

**A Risk-based Approach for In Vitro Companion
Diagnostics Device FDA Approval Process Associated
with Therapies that have Breakthrough Designation**

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GOAL


The goal of this paper is to propose modifications to standard drug/diagnostic co-development that would expedite the development of an In Vitro Companion Diagnostic Device¹ that is intended for use with a Breakthrough Therapy.

INTRODUCTION

In July 2012 Congress passed the Advancing Breakthrough Therapies for Patients Act as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). Section 506(a) of FDASIA provides for designation of a drug as a breakthrough therapy “if the drug is intended alone or in combination with one or more other drugs, to treat serious or life-threatening diseases or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies.”² Breakthrough designation is a mechanism that the FDA can grant to sponsors to expedite the development of these promising therapies. In November 2012, Friends of Cancer Research released a white paper providing recommendations for this new designation.³ This was followed by publication of an article describing standards for breakthrough drugs and diagnostics in May 2013.⁴ In July 2013, FDA released a draft guidance that describes the agency’s different regulatory tools to expedite drug development for serious and life threatening illnesses, including the Breakthrough Therapy Designation.⁵

Several of the therapies that have these promising large treatment effects are targeted agents that require an in vitro diagnostic (IVD) companion diagnostic device be used in order to prescribe the treatment to the patient population that has been shown to respond to the drug. Opportunities to expedite the development of IVD companion diagnostics were not described in the In Vitro Companion Diagnostic Devices guidance document. However, the following statement from this guidance sets the stage for development of a more flexible set of requirements for companion diagnostics associated with Breakthrough Therapies: “FDA may decide to approve a therapeutic product even if its IVD companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device.” The purpose of this paper is to explore how sponsors and FDA may be able to improve and expedite the process for the development and subsequent clearance or approval of an IVD companion diagnostic device for a breakthrough therapy. This document will offer a set of proposals focusing on five areas:

1. Automatic designation of IVD companion diagnostic devices for use as part of a breakthrough drug approval as eligible for priority review
2. Use of highly coordinated administrative processes and management commitments for review of IVD companion diagnostics associated with breakthrough therapies that are commensurate with those processes offered for breakthrough therapies.
3. Use of risk-based processes to determine required companion diagnostic device (CoDx) Analytical Studies for each assay type prior to premarket approval (PMA) or 510(k) filing


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4. Use of risk-based approaches to determine requirements for data and testing related to quality systems, manufacturing processes and software testing and documentation
 5. Use of a “Continued Access” supplement investigational device exemption (IDE) to enable a broader set of labs to be ready for testing immediately upon contemporaneous approval of the companion diagnostic and therapeutic product.

Reducing Premarket Regulatory Burden: In order for IVD companion diagnostic devices to be developed concurrently and to be available at the time of drug approval, certain aspects of diagnostic development may have to be addressed to avoid causing delay of the potential benefits of a streamlined, faster breakthrough approval pathway. The goal of this paper is to elucidate a process that may be more flexible for the premarket review in breakthrough situations. FDA can vet such a process in the context of one or more panel meetings and/or by use of FDA panel expertise through homework assignments. The earlier in the process that a breakthrough therapy with an associated companion diagnostic is recognized the earlier that these potential issues can be identified and addressed for the diagnostic thus facilitating the review and approval of both the therapy and the companion diagnostic. Determining the minimum set of data required for approval of a companion diagnostic for a breakthrough therapy requires use of a risk-based approach given the variety of diagnostic assays that may be considered (i.e., immunoassays, immunohistochemistry products, molecular diagnostics and multiplex versions of any of these products). Consideration should be made of the current regulatory status of the diagnostic assay for similar indications, if appropriate. In addition, how the assay is provided (i.e., a kit/instrument combination used by many labs or a single-lab service approach) should also be considered. Further, although some generalizations may be made, this risk-based approach will be both assay and technology specific.

Development of Companion Diagnostic Products: Commercially Distributed vs. Lab-based:

There are two common approaches when considering development of an IVD companion diagnostic device. The first is to develop a complete diagnostic system (i.e., reagents, instruments and software) and obtain FDA approval on the system. These systems are then made commercially available and supplied to clinical testing laboratories. Clinical testing can be performed in any appropriate laboratory that analytically validates use of the assay in their lab.

The second approach is for the diagnostic device to be developed completely by a single laboratory. (**Note:** in this paper we are not designating these services as Laboratory Developed Tests (LDTs) because the assumption is that for companion diagnostics, FDA clearance or approval is required. However, the development process is similar to that used for LDTs, but with the increased stringency required for FDA clearance/approval.) In this case, a CLIA/FDA compliant laboratory is required to file a PMA/510(k) but the approval is for a single laboratory to deliver results. FDA has cleared several single site lab-based assays in the past thus demonstrating the viability of this model within the current FDA regulatory framework.



A third potential option has been suggested that may be useful in developing companion diagnostics for Breakthrough Therapies. This new option, which has not been used for approval, is a combination of the two approaches. In this model, the commercial diagnostic system would be designed by the manufacturer, but only for use at a single-site CLIA laboratory. Because this approach uses a commercially available diagnostic system it may allow for later expansion to additional labs, as described in Proposal 5 in this report. It is important to note that all CDx test systems are held to the same evidentiary standards for analytical performance, manufacturing process validation, Quality Systems Regulation (QSR) requirements, and clinical evidence regardless of the site of manufacture.

Setting Appropriate Standards for IVD Companion Diagnostic Devices Associated with Breakthrough Therapies: A risk-based approach to determining the required data for diagnostic products associated with breakthrough therapies does not suggest any less vigilance in oversight. Rather, it focuses activities on those that prevent or mitigate important and likely risks related to the information the diagnostic product provides.

The suggestions for a risk based approach offered here are not designed to lower standards; it remains of paramount importance that FDA-cleared and FDA approved diagnostics maintain adequate product quality for safe patient use and that they satisfy FDA requirements for safety and efficacy (drug approval) or effectiveness (diagnostic device approval). It is believed that this risk-based approach falls within existing FDA requirements; it uses risk assessment methodologies to determine adequate mitigation of risks at product approval, and defers low-risk mitigations to post-approval activities. We recognize that all current requirements should continue to be met but it is believed that certain items could be delayed and perhaps required as post marketing commitments rather than being completed prior to PMA.

Although regulatory and legislative changes may ultimately be necessary to provide FDA with additional authority to require post market studies for diagnostic tools (for example, providing specific authority to remove devices from the market as needed and additional authority to require post-market studies), this document highlights a risk-based approach needed for review and approval of IVD companion diagnostics that accompany Breakthrough Therapies.

Because it is likely that the clinical development program of a Breakthrough Therapy will be compressed, it is also important to prioritize the data elements typically generated as part of a diagnostic development program to ensure that essential elements are collected early and do not unnecessarily slow the entire development process. To do so, we propose a risk-based evaluation of the data elements that would be absolutely necessary to establish analytical validity of an assay, as well as associated labeling requirements to ensure laboratories using the FDA approved diagnostic product appropriately validate the assay for use in each specific laboratory.

Many of the suggestions assume the PMA will be submitted in a modular fashion as is most common with companion diagnostic PMAs. Some modifications may be required if the PMA is expected to be submitted as a Traditional PMA and possibly for companion diagnostics requiring a 510(k).

PROPOSALS

Proposal 1: Automatic designation of IVD companion diagnostic devices for use as part of a breakthrough drug approval as eligible for priority review: Center for Devices and Radiological Health (CDRH) has recently published revised guidance on priority review that assures priority be given to selected products, although it does not assure review outcomes (May 2013).⁶ Due to the unique importance of an IVD companion diagnostic device for use in a breakthrough drug therapy, CDRH should routinely designate these submissions as eligible for priority review. In particular, this designation should align review timelines and ensure coordination of all branches of FDA involved in the review of the co-developed products.

Proposal 2: Use of highly coordinated administrative processes and management commitments for review of IVD companion diagnostics associated with breakthrough therapies that are commensurate with those processes offered for breakthrough therapies: In order to expedite the development of a companion diagnostic to a Breakthrough Therapy, considerable collaboration and coordination between FDA Centers and sponsors will be critical. The following enhancements are suggested as ways to foster an accelerated process for co-development:

- A. FDA should seek to ensure that the sponsor of a diagnostic product designed for use with a breakthrough therapy receives timely advice and interactive communications in order to help the sponsor design and conduct a development program as efficiently as possible. When possible pre-submission reviews should be prioritized and review cycle times reduced.
- B. For phase I studies, use of a risk-based approach to provide clear guidance on when patient safety and other rights and protections can be assured under the Investigational New Drug application (IND) and when an IDE may also be required in addition to the IND. FDA should consider earlier provision of appropriate advice to the drug sponsor in early studies (phase I) where biomarker-based pre-screening or selection is proposed by the sponsor. This is especially important for FDA to provide early guidance on best practices (such as informed consent for later diagnostic development and banking of both marker positive and negative samples) in these early studies to aid future potential market submissions for both the therapy and the diagnostic.
- C. FDA should expedite the review of these selected diagnostics by intensively involving senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review.
- D. FDA should assign a cross-disciplinary project lead for the review team to facilitate efficient review within CDRH and to manage cross-center review. FDA CDRH/CBER/CDER should establish an internal process for enhanced coordination of activity to support expedited review of co-developed products.

Proposal 3: Use of risk-based processes to determine required analytical studies for each assay type prior to PMA filing:

There are many elements in the analytical validation of diagnostic assays. The impact on product quality of each required element varies based on assay design and intended use. In this section, we have focused on identifying risk-based approaches for determining required analytical studies, as well as the design of those studies, that are most critical for diagnostic PMA associated with a breakthrough therapy. As mentioned above, this is not an attempt to avoid any current FDA requirements or reduce overall requirements for an IVD companion diagnostic device approval associated with a Breakthrough therapy but rather to give FDA the flexibility to consider critical data requirements at the time of initial approval.

Please see Table 1 (Worksheet) on page 13 for an outline of factors that we are suggesting may be involved in the proposed risk-based decision making process.

- 1) Utilize a risk-based approach when determining the type of samples required for analytical studies, especially in regards to the practical issue of lack of availability of specimens.
 - a) Determine if the use of contrived samples (e.g. cell lines, plasmids, serum spiked with recombinant protein) for analytical studies will provide a sufficient initial assessment of assay performance for PMA approval.
 - b) In the case of rare diseases and/or rare specimens, determine if it is acceptable to supplement patient specimens with contrived specimens in assessment of assay analytical performance characteristics such as sensitivity and specificity.
 - c) For assays where there may be many genetic variants, determine if all variants must be tested during analytical studies or whether panels of representative variants may be used.
- 2) Utilize a risk-based approach to consider types and design of analytical studies. In order to justify flexibility on some requirements sponsor would submit a matrix of typical studies compared with appropriate simplifications of study designs or justification for omission of studies for initial PMA approval.
 - a) Determine if correlation studies (internal to sponsor) would be acceptable in lieu of having clinical data from multiple samples types.
 - b) For multiplex assays, determine if all studies must be completed on all analytes or if representative analyte testing is sufficient to demonstrate performance of the device.
 - c) When a reference method is needed but is not readily available consider alternative approaches to determining accuracy of the device under review.
 - d) Allow the use of process verification lots in performing analytical validation studies, as long as they are representative of the final product, and perform post-validation assessment of the continued acceptability of the analytical validation studies.
 - e) Allow the use of fewer lots in performing certain analytical validation studies, with post-approval assessment of the performance of remaining lots as necessary.

- f) If an early version of the assay was used during the clinical trial but a different version of the assay will be submitted in the PMA, determine appropriate assay bridging strategies that may include samples that were not clinical trial samples. (e.g. find cohort with similar inclusion criteria from drug study and baseline demographic characteristics)
- g) Additional examples of analytical validation studies that may be simplified. This list is not comprehensive and the requirements for each analytical validation plan should be assessed independently using the risk-based approach.
 - i) Precision – Consider reducing:
 - (1) Number of sites (possibly more internal sites)
 - (2) Number of lots
 - (3) Number of instruments
 - (4) Number of operators
 - (5) Extent of panel
 - ii) Specificity – Limit the number of substances to be tested for each of the following studies:
 - (1) Cross-reactivity
 - (2) Endogenous Interferences
 - (3) Effect of Pharmaceuticals
 - (4) HAMA Effect (immunoassay only)

Proposal 4: Use of risk-based approaches to determine requirements for data and testing related to quality systems, manufacturing processes and software testing and documentation:


A Premarket Approval (PMA) application is submitted to FDA to request approval to market a companion diagnostic used to determine the use of a drug in patients. PMA approvals require that sufficient valid scientific evidence provide reasonable assurance that the device is safe and effective for its intended use or uses.⁷ As with the application for marketing approval of a drug, the required data elements to demonstrate safe and effective use of a diagnostic tool are numerous. In the case of an IVD companion diagnostic device to determine the use of a Breakthrough Therapy, optimizing processes to expedite the development and patient access may be possible. The following proposals for adapting the diagnostic development process could be applied to all types of diagnostics that accompany a Breakthrough Therapy. (**Note:** for some of the ideas in Proposal 4 to be acceptable it is likely FDA will need additional regulatory authority to require additional data to be submitted after initial PMA approval.)

Please see Table 1 (Worksheet) on page 14 for an outline of factors that we are suggesting may be involved in the proposed risk-based decision making process.

- 1) Pre-determine manufacturing control and quality system requirements at the time of the PMA submission (complete information to be filed as PMA amendments):
 - a) For manufacturers that have other PMA approved products or have recently (within two years) successfully completed a Quality System Regulation (21 CFR Part 820) inspection allow:
 - i) Submission of an abbreviated quality system and manufacturing module
 - ii) Eliminate or modify the requirements for the QSR audit specifically for the product under consideration prior to PMA approval

- b) For companion diagnostic manufacturers that do not have previous QSR inspection history:
 - i) Review existing quality documentation and determine if there are any gaps in QSR compliance. If there are gaps, consider whether existing quality documentation may be acceptable in the interim while the manufacturer completes a fully QSR compliant system; ensure complete QSR compliance is achieved within a specific time period. Provide early guidance for the design control elements that would be needed to support the submission. This would likely need to be determined on a case-by case basis but the FDA expectations could be outlined in a guidance document.
 - ii) When a device manufacturer is developing an assay for “distribution” to a single lab such as for a rare indication, determine if certain requirements may be deferred to the post-market.
- c) Utilize a risk-based approach to determine the level of manufacturing process validation required at the time of PMA submission and for approval. Considerations or approaches may include:
 - i) Does the manufacturer have other PMA approved products utilizing the same or highly similar manufacturing processes? If so, consider whether submission or re-submission of this information is necessary to determine safety and efficacy of the product.
 - ii) Review all processes during the pre-submission discussions that are required for manufacturing of reagents and instruments and determine (based on history of manufacture) the highest risk processes and require submission of data only on those processes. Completed process validation information would be required to be submitted as a PMA amendment within six months of PMA approval.
 - iii) For a lab-based assay consider the appropriate approach for process validation for reagents that are prepared in very small batches or on a per-run (per-day) basis (e.g. consider full evaluation of lot-to-lot reproducibility).
- d) Utilize a risk-based approach to determine the level of software validation required at the time of PMA submission and for approval. Considerations or approaches may include:
 - i) Determine if software documentation at the Minor level of concern could be considered sufficient for the initial PMA approval.^{8, 9, 10}
 - ii) If the instrument that is being submitted with the application has been previously cleared or approved consider whether any additional software information is required to ensure safe and effective use of the device.

Proposal 5: Use of a “Continued Access” supplement IDE to enable a broader set of labs to be ready for testing immediately upon contemporaneous approval of the companion diagnostic and therapeutic product. Under current regulations, devices cannot be shipped to laboratories until they are approved and laboratories are verified to perform the testing. Sites where clinical trials were performed are able to do testing upon approval of the companion diagnostic since the device(s) are in place and verification has been completed as part of the clinical trial. For laboratories that were not part of the clinical trial, it can take several weeks after approval until testing can be conducted. A Continued Access IDE would allow for an “extended” clinical investigation at additional laboratories so that device placement and verification could be completed to enable testing to commence upon approval of the companion diagnostic. In addition, this type of IDE could also extend testing that is being performed at a single laboratory site until PMA approval is complete.



A Continued Access IDE can be used after completion of a clinical trial to “continue to enroll subjects while a marketing application is being prepared by the sponsor and/or reviewed by the Agency if there is:

1. A public health need for the device; or
2. Preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.”¹¹

Forward Looking Regulatory and Policy Issues: Key Questions: In order to consider some of the proposals in this paper, regulatory and/or legislative changes may be required. To better understand the need for these changes, we’ve posed several key outstanding questions for discussion:

Question 1: If either the therapy or the diagnostic device is removed from the market for any reason; is the corresponding product also removed from the market?

Question 2: What is the regulatory mechanism that allows FDA to ensure complete information is filed for the IVD companion diagnostic device associated with a breakthrough therapy if initial data or documentation requirements are reduced?

Question 3: Can a PMA granted as part of a breakthrough program be designated differently than a typical PMA approval (i.e., an Interim PMA) and be given a time limit for conversion to a standard PMA (i.e. 12 months)? If not, what regulatory or statutory changes would be needed to make this possible?

Question 4: Should any of the proposals for reduced regulatory burden be considered if the IVD companion diagnostic device is measuring a marker that pertains to safety of the breakthrough therapy rather than efficacy?

Question 5: Does the concept of a “Continued Access IDE” require a change in regulations or legislation?

REFERENCES

- ¹ Guidance for Industry and Food and Drug Administration Staff - In Vitro Companion Diagnostic Devices. July 14, 2011: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm> Accessed 8/1/13.
- ² FDASIA Sec. 902 PL 112-144: <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf>
- ³ Friends of Cancer Research / Brookings Institution Conference on Clinical Cancer Research 2012. “Developing Standards for Breakthrough Therapy Designation” <http://www.focr.org/sites/default/files/CCCR12Breakthrough.pdf>. Accessed 8/1/12
- ⁴ Horning, SJ, Haber, DA, et al. “Developing Standards for Breakthrough Therapy Designation in Oncology”. *Clin Cancer Res.* Online May 29, 2013.
- ⁵ DRAFT: Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics. June 2013: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf> Accessed 8/1/13.
- ⁶ Guidance for Industry and Food and Drug Administration Staff - Priority Review of Premarket Submissions for Devices. May 17, 2013: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089698.pdf>. Accessed 8/1/13
- ⁷ FDA Center for Devices and Radiological Health: <http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/default.htm>
- ⁸ Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, May 11, 2005: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf> Accessed 8/1/13
- ⁹ Guidance for Industry and FDA Staff: General Principles of Software Validation, January 11, 2002: <http://www.fda.gov/downloads/MedicalDevices/.../ucm085371.pdf> Accessed 8/1/13
- ¹⁰ Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software Use in Medical Devices, September 9, 1999: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073779.pdf> Accessed 8/1/13
- ¹¹ Continued Access to Investigational Devices During PMA Preparation and Review. FDA, July 15, 1996 (Blue Book Memo) (D96-1) <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080260.htm>

GLOSSARY

Correlation: the relationship between two, or several, random variables within a distribution of two or more random variables

Cross Contamination: carry-over of a specimen, sample or a reagent from one reaction vessel to another

Cross-reactivity: determination whether binding of an antibody with an analyte other than its intended target

Cut-off/Specificity: for a qualitative test, the threshold above which the result is reported as positive and below which the result is reported as negative. (Clinical and Laboratory Standards Institute (CLSI), EP12-A2)

Endogenous Interference: physiologically occurring substance in a sample (e.g., bilirubin or hemoglobin) that causes interference with the analysis of another substance. (CLSI, EP7-A2)

Exogenous Interference: substance originating outside the body (e.g., a drug or its metabolites, a specimen preservative, or a sample contaminant) that causes interference with the analysis of another substance in the specimen. (CLSI, EP7-A2)

HAMA Effect: interference associated with human anti-mouse antibodies

High Dose Hook Effect: false negative due to too high of protein concentration

Interference: in Clinical Chemistry, a cause of clinically significant bias in the measured analyte concentration due to the effect of another component or property of the sample; NOTE: It may result from nonspecificity of the detection system, suppression of an indicator reaction, inhibition of the analyte (enzymes), or some other cause of specimen-dependent bias. (CLSI, EP7-A2)

Limit of detection (LOD): lowest amount of analyte in a sample that can be detected with (stated) probability, although perhaps not quantified as an exact value. (CLSI, EP12-A2)

Limit of quantitation (LOQ): lowest amount of a measurand in a material that can be quantitatively determined with stated accuracy (as total error or as independent requirements for bias and precision), under stated experimental conditions. (CLSI, EP17-A2)

Linearity: ability to provide measured quantity values that are directly proportional to the value of the measurand in the sample. (CLSI, EP17-A2)

Lot to Lot Reproducibility: measurement precision of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar samples; in a situation where multiple kits are needed, each lot must be tested in combination with every other lot

Precision: Closeness of agreement between independent test/measurement results obtained under stipulated conditions. (CLSI, EP5-A2)

Repeatability: Closeness of the agreement between results of successive measurements of the same measurand carried out under the same conditions of measurement. (CLSI, EP5-A2)

Sensitivity: the percentage (number fraction multiplied by 100) of subjects with the target condition (as determined by the diagnostic accuracy criteria) whose test values are positive. (CLSI, EP12-A2)

Specificity: the percentage (number fraction multiplied by 100) of subjects without the target condition (as determined by the diagnostic accuracy criteria) whose test values are negative. (CLSI, EP12-A2)

Stability: the ability of an IVD reagent to maintain its performance characteristics consistent over time (CLSI, EP25-A)

Stability testing plan: a written protocol, based on statistically valid sample size and testing interval considerations, designed to test the key stability attributes of a product with predefined acceptance criteria that support its labeled claims. (CLSI, EP25-A)

Table 1: Proposed Example of a Worksheet with Suggested Risk-Based Considerations for IVD Companion Diagnostic Devices Associated with Breakthrough Therapies

Proposal 3: Analytical Studies

Requirement	Considerations	Data Required from Sponsor to Justify (during pre-submission discussions)	FDA Decision
<p><u>Sample Types</u>: Patient specimens used for analytical studies.</p>	<p>Can contrived samples (e.g. cell lines, plasmids, serum spiked with recombinant protein) provide a sufficient initial assessment of assay performance? Is the specimen rare?</p>	<p>Supply FDA with a description of proposed contrived samples and a matrix of studies that will use contrived samples for initial PMA approval.</p>	<ul style="list-style-type: none"> • Patient specimens required for analytical testing • Contrived samples used for the following studies: <ol style="list-style-type: none"> 1. 2. 3. • Patient specimens supplemented with contrived specimens in assessment of assay analytical performance characteristics (sensitivity and specificity).
<p><u>Analytical Studies</u>: Full precision studies included in PMA</p>	<p>Based on risk, consider reducing number of sites (possibly more internal sites), number of lots, instruments, operators or the extent of the panel.</p>	<p>Supply FDA with a precision study plan. Describe in plan the risk from any reduced requirements and any mitigations.</p>	<ul style="list-style-type: none"> • Full precision studies included in PMA • Following precision study elements included in PMA: <ol style="list-style-type: none"> 1. 2. 3.
<p><u>Analytical Studies</u>: Full specificity studies included in PMA</p>	<p>Based on risk, consider limiting the number of substances to be tested for cross-reactivity, endogenous interferences, effect of pharmaceuticals, or HAMA Effect (immunoassay only)</p>	<p>Supply FDA with a study plan for the specificity studies. Describe in plan the risk from any reduced requirements and any mitigations.</p>	<ul style="list-style-type: none"> • Full specificity studies included in PMA • Following specificity study elements included in PMA: <ol style="list-style-type: none"> 1. 2. 3.
<p><u>Analytical Studies</u>: Bridging studies required if an early version of the assay was used during the clinical trial but a different version of the assay is submitted in the PMA.</p>	<p>Can appropriate bridging strategies include samples that were not clinical trial samples?</p>	<p>Supply FDA with study plan describing the use of samples that were not clinical trial samples.</p>	<ul style="list-style-type: none"> • Clinical trial samples only included in bridging study • Following samples included in bridging study: <ol style="list-style-type: none"> 1. 2. 3.
<p><u>Analytical Studies</u>: All analytical studies (other than those discussed above) included in PMA</p>	<p>For multiplex assays, must all studies be completed on all analytes or is representative analyte testing sufficient to demonstrate performance of the device? Can testing with a reference method that is not readily available be deferred to a PMA amendment? Can process verification lots be used in performing analytical validation studies?</p>	<p>Supply FDA with a matrix of typical studies compared with appropriate simplifications of study designs or justification for omission of studies for initial PMA approval.</p>	<ul style="list-style-type: none"> • All analytical studies included in PMA • Following specific analytical studies included in PMA: <ol style="list-style-type: none"> 1. 2. 3. • Patient specimens supplemented with contrived specimens in assessment of assay analytical performance characteristics (sensitivity and specificity).

Proposal 4: Quality, Manufacturing and Software Requirements

Requirement	Considerations	Data Required from Sponsor to Justify (during pre-submission discussions)	FDA Decision
<u>Quality Systems</u> : Full description of quality system in PMA	Does Sponsor have an approved or pending PMA submission that contains information that is the same or highly similar to the information for the IVD companion diagnostic device?	Supply FDA with PMA submission numbers and a summary of changes for the IVD companion diagnostic device	<ul style="list-style-type: none"> • Complete quality system section required • Abbreviated quality system section acceptable • Sponsor exempted from submission of quality system information except for: <ol style="list-style-type: none"> 1. 2. 3.
<u>Quality Systems</u> : Pre-Approval Inspection	Has Sponsor undergone and successfully completed an FDA QSR inspection recently (within the last two years)?	Supply FDA any previous 483 findings and associated EIRs. If 483 findings are still under consideration provide FDA with justification for why a pre-approval inspection is not necessary.	<ul style="list-style-type: none"> • Pre-approval inspection required • Targeted inspection only focused on X systems. • Sponsor exempted from requirements for pre-approval inspection
<u>Quality Systems</u> : For manufacturers without previous QSR history: Compliance with QSR	Are current quality systems acceptable (even if they do not meet full QSR compliance standards) for initial PMA approval?	Supply FDA with a gap analysis against QSR requirements; note specific risk mitigations required.	<ul style="list-style-type: none"> • Full QSR compliance required • Targeted quality system improvements required: <ol style="list-style-type: none"> 1. 2. 3. • Current compliance level acceptable for initial PMA approval
<u>Manufacturing</u> : Full description of manufacturing system in PMA including process validation plans and reports	Does Sponsor have an approved or pending PMA submission that contains information that is the same or highly similar to the information for the IVD companion diagnostic device?	Supply FDA with PMA submission numbers and a summary of manufacturing changes for the IVD companion diagnostic device compared with the previous device. Include any specific risk mitigations required for new device.	<ul style="list-style-type: none"> • Complete manufacturing section required • Abbreviated manufacturing section acceptable • Sponsor exempted from submission of manufacturing information except for: <ol style="list-style-type: none"> 1. 2. 3.
<u>Software</u> : Full software validation required in PMA	Can a minor level of concern be applied for the initial PMA approval? Has instrument been previously cleared or approved? Can verification or validation requirements be reduced for certain portions or modules of the software that are not critical to the use of the product? Can some software documentation be reviewed during the QSR inspection rather than included in the PMA?	Supply FDA with detailed information on types of software and level of concern. Supply FDA with PMA/510(k) submission numbers if instrument previously approved/cleared.	<ul style="list-style-type: none"> • Complete software documentation included in PMA • Following software documentation included in PMA: <ol style="list-style-type: none"> 1. 2. 3. • Following software documentation reviewed during QSR inspection: <ol style="list-style-type: none"> 1. 2. 3. • Sponsor exempted from submission of software documentation.

Proposal 4: Quality, Manufacturing and Software Requirements

Requirement	Considerations	Data Required from Sponsor to Justify (during pre-submission discussions)	FDA Decision
<u>Continued Access</u> : Devices cannot be shipped to laboratories until after device approval and the laboratories are verified to perform the testing	Laboratories that were not part of the clinical trial may require several weeks after approval until testing can be conducted.	Supply FDA with a description of the public health need for the device.	<ul style="list-style-type: none">• Approve Continued Access IDE• Continued Access IDE not approved

