Technical Assistance on VALID Act of 2018

These comments are intended only to provide technical assistance and are by no means to be interpreted as any kind of approval or endorsement of the legislation by the Department of Health and Human Services and its agencies or the Administration.

HHS, including FDA, CMS, and CDC, appreciates the opportunity to provide technical assistance to the sponsors of this legislation on diagnostic reform. This document provides feedback on the preliminary discussion draft of the Verifying Accurate Leading-edge IVCT Development Act of 2018, or VALID, issued by Representatives Bucshon and DeGette and Senators Bennet and Hatch, on December 6, 2018. We look forward to continuing discussion with the sponsors and the stakeholder community as Congress works to develop this legislative framework.

1. FDA Should Oversee IVCTs

HHS supports the proposal in VALID to task FDA with the responsibility for oversight and assessment of the analytical and clinical validity of IVCTs. HHS maintains that FDA's longstanding history and experience in premarket review of diagnostics and deep knowledge of clinical research methodology pertinent to establishing analytical and clinical validity make FDA the appropriate Agency for jurisdiction over IVCTs.

An oversight approach should be undertaken in an efficient manner that allows labs to effectively leverage, without duplication, the activities they already perform to comply with CLIA requirements. To this end, we support the discussion draft language indicating that CLIA-certified labs would only need to comply with a subset of QS requirements for their IVCTs, effectively leveraging work they already do under CLIA. HHS notes that the VALID proposal does not duplicate CLIA requirements.

2. FDA Needs Sufficient Resources for Oversight of IVCTs

To protect the public health, it is critical that any IVCT oversight framework can be implemented with maximum efficiency and without significant delays. This can be achieved with legislation that is as self-implementing as possible that also avoids unnecessarily burdensome processes.

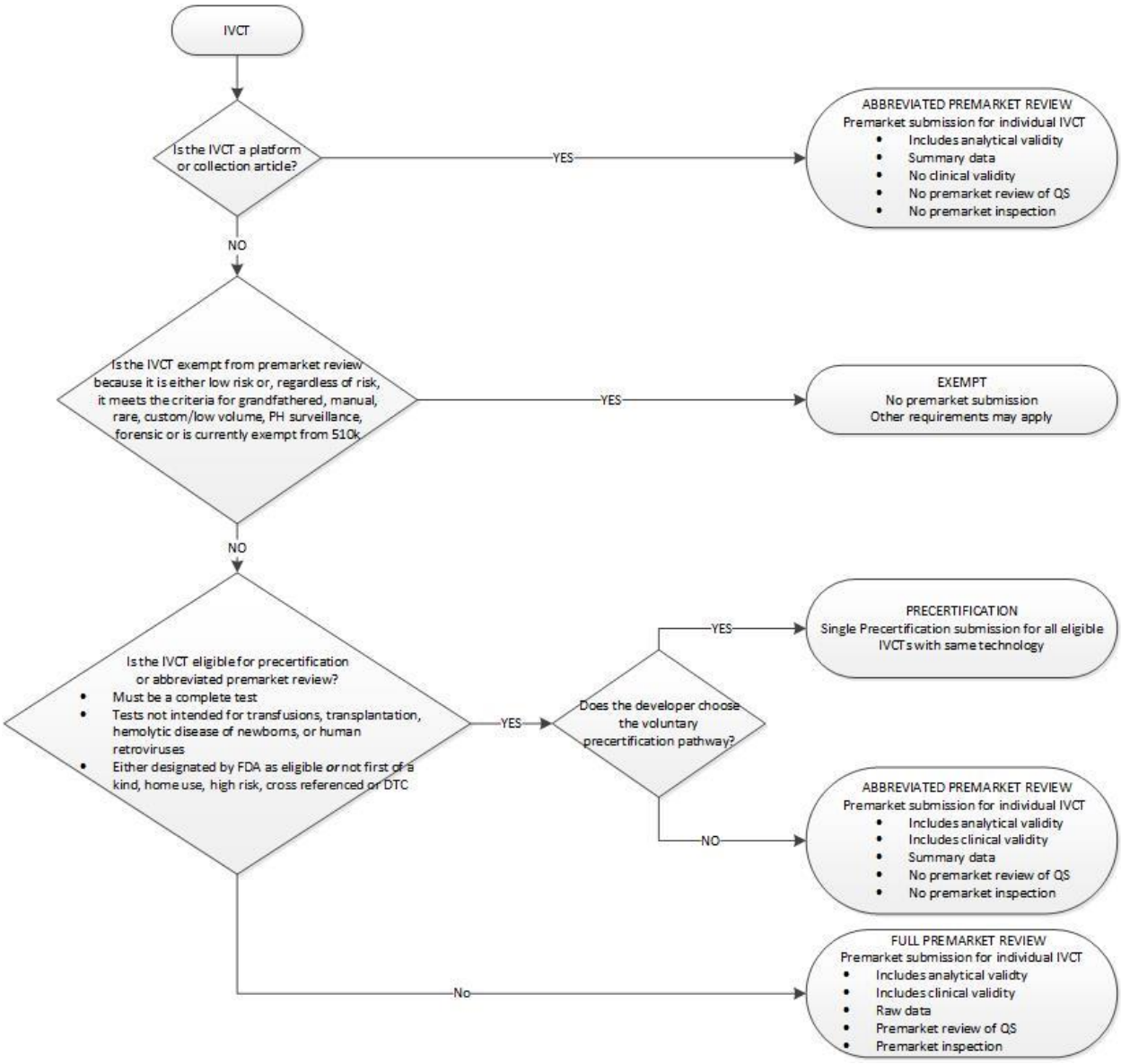
FDA must be provided with sufficient resources to stand up and run this new program and to ensure that it is successful by allowing FDA to continue to carry out its core mission of protecting the public health, while also ensuring timely review of medical products. We appreciate that the sponsors included the establishment of a new user fee program in the legislation, which we believe is intended to help ensure FDA has appropriate resources. We include some comments on the user fee language later in this document for the sponsors' consideration.

The Comprehensive Test Information System (CTIS) is a key resource needed for efficient oversight, while also bringing much needed transparency to patients and healthcare providers about the tests they are using. CTIS would include information about every IVCT, including

analytical and clinical validity, and provide both test developers and FDA with a single system that could be used for notification, submissions, and adverse event reporting. Each IVCT would be assigned a unique number to enable tracking across all processes, and the system would be searchable across all fields, including by test uses and test developers. Further, CTIS would help FDA monitor tests in the postmarket space, which is especially important in a framework where the majority of tests are not reviewed individually premarket. No such system currently exists to provide information about all tests being offered in the United States. The availability of this information would help patients and healthcare providers to make informed medical decisions. This system would also provide clarity for test developers around how FDA is evaluating IVCTs similar to their own.

3. Flexible Regulatory Pathways

HHS supports the regulatory pathways outlined in VALID. We continue to believe that risk-based classification of all IVCT test groups is not necessary. Elimination of classification will reduce the administrative burden on the Agency and will streamline the path to market. Risk should be a key factor in determining the regulatory requirements for a given test; however, other factors should also be considered, particularly those outlined in the exemptions described in the applicability section and the ability to identify measures to mitigate risk. The following flowchart outlines HHS's thinking, which is consistent with VALID, regarding the premarket requirements for a given IVCT:



As indicated in the flowchart above, there are four potential categories an individual IVCT may fall into for premarket requirements:

1. Premarket Exempt
2. Precertification of eligible tests (voluntary pathway)
3. Abbreviated Premarket review (for platforms; collection articles; and IVCTs eligible for precertification for which the developer did not choose the voluntary precertification pathway)
4. Full Premarket review for IVCTs not eligible for precertification

The second and third pathways (i.e., precertification and abbreviated premarket review) would be applicable to the same population of IVCTs (precertification-eligible IVCTs); it would be up to developers to choose the pathway they prefer. It may be helpful to incorporate terms such as "abbreviated premarket review" and "full premarket review" into VALID to distinguish the differences in premarket submission contents.

The VALID discussion draft outlines explicit criteria for determining if a test is exempt from premarket review, as well as some explicit criteria for determining eligibility for precertification or abbreviated review. For the small portion of tests that do not meet these criteria, premarket review is required unless FDA determines that sufficient mitigating measures to ensure analytical and clinical validity of such tests exist. In such cases, FDA would have the flexibility to use the provisions in Sec 587F Regulatory Pathway Designation to move some such tests into precertification eligibility or a low risk exemption. FDA anticipates that the regulatory requirements for a given category of tests may be adjusted over time, as it gains more experience with such tests. HHS believes this framework would allow FDA to continuously re-evaluate the appropriate level of oversight for these tests based on growing scientific knowledge and clinical experience.

The small proportion of tests that would generally need premarket review, unless Section 587F is invoked, are:

- tests that are high-risk, as these have a greater potential to cause patient harm in the event of a false result;
- tests that are first-of-a-kind, as these have never been reviewed by FDA and therefore, the risks and potential mitigations are unknown until the first review is complete;
- tests that are cross-referenced, as these must be developed and validated for use with another medical product, necessitating inter-Center review; and
- tests that are offered direct to consumer or for home use, as these require review of the ability of a lay user to understand test results provided directly to the user, and in the case of home use, to perform the test themselves.

In addition, we agree that certain tests related to the safety of the blood and tissue supply, including tests that are intended for use in the determination of donor eligibility, donation suitability or compatibility between donor and recipient; hemolytic disease of newborns, or diagnosing or monitoring of human retroviruses or human retrovirus infections, would need premarket review.

Risk remains a key driver of regulatory pathway in the proposed framework, but risk does not directly correlate with the regulatory pathway. This is similar to the existing medical device framework in which we have some Class 1 devices that are "reserved" and require premarket notification and some Class 2 devices that are exempt from premarket notification. Given the lack of direct correlation between risk and regulatory pathway, HHS believes the risk classification process is not necessary in this framework and would only delay implementation.

4. Definition of Low Risk

On page 10, lines 8-10, clause (ii) says that a test can be low risk if an undetected inaccurate result "could cause non-life threatening injury or injury that is medically reversible, or delay necessary treatment." We suggest combining this language with subparagraph (B) at lines 11-17 (as suggested below) so that such tests can only be considered low risk if the above criteria is met **and** "mitigating measures are sufficient to prevent such inaccurate results, detect such inaccurate results prior to any adverse patient impact or adverse public health impact, or otherwise sufficiently mitigate the risk associated with such inaccurate result." Suggested edits to "Low-Risk" definition:

> "(8) LOW-RISK.—
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> "~~(A) Subject to subparagraph (B), t~~The term 'low-risk', with respect to an in vitro clinical test or category of in vitro clinical tests, means that an undetected inaccurate result from such in vitro clinical test, or such category of in vitro clinical tests, when used as intended—
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> "(~~i~~A) would cause minimal or no harm or disability, or immediately reversible harm, or would lead to only a remote risk of adverse patient impact or adverse public health impact; or
>
> "(~~ii~~B) could cause non-life threatening injury or injury that is medically reversible, or delay necessary treatment, ~~. "(B) Such term does not include an in vitro clinical test if~~ and mitigating measures are sufficient to prevent such inaccurate result, detect such inaccurate result prior to any adverse patient impact or adverse public health impact, or otherwise sufficiently mitigate the risk associated with such inaccurate result.

5. Certain Provisions Related to Blood and Tissues

On page 16, line 22, through page 17, line 6, paragraph (2)(C), refers to the continued authority of the Secretary with respect to human blood and cell and tissue establishments. We note that some cell and tissue establishments are regulated solely under Section 361 of the Public Health Service Act, and as such we recommend that section 361 be included on page 17, lines 5 and 6, as follows:

> "(C) BLOOD AND TISSUE.—Nothing in this subchapter shall be construed to modify the authority of the Secretary with respect to laboratories, establishments, or other facilities to the extent they are engaged in the propagation, manufacture, or preparation, including filling, testing, labeling, packaging, and storage, of blood, blood components, human cells, tissues, or tissue products under this Act or section 351 or 361 of the Public Health Service Act.

In addition, we agree, as set forth in page 4, lines 6-12, of the discussion draft, that it is important that FDA be able to regulate blood, blood components, or human cells or tissues that are used as components of such tests under existing authorities until they are released to be incorporated into an IVCT. This would help to ensure that certain protections currently in place for these products, including donor screening and eligibility requirements, are applied to such components. However, on a technical note, we believe it would be more accurate to delete the reference to interstate commerce, as some blood or tissue establishments may also be the developer of test and, therefore, may not place the blood, blood component, or tissue in interstate commerce. We recommend you revise the text as follows:

> "(A) Blood, blood components, or human cells or tissues, from the time of donation or recovery of such article, including determination of donor eligibility, as applicable, until such time as the article is released ~~into interstate commerce~~ as a component or part of an in vitro clinical test by the establishment that collected such article.

6. Applicability for Emergency Use

On page 24, lines 2-3, clause (i) refers to the Secretary making "a declaration under section 564(b) for an in vitro clinical test." Section 564(b) states that "[t]he Secretary may make a declaration that the circumstances exist justifying the authorization under this subsection for a product on the basis of – . . . (C) a determination by the Secretary that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents." Given the declaration is for the public health emergency, and not the product, you may wish to consider the following edits in lines 1-9:

> "If the Secretary makes a declaration under section 564(b), ~~for~~ an in vitro clinical test that was offered for clinical use under an exemption under subsection (b), (c), (d), (e), (f), (g), (h), or (k) of section 587A~~B~~ prior to the declaration, ~~such test~~ may continue to be offered for clinical use after such declaration only if –"

7. Grandfathering

HHS supports the exemption from premarket review, quality system requirements, and most labeling requirements for grandfathered tests, as described in VALID. As written on page 28 lines 9-14, the provision exempts a grandfathered IVCT when it is run for the first time in a different lab within the same corporate organization and under common ownership by the same parent corporation. HHS suggests that this concept should also be applied to CDC's laboratory networks. You may wish to consider the following additional text in this provision:

> "…is performed in the same laboratory in which it was developed, ~~or~~ by another such laboratory for which a certificate is in effect under section 353 within the same corporate organization and having common ownership by the same parent corporation, or by a

laboratory within a public health laboratory network coordinated or managed by the Centers for Disease Control and Prevention;"

8. Public Health Surveillance Activities

HHS encourages the adoption of the definition of Public Health Surveillance published in the Common Rule (45 CFR 46.102(l)(2)). For your consideration, suggested redlines to page 38 lines 10-23 follow:

''(i) PUBLIC HEALTH SURVEILLANCE ACTIVITIES

(1) IN GENERAL.—The provisions of this subchapter shall not apply to a test intended to be used solely for public health surveillance.

(2) DEFINITION.—In this subsection, the term 'public health surveillance' means ~~ongoing systematic activities, including collection, analysis, and interpretation of health-related data, essential to planning, implementing, and evaluating public health practice.~~ activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

(3) EXCLUSION.—An in vitro clinical test is not excluded from the provisions of this subchapter if it ~~that~~ is either intended for use in making clinical decisions for individual patients ~~or other purposes not described in paragraph (2)~~ or ~~whose~~ if the test's individually identifiable results ~~may~~ are intended to be reported back to an individual patient or the patient's health care provider even if also intended for public health surveillance purposes.

9. Premarket Review to Ensure Analytical Validity of Platforms

HHS supports the requirement in VALID for premarket review of platforms.

All platforms that are exempt from premarket notification requirements today (e.g., clinical chemistry analyzers, mass spectrometers, and next generation sequencing instruments) are currently reviewed when an assay using such platform is submitted to the FDA. This is described

in our Replacement Reagent and Instrument Family Policy[1] as follows: "Although most automated clinical analyzers by themselves are class I and exempt from 510(k), reagent/instrument systems are considered ***"combination devices."*** FDA's Guidance on the CDRH Premarket Notification Review Program provides: In its review of the 510(k), the Center will subject the "combination device" to the same sorts of questions and documentation requirements that are applied to a single device. When such a device is found to be [substantially equivalent to the predicate device], it combines devices from different classes and is *classified in the highest of the predicate device classifications* unless the combined devices are regulatable as separate articles, e.g., they are detachable. In that case, the separately regulatable articles will be regulated in separate classes." One example of this in practice is FDA's recent clearance for a thyroid hormone assay run on a clinical chemistry analyzer where we reviewed and cleared both the assay and the platform, even though the platform is exempt on its own. [2] While review of platforms in the context of assays that utilize them works under FDA's current framework that includes premarket review of moderate and high risk assays, the focus of oversight is shifted under the VALID framework such that most assays would not be subject to individual premarket review, making a model where platforms are not individually reviewed dangerous.

FDA premarket review of platforms, as proposed in the discussion draft, is necessary because of the potential for inaccurate test results due to platform issues. As provided under the proposed regulatory framework, a wide variety and large number of tests could be run on a platform under precertification (or other exemption), and therefore it is necessary to ensure that platforms are analytically valid. Without this review, we would be concerned about the broad public health impact of platforms being used for many types of tests for which the platform is potentially invalid or outside of its specifications. FDA has seen such issues impact test results, in some cases resulting in a safety alert[3] or recalls[4]. These examples illustrate the importance of the platform to the assay results.

We also believe that a stand-alone review of platforms covering all marketed functionalities will be more efficient than reviewing limited functionality of a platform in the context of each submission for each assay run on the platform. One-time platform review would include analytical validation across all functionalities, labeling, software validation, electromagnetic

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1 https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM598031.pdf

2 For example, see https://www.accessdata.fda.gov/cdrh_docs/reviews/K162606.pdf

3 For example, see http://wayback.archive-it.org/7993/20171115052211/https:/www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm518830.htm

4 For examples, see https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=165791, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=164973, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=165298, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=158468, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=155029, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=129116, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=147815, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=99600, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=88235, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=33671, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=35321

compatibility and electrical safety; however, platforms would only be required to have Quality System (QS) documentation on file and they would not be subject to premarket review of QS documentation or preapproval inspection, nor would the developer be required to provide raw data by default. Premarket review of platforms would enable developers to market their platforms as FDA-authorized for other test developers to incorporate into their IVCTs, regardless of whether those IVCTs are exempt from premarket review. Further, developers would be required to utilize only those platforms that are FDA-authorized.

Recognizing that platforms are a significant investment for laboratories, we continue to support allowing a 5-year grace period for development of new IVCTs on platforms that have not been authorized by FDA, as is currently proposed in VALID.

Also recognizing that some entities develop both platforms and assays, we are amenable to language clarifying that developers may submit concurrent submissions for platforms and IVCTs, leveraging the same data sets as applicable (i.e., for the single representative assay). For example, a developer could submit concurrent submissions for a precertification ineligible test, a platform, a collection article, and a precertification, or any subset of combinations. This set of concurrent submissions would use the precertification ineligible test as the representative assay for the platform, collection article, and precertification, provided it appropriately covers the scope of all submissions leveraging it. This would allow the developer to leverage the same AV and CV data from a single representative assay and receive: (1) approval for a precertification ineligible IVCT, (2) approval for a platform, (3) approval for a collection article, and (4) precertification for the specified technology. In this example, the developer would submit the assay validation in their full premarket submission and include a reference to this submission for the representative assay requirements in the other three submissions (i.e., for the platform, collection article and precertification). This could streamline premarket submission and review for developers and FDA while maintaining an appropriate level of oversight.

10. Data requirements

The Department supports the discussion draft's approach for ensuring FDA is able to obtain enough information to make regulatory decisions, as this is critical for protecting the public health. HHS believes that submission of summary data in a premarket application is appropriate for most tests, but FDA must be able to obtain additional information if needed without undue burden, particularly to evaluate the relatively small proportion of tests that would require full premarket review. For certain tests, FDA's ability to determine whether a test is analytically and clinically valid depends on its ability to review the underlying raw data. In FDA's experience reviewing IVDs, it has seen a variety of serious issues during premarket review that were only identified because FDA was able to review the raw data.

11. Streamlined, Efficient Approach to Modifications

HHS supports the requirements regarding modifications in VALID. We note that under the proposed regulatory framework, FDA would be reviewing less than half of the modifications we currently review prior to implementation. HHS believes this approach is appropriate as it will give FDA a premarket check on the most impactful modifications and still require

documentation to design control files for all modifications, which would be subject to postmarket review upon inspection.

Specifically, precertified developers would be able to modify their tests without submitting anything to FDA for review, as long as the modification did not cause the test to fall outside the scope of the precertification or render the test ineligible for the program. For the small proportion of tests for which premarket review is required or for which the developer elects abbreviated premarket review, FDA would incorporate review of prospective change protocols in initial submissions that would enable timely improvements and other important changes to tests without requiring premarket review of the modification. Such prospective change protocols could potentially cover certain types of modifications relating to specimen type or stability, addition of new clinical context of use or new target variants, among others.

FDA needs clear authority to review modifications to such tests outside of an approved change protocol if the modifications adversely affect performance, change performance claims, or constitute a change in intended use as described by the seven key notification elements: substance(s) measured, specimen/sample type(s), test method, disease or condition for which the test is intended for use, intended patient population, test purpose, and context of use. Such modifications impact the analytical and clinical validity of a test or could result in an entirely new intended use.

12. Least Burdensome

HHS supports the least burdensome provisions provided in brackets beginning on page 64.

13. Priority Review and Breakthrough

HHS supports the concept of priority review in VALID, which is consistent with existing breakthrough provisions for medical devices. The breakthrough provisions instituted by 21st Century Cures have already led to successful authorizations of in vitro diagnostics, including the Foundation One CDx oncopanel and the Banyon Biomarkers blood test for traumatic brain injury. HHS supports leveraging the existing criteria and framework in VALID. For your convenience, HHS notes some potential drafting issues for your consideration.

- Subsection “a” on page 66 lines 12 and 14-15 refer to granting of approval under subsection “f”; this subsection “f” on page 69 lines 20-23 refers to annual reporting requirements and does not mention approval.
- Subsection “c” on page 67 line 21 refers to “breakthrough approval or approval under this section”; however, an approval process is not currently described in this section.

Subsection “e” on page 69 line 18 includes a placeholder for “Breakthrough In Vitro Clinical Tests.” HHS would support a provision that enables a time-limited approval based on probable clinical validity, provided the approval would automatically lapse if clinical validity was not established and full approval obtained within a specified timeframe.

14. Precertification is a Key Component of a New Flexible Regulatory Framework

HHS continues to believe that a precertification pathway provides a flexible option for eligible developers with eligible tests, and supports its inclusion in VALID. The feasibility of the overall regulatory framework depends on inclusion of the precertification pathway to enable efficient FDA oversight of a large volume of tests. Under precertification, FDA would evaluate test developers and their processes for developing certain tests to ensure that current and future tests developed under that precertification are analytically and clinically valid. Precertification would benefit test developers who would be able to bring new tests to market under a precertification quickly, patients who would have access to these tests more quickly, and FDA which would be able to appropriately focus resources to best protect the public health. HHS believes that precertification is an efficient and appropriate way to provide oversight for certain categories of tests.

HHS supports the VALID proposal that the scope of an individual precertification be limited to all eligible IVCTs within a single technology. Accordingly, a single precertification scope could cover many test groups. For example, a developer could request a precertification scope covering the use of polymerase chain reaction (PCR) on a variety of sample types and in different clinical areas, such as diagnosing infectious diseases from microbial DNA and/or germline diseases from human DNA. Although HHS's prior TA suggested limiting the scope by both technology and medical subspecialty, HHS agrees that many medical specialties can be addressed in a single precertification provided they are stated up front by the developer, supported by appropriate procedures for establishing clinical validity, and contemplated in the selection of a representative assay for purposes of recertification.

Potential risks associated with allowing precertified developers to market eligible tests without FDA premarket review are mitigated by key provisions in VALID: The requirement for periodic re-certification with a new representative assay would enable FDA to monitor a developer's ongoing application of its procedures to developing and validating tests appropriately. The requirement for transparency regarding IVCT intended use and performance in the CTIS would enable FDA and the public to efficiently monitor the tests introduced under precertification and the developer's claims associated with them. This powerful database combined with adverse event reporting requirements would enable FDA to identify issues. Finally, if issues do arise, the provisions for temporary suspension and withdrawal of precertification would allow FDA to address them appropriately.

VALID includes requirements for annual reports to Congress for the first five years of the program as well as a public meeting between the fourth and fifth annual report. HHS appreciates the need for transparency and accountability as this novel program is implemented. Since much of the data requested in the Report to Congress would be publicly available through CTIS, we recommend that FDA provide a public update published on its website, instead of through a Report to Congress, to ensure all affected stakeholders have the opportunity to review and comment on the update.

15. Presubmissions

HHS supports the presubmission provisions beginning on page 95, including the bracketed language allowing presubmission discussions to cover regulatory pathways and investigational plans.

16. National Security Considerations for Registration and Notification and for Publication of Approval Orders

HHS supports the transparency that will be afforded to all stakeholders through the Comprehensive Test IT System as well as the safeguard against public disclosure of sensitive information that could compromise national security. We suggest the following revisions to improve clarity and consistency within the legislation.

With respect to publication of approval orders on page 56, we suggest:

> "(D) PUBLICATION.—The Secretary shall publish each order approving an application pursuant to this paragraph on the public website of the Food and Drug Administration and make publicly available a summary of the data used to grant the approval, except to the extent the Secretary determines that such order relates to national security or countermeasures or ~~data~~ is restricted from disclosure pursuant to statutory provisions other than this section.

With respect to registration and notification on page 104, we suggest:

> "(3) The registration and notification information requirements described in subsections (a) and (b) shall not apply to the extent the Secretary determines that such information relates to national security or countermeasures or is restricted from disclosure pursuant to another statute~~, including information relating to national security or countermeasures~~.

17. Quality System (QS) Regulation

HHS supports the discussion draft's approach of requiring QS to ensure that the tests developed are of sufficient quality and meet the developer's specifications. The QS requirements help to ensure that IVCTs perform as intended and establish mechanisms to detect quality problems and promptly address any issues that may arise.

For developers that are CLIA-certified, FDA would only evaluate a subset of the QS requirements: design controls, purchasing controls, receiving and acceptance activities, CAPA, and records (including the subsections that fall under records in 21 CFR 820, such as complaint files). This subset of FDA QS requirements is necessary to ensure the design and development of high quality tests.

HHS suggests the addition of "distribution" to the list of IVCT activities to which the quality system requirements of the section should apply (page 107 lines 1-10):

> ''(1) IN GENERAL.—The quality system requirements applicable under this section shall, including applying or amending part 820 of title 21 of the Code of Federal Regulations as provided in subsection (a)(4)—
>
> ''(A) apply only with respect to the design, development, validation, production, manufacture, preparation, propagation, distribution, or assembly of an in vitro clinical test, offered under this subchapter;"

HHS supports the provision that allows developers to share protocols with other laboratories within the same corporate organization. HHS suggests enabling CDC to utilize this provision for all of their laboratory networks. HHS also suggests explicitly stating that laboratories that run protocols developed by another laboratory within their corporate organization, or within the public health laboratory network, must do so without modification to meet this provision. For your consideration, redlines to this section which begins on page 109 are provided:

> ''(3) QUALITY SYSTEM REQUIREMENTS FOR CERTAIN LABORATORIES DISTRIBUTING PROTOCOLS WITHIN ORGANIZATIONS OR PUBLIC HEALTH NETWORKS.—
>
> ''(A) With regard to establishing quality system requirements under this Act, including applying or amending part 820 of title 21 of the Code of Federal Regulations as provided in subsection (a)(4), quality system requirements applicable to the developer and in vitro clinical test distributed under subparagraph (B) shall consist of the following provided that the conditions of subparagraph (B) are met:
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> ''(i) The requirements in paragraph (2).
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> ''(ii) The labeling requirements in subparagraph (1)(L).
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> ''(iii) The requirement to maintain records of the laboratories to which the test protocol is distributed.
>
> ''(B) To be eligible for subparagraph (A), the following conditions must be met—
>
> ''(i) the laboratory distributing the protocol is certified by the Secretary under section 263a of title 42 of the United States Code and meets the requirements for performing high-complexity testing;
>
> ''(ii) the laboratory develops its own in vitro clinical test or modifies another developer's in vitro clinical test in a manner described in section 587(6); and
>
> ''(iii) the laboratory distributes the test protocol for such test only to another laboratory that—
>
> ''(I) is certified by the Secretary under section 263a of title 42 of the United States Code and meets the requirements for performing high-complexity testing; ~~and~~''
>
> (II) is within the same corporate organization and having common ownership by the same parent corporation; or as applicable, is

~~within the Laboratory Response N~~ a laboratory within a public health laboratory network ~~of~~ coordinated or managed by the Centers for Disease Control and Prevention~~.~~; and
(III) implements the test protocol without further modification.

18. FDA Must have Strong General Postmarket Authorities

HHS appreciates that the discussion draft provides FDA strong general postmarket authorities. Under the proposed regulatory framework, the ability of FDA to continue to fulfill its mission of protecting the public health depends on FDA's ability to monitor tests in the postmarket setting and enforce when necessary. HHS believes that the shift away from premarket review for most tests necessitates clear, workable postmarket monitoring and enforcement authorities, such as postmarket surveillance, adverse event reporting, inspections, recalls, corrections and removals.

It is also critical for FDA to have reasonable enforcement standards, including, when necessary, the ability to require a premarket submission for tests offered under an exemption or to revoke an exemption. FDA must have the ability to address problematic IVCTs, including those that may be grandfathered, when they are not analytically or clinically valid, do not have sufficient valid scientific evidence to support analytical and clinical validity, have false or misleading labeling or advertising, and where there is a reasonable potential that the IVCT will cause death or serious adverse health consequences, including by causing the absence, delay, or discontinuation of appropriate medical treatment.

19. Restricted IVCTs

HHS supports the provisions for Restricted IVCTs beginning on page 122. We note there is a placeholder for "Labeling and advertising of a restricted IVCT." HHS suggests the following language for this subsection which is consistent with current medical device provisions:

> "(1) The label, labeling, and advertising of an in vitro clinical test to which restrictions apply under subsection (a) shall bear such appropriate statements of the restrictions as the Secretary may prescribe in the approval, [breakthrough approval], precertification, or regulation, as applicable.
>
> "(2) Except in extraordinary circumstances, the Secretary shall not require prior approval of the content of any advertisement, and no advertisement of a restricted in vitro clinical test, published after the effective date of this section shall, with respect to the matters specified in this section or in orders or regulations issued hereunder, be subject to the provisions of sections 12 through 15 of the Federal Trade Commission Act (15 U.S.C. §§52-55). This subparagraph shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 201(m).

20. Investigational Use

HHS supports the provision in VALID for exemptions for Investigational Use. For studies of IVCTs that are nonsignificant risk, HHS does not believe a submission to the Secretary is

necessary, consistent with current practice. We suggest the following edits on page 135 of VALID to clarify this:

"(B) In the case of an in vitro clinical test, the investigational use of which does not pose a significant risk—

"(i) the sponsor of such investigation shall ~~comply with~~ —

"(I) conduct such investigation in compliance with an investigational plan and labeling ~~the requirements~~ specified in paragraph~~s (3)(A),~~ (3)(B)~~, and (5)(A)(iii)~~; and

"(II) ensure each investigator obtains informed consent under part 50 subject to the exceptions set forth in paragraphs (5)(A)(iii)(I) and (II) and (5)(B)(iii); and

"(III) comply with such other requirements as the Secretary may determine to be necessary for the protection of the public health and safety, including the monitoring of investigations conducted with such test, the establishment and maintenance of records, or the submission to the Secretary of reports of data obtained as a result of the investigational use of the in vitro clinical test during the period covered by the exemption; and

"(IV) maintain records with respect to all requirements in this subparagraph.

"(ii) the sponsor may rely on any exception or exemption identified in paragraph (5)(B) or as established by the Secretary in regulations issued under subsection (b).

Additionally, we noted an incorrect reference in the Investigational Plan Requirements and suggest the following edit on page 138 of VALID:

"(5) INVESTIGATION PLAN REQUIREMENTS.—

"(A) IN GENERAL.—With respect to a plan submitted under paragraph (2~~3~~)~~(B~~), the sponsor submitting such plan shall—

The following conforming edit to the Application Contents on page 136 of VALID may be helpful:

"(2) APPLICATION CONTENTS.—An investigational use application shall be submitted in such time and manner and contain such information as the Secretary

may require in regulation. The application ~~and~~ shall include an investigational plan and assurances to the satisfaction of the Secretary that the sponsor involved shall, with respect to the in vitro clinical test that is the subject of the application—

21. FDA Supports Leveraging External Expertise

The Department supports the mechanisms the discussion draft has provided to allow FDA to leverage external expertise for oversight of IVCTs. FDA should be able to leverage external expertise and assistance in the context of third party review and inspection to realize efficiencies, particularly as some existing CLIA Accrediting Organizations (AOs) may seek accreditation from FDA to conduct third party reviews or inspections, perhaps combined with CLIA inspections. At the very least, using CLIA AOs to perform FDA inspections would allow labs to continue to interact with the inspectors they are already familiar with.

FDA should also be able to engage with public and private sector members to proactively work together to solve shared problems. Engagement with such continuing forums, which we have termed "Collaborative Communities," would allow FDA to seek input from a broad array of stakeholders on a variety of topics, such as standards development activities and mitigating measures.

22. Transition

HHS supports the transition provisions starting on page 184 in VALID. Specifically, we agree that grandfathered in vitro clinical tests that meet the criteria starting on page 26 of VALID, including being offered for clinical use at least 90 days prior to enactment, should be "grandfathered" and exempt from premarket review and QS requirements. The 90 day window pre-enactment is critical to prevent rush to market to obtain grandfathered status.

Developers of transitional in vitro clinical tests (as defined starting on page 186 of VALID) offered for clinical use between 90 days pre-enactment and the effective date could choose between voluntary compliance with medical device provisions or temporary enforcement discretion until review of an IVCT submission (e.g., precertification, abbreviated premarket review, or full premarket review, as applicable) is complete following the effective date.

HHS believes this is the smoothest way to transition into the new framework in a reasonable amount of time. HHS appreciates that the discussion draft would not require simultaneous operation of two different oversight systems for the same products.

23. User Fees

HHS appreciates the inclusion of a user fee provision in VALID, as a healthy user fee program is critical to its success. Under user fee programs, FDA and stakeholders come together on a regular basis for the shared purpose of advancing the field and helping patients. For example, FDA and industry created the Dual 510(k) and CLIA Waiver by Application pathway under the Medical Device User Fee program. This strategic pathway enables developers of tests intended for use by lay users to conduct one clinical study and submit one submission to obtain both

marketing authorization and CLIA waiver status. This is more efficient for all parties and furthers timely patient access to accurate and reliable tests. Resources from user fee programs enable FDA staff to dedicate time to developing innovative policies such as this as well as to interacting with sponsors for more efficient reviews of submissions.

As written in the discussion draft, FDA would not be able to use user fee funding to support all activities under the IVCT program, particularly those outside of premarket application review. In addition to the premarket review of in vitro clinical tests, the IVCT framework relies on an enhanced postmarket focus for the assurance of in vitro clinical test analytical validity and clinical validity. All activities related to IVCT oversight that provide the assurance of in vitro clinical test analytical validity and clinical validity (e.g., registration, notification, premarket review, precertification, adverse event monitoring, inspections, and other postmarket surveillance activities) should be supported by a healthy user fee program in order to ensure the workability and success of the program. To enable FDA to apply user fees to all such activities, we suggest replacing the phrase "the process for the review of in vitro clinical tests" with "activities related to oversight of in vitro clinical tests" throughout the section.

We are open to a novel user fee framework but note that some deviations from FDA's existing medical product user fee programs may have unintended consequences as described below.

- The discussion draft limits fees to submissions, which could result in unstable funding. FDA experienced unintended consequences with such a structure under MDUFA I that required the MDUFA stabilization act to correct. Since that time FDA's MDUFA reauthorization discussions with industry first focus on a total cost for a given package of performance goals and process improvements; then FDA works together to negotiate a fee structure that provides such funding in a stable manner. For example, under MDUFA FDA has facility registration fees. The relatively smaller fees on a large number of facilities ensures more stable funding than relatively higher fees tied to less frequent activities subject to fluctuations in frequency. A stable base is critical for the program, since premarket submission volumes often fluctuate.

- Submission fees have traditionally not been commensurate with the effort for the particular submission type. Instead, the funds necessary for the entire program are determined, and fees are assigned to particular submission types in a strategic manner, knowing that the fees will be used to support activities across the entire program, not only a particular submission. For example, the MDUFA IV agreement includes funding for additional review staff to meet performance goals on Pre-Submissions. There are no fees on Pre-Submissions themselves; the staff are supported by fees associated with facility registrations and other submissions. The ability to consider the program and ecosystem holistically has been useful to all parties to MDUFA reauthorization.

HHS suggests aligning the authorization timeframe with the reauthorizations for MDUFA and PDUFA programs, which would allow them to be included in a single legislation. Further, removing IVDs from the current MDUFA program would upset some of the assumptions of the negotiated agreement, particularly with respect to submission volumes and their impact on fee setting. A clean break could take place between MDUFA IV and MDUFA V, which will begin

on October 1, 2022. It would be most helpful if this could be anticipated at the time MDUFA V negotiations begin in 2020, so that appropriate assumptions can be taken into consideration for the medical device program under MDUFA V.

Further, HHS recommends removing audits from the statutory provision and leaving discussion of such independent assessments to the user fee negotiations. We note that both MDUFA and PDUFA programs include independent assessments, the details of which are outlined in the Commitment Letters. This approach would allow meaningful discussion among affected stakeholders and the ability to craft appropriately tailored provisions for an independent assessment that fit with the overall package to be negotiated. Any such provisions for an independent assessment could be included in the Commitment Letter to ensure accountability.