in vitro* diagnostic (IVDs) assays and systems. The research and development process depends on the testing of biospecimens to demonstrate safety and effectiveness of the product. For the Department of Health and Human Services (HHS) to understand fully the potentially adverse effects of the NPRM on the IVD industry and, ultimately, on the public health by stifling innovation of important and potentially life-saving and life-sustaining IVDs, AdvaMed describes the three categories of IVD device studies used to support acceptable IVD performance:

1. For the majority of IVD products, acceptable development and/or performance is performed using **leftover surplus specimens**. Following current regulations and FDA guidance documents, institutional review boards (IRBs) generally waive informed consent in testing leftover specimens that are not individually identifiable. As a result, the cost of contracting laboratories to evaluate a new device is kept to a minimum, and manufacturers can afford to continually improve products and processes, offering innovative and enhanced solutions that increase accuracy of results and turnaround time in care of the patient. Requiring consent before testing of fresh leftover surplus specimens would virtually eliminate these types of studies (there are too many diffuse sources of the specimens – physician’s private and group practice offices, inpatient settings in community hospitals, and public clinics - to achieve timely consent). Our experience is that a study that requires specimens obtained with subject consent costs between 10 and 50 times more than a study using surplus specimens, and can take months to years to achieve versus current completion of biospecimen collection and testing in days/weeks. Manufacturers will be faced with the choice of conducting or sponsoring fewer studies – resulting in fewer innovations reaching patients and healthcare professionals in the U.S.

2. A second category of IVD device studies demonstrates acceptable performance of the device by testing of **leftover surplus specimens and of prospectively collected specimens**. This represents research and development activities underlying the second most common group of IVDs. Testing of the unidentified surplus specimens in the laboratory is supplemented with the testing of prospectively collected specimens. These specimens may come from a sample bank, may have been
prospectively collected with consent, and/or may be leftover from routine testing. As discussed above, if consent were to be required for all biospecimens, even those not individually identifiable and leftover from routine testing, the resource burden and development time would be greatly increased. In addition, in some cases the banks of leftover specimens are irreplaceable as the disease/marker prevalence is rare and it is difficult if not impossible to find subjects from whom to collect any new specimens.

3. Acceptable performance of a third category of devices can only be demonstrated by testing prospectively collected specimens with extensive subject histories. Specimens for these studies are always collected with informed consent. The research sponsor must pay the associated costs of overhead (frequently >15% of the total contract), additional IRB costs for creating and reviewing informed consent forms, time for medical staff to consent the subject, independent verification of the consent form and process (i.e., clinical trial monitoring) and long-term documentation storage. The cost of prospective specimen collections could range from $500 to $4,500 or more per subject depending on the study. Individual studies in this third category can total millions of dollars versus the few hundred thousand dollars for studies based primarily on testing of surplus specimens. By contrast, testing of surplus specimens averages $5 to $25 per specimen.

In addition, testing for rare markers or specimens with markers at the high or low end of the assay range is frequently accomplished with samples from sample banks. In some cases the banks of leftover specimens are irreplaceable as the disease/marker prevalence is rare and it is difficult if not impossible to find subjects from whom to collect any new specimens. As discussed above, if consent were to be required for all biospecimens, even those not individually identifiable and leftover from routine testing, the resource burden and development time would be greatly increased.

AdvaMed’s position on biospecimens is clear: for the use of identifiable biospecimens, AdvaMed agrees that informed consent is appropriate and that subjects should be able to control the use of their biospecimens.

However, in order to advance and enhance the development of precision medicine (for example, identifying multiple biomarkers for cancer and other diseases in response to treatment), and the development of IVDs for existing diseases and conditions, emerging diseases, and pediatric and rare diseases, where future research involves the secondary use of biospecimens that are not individually identifiable, we strongly urge the Secretary of HHS to continue to allow use of those biospecimens for such purposes without a mandate for informed consent. Ensuring that biospecimens are not individually identifiable protects subject privacy while contributing greatly to public health through the development of diagnostic and predictive tests.
B. Importance of the Current Federal Regulatory Framework

Since 1991, the Common Rule has excluded de-identified biospecimens from the definition of “human subject.” In 2008, the Office for Human Research Protections (OHRP) clarified that “coded” biospecimens are not “human subjects.” Since at least 1999, FDA has stated that samples not traceable to a human subject would not be subject to informed consent requirements, and confirmed in 2006 the position that FDA would not enforce informed consent requirements for minimal risk device research involving the use of de-identified or coded biospecimens. The NPRM would reverse decades of federal policy on which the medical device community has relied extensively to research, develop, and produce safe, reliable, effective, and high-quality devices, particularly in vitro diagnostics. The NPRM does this without articulating a clear and compelling regulatory, scientific, public health, human subject protection or policy justification.

In 2006, when FDA issued its Leftover Specimen guidance, the Agency, trade associations, and research institutions identified the challenge of obtaining informed consent for the use of leftover specimens as an unnecessary obstacle and expense for investigational efforts. In response to these widespread concerns, FDA concluded that:

[I]t is possible in certain circumstances for IVD device investigations to be conducted using leftover specimens obtained without informed consent while protecting the human subjects who are the source of such specimens. When IVD study sponsors use leftover specimens for which the subject cannot be identified and where results of the investigational test are not communicated to or otherwise associated with the identified subject, concerns associated with privacy are minimized.

The Leftover Specimen guidance articulated an enforcement discretion policy that applies to leftover specimens that are not individually identifiable and collected for clinical care or analysis, or for other research purposes. Specimens are not “individually identifiable”

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6 The current regulatory definition of “human subject” means “a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information.” 45 CFR 46.102(f).
7 HHS does not consider research involving only coded biospecimens to meet the current definition of “human subject” if (i) the biospecimens were not collected specifically for the proposed research through interaction or intervention with living individuals, and (ii) the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded biospecimens pertain – because, for example, the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators, or there are IRB-approved written policies for a repository that prohibit the release of the key to the investigators. “OHRP Guidance on Research Involving Coded Private Information or Biological Specimens,” (2008).
8 FDA Guidance, “Regulating in vitro diagnostic device (IVD) studies” (1999).
9 Leftover Specimen guidance.
10 Leftover Specimen guidance at 7.
11 Leftover Specimen guidance at 8.
when the identity of the subject is not known to, and may not readily be ascertained by, the investigator or any other individuals associated with the investigation, including the sponsor. Further, if the specimen is coded, it will not be considered “individually identifiable” if neither the investigator(s) nor any other individuals associated with the investigation or the sponsor can link the specimen to the subject from whom the specimen was collected, either directly or indirectly through coding systems.12

The current federal regulatory framework enables important, life-sustaining, and life-supporting medical innovations that benefit patients and public health. Reagent development and IVD instrument verification and validation require the availability of large biospecimen repositories. For example, new IVD analytical performance evaluations of hematology systems require testing with a large volume (tens of thousands or more) of biospecimen samples that are representative of the human population, including biospecimens of chronically ill patients such as hospitalized patients with cancers who are being treated with chemotherapy, or patients recovering after a recent organ transplant. Under the NPRM, researchers would be required to seek research consent from these sick patients to obtain extra biospecimen samples. AdvaMed views this requirement to be unethical because researchers would be requesting additional samples when similar leftover biospecimens that are not individually identifiable already exist. The proposed rule will place additional burdens (e.g., additional blood draws, biopsies, etc.) on already sick patients which poses an ethical dilemma for clinicians when caring for these vulnerable populations. It should be understood that biospecimens are needed over the course of an illness (pre-treatment, during and post-treatment) to demonstrate that the IVD can be used for diagnostic, predictive, and/or monitoring purposes.

One AdvaMed member has indicated that more than 90 percent of its research and development projects rely on biospecimen repositories, including previously collected and frozen biospecimen samples, fresh samples, samples that are leftover from routine clinical testing, and specimens purchased from an independent source.

According to AdvaMed membership, most IVD studies are conducted using leftover biospecimens that are not individually identifiable. Requiring consent for all biospecimens would be highly impracticable, burdensome, and would greatly impact innovation and delivery of safe and effective health care solutions in the U.S. Specifically, IVDs in the areas of hematology, immunology, chemistry, and blood screening rely heavily on the Leftover Specimen guidance to acquire leftover biospecimens that are not individually identifiable for testing to demonstrate product performance. All of these efforts would be impeded – and public benefits correspondingly reduced – by a regulatory reform that would require broad prospective consent for all biospecimen research, even research using biospecimens that are not individually identifiable under the well-established circumstances currently enumerated in FDA guidance.

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12 Leftover Specimen guidance at 8.
C. NPRM Would Not Enhance Human Subject Protections

The NPRM identifies two bases for this proposed radical shift in federal research policy. First, re-identification of de-identified biospecimens and data is technologically possible. Citing a 2013 *Science* article in which the identity of individual research subjects could be ascertained by collating and analyzing certain types of genomic data, including genomic data from publicly available information sources,\(^\text{13}\) the NPRM concludes that, “the possibility of fully identifying biospecimens and some types of data from which direct identifiers had been stripped or did not originally include direct identifiers has grown, requiring vigilance to ensure that such research be subject to appropriate oversight.”\(^\text{14}\) We agree fully that ensuring proper oversight of research involving genomic data is necessary. In fact, the cited article concludes:

\[\text{[T]he appropriate response to genetic privacy challenges is not for the public to stop donating samples or for data sharing to stop. These would be devastating reactions that could substantially hamper scientific progress. Rather, we believe that establishing clear policies for data sharing, educating participants about the benefits and risks of genetic studies, and the legislation of proper usage of genetic information are pivotal ingredients to support the genomic endeavor.}^{15}\]

AdvaMed supports the conclusion that education, appropriate policies on data sharing, and limitations and sanctions on unauthorized re-identification are the appropriate solutions, not a broad consent mandate that could, in the words of the *Science* authors, “substantially hamper scientific progress.” Rather than virtually eliminate or severely limit use of de-identified samples, we encourage HHS under its existing statutory authorities or under new authorization sought from Congress, to impose administrative, regulatory, civil, and even criminal penalties on institutions, investigators, or others for the unauthorized re-identification of biospecimens that are not individually identifiable. For example, those who create software to re-identify biospecimens or data that are not individually identifiable should be specifically called out for penalties. In addition, publicizing a list of those institutions, investigators and others who violate requirements related to re-identification would provide a second level deterrent. By focusing on penalizing those who violate rights and privacy of individual subjects through unauthorized re-identification of samples, HHS more appropriately focuses on the problem that needs solving, without negatively impacting the valuable research that drives diagnostic innovation.

\(^{14}\) 80 Fed. Reg. at 53938.
\(^{15}\) Gymrek at 324.
Second, the NPRM claims that “many prospective participants want to be asked for their consent before their biospecimens are used in research.”\(^{16}\) However, the question is whether individuals would strongly prefer to provide consent before their biospecimens that are not individually identifiable are used in minimal-risk research, appreciating that the mandate for consent could adversely impact medical innovation. The NPRM cites four articles as footnote support for this proposition, but a close reading of each of these studies demonstrates that none directly supports the NPRM proposal on these issues, especially as related to minimal-risk IVD-related research using stored biospecimens:

1. To the contrary, the Kaufman article reported that nearly 50% of the respondents for an NIH-sponsored genetic research study would agree that, “If I Could Not Be Identified, I Would Be Willing to Have My Information and Research Results Available on the Internet to Anyone,”\(^ {17}\) showing that nearly half of the respondents would not place any restrictions on the use or availability of their de-identified information. Moreover, the article concluded that “Despite ubiquitous concerns about protection of privacy among our survey respondents, six in ten would participate in the large cohort study if asked, and most would share their research data with academic, government, and industry researchers.”

2. The Trinidad article focused on large-scale genomic research studies which can require massive volumes of data. The authors reported that 90% of respondents would prefer to be asked permission for data-sharing, but the relevant data at issue in the study were identifiable, not de-identified or coded.\(^ {18}\)

3. The Vermeulen article compared Dutch cancer patient preferences of broad consent, an opt-out, and the standard hospital practice for use of residual tissue in medical research.\(^ {19}\) Survey results of study participants showed that “Nearly all patients (99%) consented to research with residual tissue,” but did not study whether individuals strongly desire to provide consent before their de-identified or coded biospecimens can be used for low-risk medical research, which is the category of biospecimen research often used for IVD development purposes.

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\(^{16}\) 80 Fed. Reg. at 53938.


4. The Simon article concluded that broad consent is favored over study-specific consent for the purposes of future research use, but again, did not address whether individuals strongly desire to provide consent before their de-identified or coded biospecimens can be used for low-risk medical research.

Merely requiring that individuals provide broad consent, which to the extent implemented would likely be routinized and not constitute informative, meaningful, or effective legal consent, would not solve the issue of potential unauthorized re-identification and is not an approach that the cited empirical literature supports.

In fact, the current regulatory frameworks and industry practices adequately address privacy and confidentiality concerns regarding research involving biospecimens that are not individually identifiable. The IVD industry follows the requirements of the Health Insurance Portability and Accountability Act (HIPAA) where appropriate for de-identification of biospecimens to protect and safeguard the privacy and confidentiality of individuals. In general, when IVD companies obtain biospecimens, no directly identifiable patient health information is collected along with the biospecimens. In addition, IRB oversight is required for all collections and acquisitions of specimens for studies that generate data for FDA submissions. The IRB carefully reviews the protocol and, before determining whether to waive consent, ensures that the use of the specimens meets the criteria in the FDA’s Leftover Specimens guidance. The risks to subjects are thus minimal.

D. Re-Obtaining Consent for Residual Biospecimens Would Not Be Feasible

By requiring broad consent for the secondary research use of biospecimens, even those that are not individually identifiable, researchers would be forced to attempt to re-contact patients to obtain research consent for residual specimens collected during the course of routine care or collected as part of a different research protocol. The NPRM stipulates that IRB waiver of informed consent “will occur only in very rare circumstances.” Without the realistic availability of the waiver mechanism, researchers would be bound to expend considerable resources to attempt to relocate patients whose biospecimens may have been collected years prior. Smaller institutions without substantial resources may be predominantly affected and, as a result, certain subpopulations and demographic groups served by such institutions may be excluded from important research (e.g., economically disadvantaged or minority populations). The result may be research findings without the potential for generalizability to such populations or the findings may be potentially confounded due to selection bias. Moreover, re-contacting a patient months or even years after a traumatic medical episode may be intrusive and an unwarranted invasion of privacy, without any countervailing enhancement of human subject protections.

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E. Arbitrary 10-Year Limitation on Validity of Broad Consent for Collection of Biospecimens and Identifiable Data (§ .116(c)(1)(ii)(B))

The NPRM would limit the validity of broad consent to 10 years after the date of consent for the collection of biospecimens and identifiable data, if the initial collection were for non-research purposes. The NPRM does not provide an adequate regulatory, scientific, public health, human subject protection, policy basis or any other foundation for this arbitrary proposal. Instead, the NPRM claims that, “individuals will not know what biospecimens and information about them will be collected by an institution in the future. The 10-year time limit may make it more likely that an individual will have a better understanding of the biospecimens and information that would be covered by the broad consent.”

The logical implication of the NPRM is that an individual will have a better sense of what biospecimens may be collected over the next 10 years, but not at year eleven and beyond. No empirical, survey, or qualitative data are cited to support this questionable premise. It is unlikely that an individual would have any better idea of the types of biospecimens that would be collected in four years or nine years, than in fifteen years. With the unpredictability of diseases, conditions, and human health in general, and the rapid advance of medical technology, the 10-year limitation is grounded only in speculation and conjecture.

Importantly, a 10-year limitation would impose hefty burdens on research. First, researchers, institutions, and recipients of biospecimens would be forced to track each individual’s broad consent to ensure that no biospecimen or identifiable data collection occurs after 10 years. Second, if researchers and institutions sought to re-consent subjects for the continued collection after 10 years, an inordinate time, financial, and resource expense would be required to re-identify, relocate, and re-consent those subjects, with no discernable benefit to subjects. Further, the research enterprise should respect an individual’s consent and only seek to limit consent if obtained under duress or coercion, or the subject withdraws. In the absence of any of these factors, an individual’s consent should be honored and should endure indefinitely, unless otherwise promised in the consent form or unless revoked by the individual.

Finally, the 10-year limitation would only apply if the initial collection occurred during non-research purposes. No limitation would be imposed if the initial collection were part of a research protocol. As a consequence, researchers and institutions could seek to avoid the burdensome 10-year limit by initially collecting the biospecimens and information for a “research” purpose as part of a broad databanking or biobanking study protocol. This “easy way around” the 10-year collection limitation itself suggests that the limitation, even if appropriate, is woefully under-inclusive. More likely, the easy availability of an alternative suggests that the 10-year limitation lacks a compelling rationale.

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F. Withdrawing Consent For Biospecimens That Are Not Individually Identifiable Would Pose Significant Challenges (§_.116(c)(1)(iv))

The NPRM would require that subjects be informed that at any time and without penalty or loss of benefits, they may withdraw consent, if feasible, for research use or distribution of the subject’s information or biospecimens. However, information and biospecimens with identifiers stripped might not be traceable. In fact, retaining a link that identifies biospecimens and information for the sole purpose of allowing potential future withdrawal of consent would increase – not decrease or ameliorate – the privacy risks posed by the tracking (and the requirement to track over time) of biospecimens that are not individually identifiable. Importantly, the tracking of broad consent that would be necessary to comply with the NPRM would compel researchers to generate and maintain a key to identify the human source. Subjects would be better protected by ensuring that biospecimens are not individually identifiable.

Moreover, AdvaMed is concerned that the NPRM does not contemplate the tremendous adverse impact on research that can occur if subjects withdraw consent for the use of their biospecimens that are not individually identifiable in research. For example, even if removal of a biospecimen from a previously collected set of biospecimens is possible, removing a subject’s data or biospecimens from a data pool can skew study results and lead to bias. In some cases, this selection bias could undermine the validity of study conclusions.

G. Tracking Broad Consent Would Impose Significant Costs, Resources, and Infrastructures

The NPRM would mandate that any institution (e.g., physician’s offices, public health clinics, rural and tertiary hospitals) collecting biospecimens, and researchers and medical device companies conducting secondary research on those biospecimens, implement sophisticated electronic and workplace infrastructures to track biospecimens and broad consent to:

1. Ensure that only biospecimens with associated broad consent are used for research;

2. Ensure that no biospecimen or identifiable information collection from an individual who provided broad consent occurs after 10 years (an arbitrary timeframe as noted above) from the date of consent for the non-research collection (or if the subject is a child, the earlier of 10 years from the date of parental permission or the age of majority);

3. Ensure that if a subject refused to provide broad consent, an IRB cannot waive consent for the storage, collection, or secondary research use of that subject’s biospecimen;
4. Ensure that the right to withdraw consent from study participation is respected by developing a mechanism to allow for re-identifying biospecimens; and

5. Ensure that each biospecimen is used only for the duration specified in the consent form (which could be indefinitely).

This detailed tracking infrastructure necessary to comply with the extensive NPRM proposals would require sizable financial and resource expenditures for those institutions and biospecimen recipients that are even capable of such investments. For institutions and biospecimen recipients, including public and community hospitals, public health clinics, physician offices, and small device companies, the NPRM would prevent these entities from engaging in or supporting important medical device research and development, and as a result, could skew research data by excluding certain underrepresented and diverse subpopulations. Given the costs and potential liability associated with tracking broad consent and maintaining related data systems, as would be required, in effect, by the NPRM, it is unclear that any institution (even large academic medical centers) would be willing or able to incur the additional expenses, resources and long-term tracking systems required under the NPRM.

H. Restrictive Biospecimen Waiver Criteria (§_.116(f)(2))

Currently, biospecimen research may occur if an IRB waives consent pursuant to the regulations. However, a waiver mechanism under the NPRM proposal would not be an adequate alternative if broad consent were not obtained. The NPRM would impose stringent waiver conditions on research involving biospecimens. Specifically, the NPRM proposes that: (i) there be “compelling scientific reasons” for the research use of the biospecimens; and (ii) the research could not be conducted with other biospecimens for which informed consent was or could be obtained. The NPRM proposes to prohibit IRBs from waiving informed consent if individuals were asked and refused to provide broad consent to the storage and maintenance for secondary research use of biospecimens and identifiable private information.

AdvaMed is concerned by the severe narrowing of the waiver of consent mechanism. Currently, IRBs, institutions, researchers, and medical device companies rely on the waiver mechanism to ensure that important research is conducted if adequate protections are in place and consent was not practicable. The NPRM would needlessly tighten the waiver criteria, impeding valuable, medical device research on residual biospecimens. The NPRM asserts that waiver “will occur only in very rare circumstances.”

The “compelling” standard may deter or inhibit worthwhile exploratory device research. Moreover, to determine whether a research project could be conducted using “other

biospecimens for which informed consent was obtained or could be obtained” would create a considerable due diligence effort and present logistical challenges for a researcher to survey all potential biobanks and determine the availability of the banked biospecimens. This would be resource-intensive and time-consuming and would impede research while doing little or nothing to protect research subjects.

I. Narrow Exclusion for Certain Assay Research (§ 715.101(b)(3)(i))

The NPRM exclusion addressing IVD research—although a welcome concept—is too narrowly constructed to facilitate secondary research use of biospecimens. The exclusion would only apply to research that obtains information about an individual that is already known. IVD research, however, often explores potentially related diseases, conditions, and biomarkers, especially in cancer. Exploratory IVD research frequently uses known diseased or un-diseased samples to investigate other related or unrelated diseases or conditions. This is also particularly true in infectious diseases where leftover samples are found to contain a new genetic subtype or variant and this discovery supports enhancements to the product to improve testing efficacy and ensure better detection or diagnosis and/or blood product safety.

In addition, subsequent pathological testing of a sample that is not individually identifiable could yield a different disease diagnosis than the initial clinical evaluation, which would create information not already known to the individual, and therefore preclude from exclusion the secondary research use of the biospecimens that are not individually identifiable. For example, a clinical assessment of an individual’s signs and symptoms may lead a clinician to determine that the individual does not suffer from a particular disease, and the individual’s specimen may not be individually identifiable and labeled as negative. If subsequent pathological evaluation concludes that the sample, in fact, tests positive for the disease in question, the secondary research use of the pathological sample that is not individually identifiable would not be encompassed by the exclusion because the information (testing positive for the disease) would not be known to the individual.

Further, the exclusion only applies to “non-identified” biospecimens, which is a stricter de-identification standard than the Leftover Specimen guidance, which permits research on coded specimens without informed consent. Thus, the NPRM exclusion for assay research would be of severely limited utility.

J. Conclusion

Without a clear, compelling, and well-supported regulatory, scientific, public health, human subject protection, or policy justification, the new requirement to obtain consent for secondary research involving biospecimens that are not individually identifiable could be considered devoid of reasoned decision-making and thus arbitrary and capricious, in
violation of the Administrative Procedure Act. 25 To provide a brief glimpse into the potentially debilitating repercussions, one AdvaMed member indicated that 100,000 or more biospecimens that are not individually identifiable are relied on every year for its own internal research. This number would be replicated many times over, if extrapolated to the entire AdvaMed membership and beyond.

Requiring broad research consent at every point of entry into clinical care, including physician’s offices, clinics, emergency departments, and hospital floors, and managing the consent process in accordance with Good Clinical Practices would be nearly impossible, and doing so in a timely manner to support the testing of fresh biospecimens would be even more difficult. The amount of time necessary to collect the same representation of the population if consent were required would take months or years to achieve what can currently be done in days or weeks by testing leftover biospecimens that are not individually identifiable.

AdvaMed strongly urges HHS to consider alternative solutions to address any perceived deficiency in the current federal regulatory frameworks that could allow unauthorized, re-identification without appropriate sanctions. Broad consent, which likely would not be informative, meaningful, or effective legal consent, would not deter or otherwise address the NPRM stated concern of unauthorized re-identification.

Moreover, the revised waiver mechanism would not be an adequate alternative to broad consent to allow secondary research use of biospecimens that are not individually identifiable. As described above, the revised waiver criteria are too rigorous to be applied broadly, and the NPRM acknowledges that waivers would only be used in very rare circumstances. The Federal Food, Drug, and Cosmetic Act (“FD&C Act”) currently does not authorize waiver of consent for device studies except under emergency research, 26 and thus it is unclear, if FDA were to adopt the same NPRM requirements for broad consent, whether waiver would be available for FDA-regulated secondary research using biospecimens outside of emergency research. Finally, HHS should also consider the potential of the NPRM to drive medical device clinical trials outside the U.S., where the regulatory frameworks would not be as restrictive. Even the most rigorous of FDA’s European counterparts do not impose such requirements. Imposing such invariable, uncalibrated requirements could push biospecimen research for the IVD industry out of the U.S. and into Asian and other countries that are actively seeking private research funding and opportunities.

26 Section 520(g)(3)(D) of the FD&C Act.
II. **Transition Provisions That Could Render Millions of Biospecimens Unavailable**

(§ .101(k))

The NPRM would apply transition provisions to biospecimens collected before the NPRM’s compliance date, if the research use of the biospecimens occurs after “removal of any individually identifiable information associated with the biospecimens.” Thus, banked biospecimens would only be grandfathered if individually identifiable information is removed, which would not allow for the grandfathering of coded or linked biospecimens. The consequence would be that all biorepositories and biobanks that house coded biospecimens would be required either to (i) strip all individually identifiable information, which may not be an option if the research requires linkage back to the individual; or (ii) re-identify, relocate, re-contact, and re-consent millions of human sources of the biospecimens. Otherwise, such biospecimens and repositories would no longer be available for important medical device research and development, and future research with coded, banked biospecimens would be obstructed. Certain types of biospecimens with unique properties such as rare diseases or mutations are irreplaceable, making their potential loss to future medical research an unethical outcome that does not serve the best interest of subjects, patients, or the public health.

As described above, waiver of consent to permit the secondary research use of coded biospecimens would not be a widely available or adequate pathway. By effectively rendering unavailable huge sets of collected biospecimens, the device research community would be forced to duplicate efforts to create the same specimen collections, thereby exposing future human sources of biospecimens to unnecessary risk and inconvenience and imposing a major cost burden on researchers, institutions, and the medical device industry. For some biorepositories, the specimens cannot be easily replaced due to prevalence of the diseases, and for all biorepositories, the amount of time to recollect and rebuild the same representation of the population would take months or years to achieve.

III. **Significant Limitations on the Transfer of Biospecimens Collected in Research**

(§ .105(c))

Under the NPRM, unless otherwise required by law, institutions and investigators may release biospecimens collected for research subject to the Common Rule only for, among other purposes: (1) any lawful purpose with the consent of the subject; or (2) other research purposes if the institution or investigator has obtained adequate assurances from the recipient that:

A. The recipient will implement and maintain Common Rule-prescribed data security safeguards;

B. Except for certain low-risk research, the research has been approved by an institutional review board (IRB) before release of the biospecimens; and
C. The recipient will not further release the biospecimens except for Common Rule-regulated human subject research, or other permitted purposes.\textsuperscript{27}

The NPRM would mandate that “recipients” of biospecimens, even biospecimens that are not individually identifiable, would become subject to the NPRM’s requirements of data security protections and IRB review unless the subject consents to the release of the biospecimens to the recipient. The NPRM proposal would require that the medical device industry subject its internal, non-federally funded biospecimen research to IRB oversight and implement HIPAA-type data security safeguards, based on the receipt of biospecimens that were collected during federally-funded research. Device manufacturing companies also would be required to implement data security measures at foreign facilities that receive transferred biospecimens subject to the Common Rule.

The NPRM also would preclude medical device companies from further transferring such received biospecimens unless the subsequent recipient would be conducting biospecimen research subject to the Common Rule. Thus, the NPRM could inhibit valuable research efforts by preventing recipient medical device companies from sharing even completely de-identified biospecimens with a contract research organization or an authorized laboratory for the further analysis or processing of the biospecimens.

IV. Single IRB Mandate for Cooperative Research May Exclude Local and Institutional Values (§ .114)

The NPRM would mandate that all institutions located in the United States engaged in cooperative research covered by the Common Rule rely on a single IRB as the reviewing IRB for that study.\textsuperscript{28} The NPRM explains that this proposal would not relieve any site of its other obligations under the regulations to protect human subjects. Although a local IRB may conduct its own additional internal review, such a review would not be binding on the local site if not adopted by the single IRB, and its terms would not be enforced by OHRP. The proposal fails to elucidate how a local IRB can ensure compliance with this regulatory requirement of continuing to fulfill oversight obligations when a central IRB holds full regulatory and legal responsibility for reviewing and approving the research.

Although AdvaMed supports the efficiency and administrative ease of a central IRB, AdvaMed also recognizes the importance of local IRB review, and thus opposes a mandate. Ultimately, AdvaMed believes that there is value in having the flexibility to utilize a local IRB or a single IRB to ensure that local customs are appropriately considered. One issue with mandated, outsourced IRB review is that some hospitals and health care systems have unique requirements that would require allowances or variances under federal law. For example, some hospitals ascribe to certain religious or moral beliefs that may require unique language in

\textsuperscript{27}§ .105(c) (80 Fed. Reg. at 54049-54050).

\textsuperscript{28}§ .114(c)(1)(iii) (80 Fed. Reg. at 54052).
their informed consent documents that is different from other U.S hospital systems. Forcing external review of informed consent documents without provisions at the local level may, for example, force hospitals to decide to forego participation in the research protocol. In addition, given the diversity of U.S. human subjects, maintaining flexibility for use of either a local or single IRB ensures that unique local community, cultural or religious issues can be considered. We would note that in many instances, local IRBs are willing to cede their review to a central IRB.

V. Unnecessary Data Security Safeguards (§ .105)

The NPRM proposes to require, for the first time, that institutions conducting research subject to the Common Rule implement specific data security safeguards. As described above, medical device companies would be required to implement these safeguards if they receive biospecimens that were collected in federally-funded research, for which no consent was obtained permitting the release of the biospecimen to the device company. The NPRM would allow investigators and institutions to implement either (i) safeguards that meet the standards in the HIPAA rules, or (ii) specific measures published by the Secretary of HHS. AdvaMed believes that HIPAA-type protections, especially for recipients of biospecimens that are not individually identifiable, would be unnecessary and excessive to provide adequate protections of a subject’s privacy and confidentiality. AdvaMed proposes that the HHS-developed measures be calibrated more accurately to the degree of risk posed by the receipt and use of biospecimens that are not individually identifiable, especially considering that many medical device companies are not currently subject to HIPAA and thus may not have a HIPAA-compliant data protection system in effect.

VI. Adverse Effects of Posting Consent Forms (§ .116(h))

The NPRM proposes to require that a copy of the final version of the consent form for clinical trials conducted or supported by a Common Rule department or agency be posted on a publicly available Federal website within 60 days after a trial closes to recruitment.

Although other provisions of the NPRM intend to streamline and shorten consent forms, AdvaMed is concerned that the posting of consent forms, which would subject the documents to post hoc scrutiny by academic researchers, the federal government, and plaintiffs’ attorneys, will cause the documents to be overwhelmed with even more risk-management-based, unnecessary, and remote study information, disclosures, and disclaimers, making them even more difficult for subjects to comprehend. AdvaMed also believes that this NPRM proposal could result in the unauthorized disclosure of certain proprietary information that may be included in sponsor-funded studies (e.g., study design, and device development and

29 § .105(b) (80 Fed. Reg. at 54049).
commercialization strategies). Further, the public posting of consent forms for clinical trials appears to add burden without adding clear benefit. For example, it would presumably create the administrative burden of responding to public comments, questions or criticism on the posted consent forms.

VII. **Rigid Broad Consent Template (§ .116(d))**

The NPRM proposes that the HHS Secretary will publish in the Federal Register broad consent templates containing all required elements of consent, and that use of the broad consent template would be required for exemption under § .104(f). AdvaMed is concerned that the federally-developed broad consent template may not permit sponsors to adapt and tailor the consent document to reflect or address pertinent details of the specific nature of a biospecimen collection, storage, or secondary research use.

VIII. **Return of “Clinically Relevant” and Reliable Research Results (§ .116(b)(8))**

The NPRM would impose an additional element of informed consent, when appropriate: “A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.” AdvaMed strongly recommends that prospective human subjects only be informed of “clinically relevant” results when the IVD that is being tested is shown to be analytically and clinically accurate and reliable. Otherwise, the risk of providing subjects with inaccurate research results could exceed the value that a subject may gain from having such information. In fact, false results could lead to subject harm.

IX. **Publicly Posting De-Identified Data Without Adequate Protections (§ .116(c)(1)(viii))**

The NPRM would require that broad consent forms contain an option, if relevant, to allow subjects to agree to the inclusion of the subject’s data, with removal of HIPAA-identifiers, in a database that is publicly and openly accessible to anyone. This option must be prominently noted, and must include a description of risks of public access to the data. AdvaMed is concerned that efforts to increase transparency by public posting of de-identified participant-level clinical trials data (for example, the results of IVD testing of de-identified biospecimens) without adequate protections, would increase the risk that these de-identified biospecimens can be traced back to the human source through advances in re-identification science. To ensure that adequate protections are in effect to safeguard subjects’ privacy and confidentiality, AdvaMed would strongly encourage that this proposal only be adopted in tandem with the establishment of appropriate standards regarding patient protection (e.g., time limits and data stewardship standards, which could be detailed in a Data Use Agreement), and the prohibition, with civil and criminal penalties, on the re-identification of publicly posted de-identified datasets.
X. **Underestimated Projected Costs**

AdvaMed notes that a significant cost absent from the NPRM analysis is the potential for rebuilding existing biorepositories and databanks that may be invalidated under the NPRM because: (i) the samples were collected without initial broad consent, (ii) the samples are coded and thus not eligible for the transition provisions, (iii) consenting all human sources would not be feasible, and (iv) the revised and limited waiver mechanism would not be available. To replace millions of biospecimens would consume unprecedented and extraordinary time, resources, and finances.

AdvaMed also questions the NPRM estimates for the amount of time necessary to obtain broad consent and input the detailed information into an appropriate tracking system. The NPRM concludes that such a process would only require 10 minutes, but AdvaMed believes that a robust broad consent process to apprise fully a prospective participant about the concepts of broad consent and biospecimen research and allow an adequate opportunity to discuss, as well as entering all of the details necessary for compliant tracking, would necessitate considerable time.

XI. **Inadequate Public Process and Complexity of NPRM**

AdvaMed firmly believes that significant revisions to the Common Rule require a more deliberate and participatory public process. Substantially modifying the regulatory framework governing clinical research would severely impact the research, development, and marketing of important medical devices. Additionally, the proposed revisions to the Common Rule are complex, key terms are used inconsistently, and it is difficult to understand the rule's intent in many areas. This complexity will make it challenging for those who are committed to following best human subject protection practices and who conduct clinical trials to implement the rule, without continuing legal advice and counsel.

President Obama signed the Plain Writing Act of 2010, which requires federal agencies to promote “clear Government communication that the public can understand and use.” He also signed Executive Order 13563, Improving Regulation and Regulatory Review, which states that “[our regulatory system] must ensure that regulations are accessible, consistent, written in plain language, and easy to understand.”

To ensure that safe, reliable, effective, and high quality medical devices continue to be innovated and brought to the market, AdvaMed strongly encourages HHS to engage in a more transparent administrative process that permits the involvement of key stakeholders.

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Expediting the promulgation of a set of rules that seeks to ensure public trust in the research enterprise, adequate protections of research participants, and the availability and continued development of safe and effective medicines, would be a misguided governmental and public health effort.

We strongly urge HHS to revise the proposed rule to address, first and foremost, the deep concerns that we have identified above. HHS also should issue a revised proposed rule for public comment with a simple, straightforward narrative summary of the intent of the rule, and with revised regulatory language that is plain and understandable to those who conduct clinical trials per the Plain Writing Act of 2010 and related Executive Orders.

XII.  Summary

AdvaMed supports the overall aims of the NPRM as well as specific provisions, such as eliminating continuing review for minimal risk studies (§_.109(f)) and facilitating and encouraging meaningful and understandable informed consent (§_.116). However, as noted above, the NPRM also includes extensive and substantive proposals that could be devastating to medical device research and impede development of new products. Before any finalization of changes to the Common Rule, AdvaMed strongly encourages HHS to consider seriously whether the proposals further the stated goals and are supported by adequate and legitimate justification. To that end, AdvaMed welcomes the opportunity to speak further with HHS about these important public health and regulatory science matters.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs