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IVD STUDIES ARE DIFFERENT:

A strategic approach to regulatory compliance

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A strategic approach to regulatory compliance

As diagnostic manufacturers begin the development process of their assay, a crucial first step is developing a comprehensive regulatory strategy that will inform program planning and study design. How manufacturers approach regulatory strategy development is pivotal, as the regulations and compliance requirements for in vitro diagnostic (IVD) clinical studies are unique and dependent on a multitude of factors.

Guidance and oversight from experts who understand the shifting IVD landscape, and how it differs from that of pharmaceuticals and medical devices, can help manufacturers avoid untimely program delays and budget overruns. This whitepaper seeks to highlight key considerations during regulatory strategy development that will help ensure an IVD or companion diagnostic (CDx) product successfully reaches the market.

Because IVDs are tests conducted on samples taken from the human body for a medical purpose, they are subject to regulatory requirements and standards that are discrete from other medical devices and pharmaceuticals. A few key differences include:

1. Clinical performance of an IVD depends on whether the intended user can reliably conduct the test and interpret the result correctly, unlike pharmaceuticals. Further, while most other medical devices are used by trained professionals in controlled settings, an IVD may be used by a variety of users in different environments. Therefore, the intended user and setting impact the IVD risk classification, along with the necessary IVD regulatory pathway and requirements.
2. Studies supporting IVDs are conducted on patient samples, and the IVD does not typically come into direct contact with the patient's body, in contrast to pharmaceutical and medical device studies. During an IVD study, samples (e.g., blood, urine, tissue, or another sample matrices) are collected from the patient and tested either immediately or at a later time or date in a location away from the patient. Sample collection, processing, and testing should be well documented and performed in alignment with the applicable standards and regulatory requirements.

Given these differences, diagnostics manufacturers face many regulatory requirements that are IVD-specific, such as the number and type of studies that are required for regulatory compliance, along with unique considerations for how studies need to be designed, depending on an IVD's specific characteristics. The unique challenges faced by IVD sponsors are further compounded by the variance in regulatory strategy between different types of IVDs, and a regulatory landscape that is evolving and regionally distinct.

Even sponsors who are intimately familiar with IVDs benefit from partnering with a contract research organization (CRO) with established experience navigating IVD regulatory pathways that can anticipate shifts in the regulatory landscape and facilitate more effective engagement with regulators to expedite the review and approval process. Advancing IVD development across technologies and intended uses is also pivotal to guide, design and implement studies best suited to an IVD's specific regulatory strategy.

At Beaufort, a CRO specializing in advancing IVD development, we have conducted more than 1,000 IVD clinical studies in the last twenty years, and cultivated long-standing working relationships with regulatory agencies, including the United States Food and Drug Administration's (FDA's) Office of Health Technology 7 (OHT7), which is responsible for the total product lifecycle activities for IVDs. During the past two decades, we've gained extensive experience with every step of the regulatory, clinical, and quality process, so that sponsors can take the most efficient path to regulatory clearance or authorization. Here, our IVD experts offer their insights into an initial, and pivotal, step of the IVD development process – creating a regulatory strategy and regulatory-aligned study planning

Beaufort's IVD Expertise

20+
YEARS IVD EXPERIENCE

1000+
IVD STUDIES CONDUCTED

500+
GLOBAL REGULATORY SUBMISSIONS

The following overview of the factors that contribute to initial regulatory strategy and study planning will help sponsors have a more comprehensive understanding of the regulatory requirements and study considerations specific for IVDs. Readers can expect to learn:

- Distinctions between regional regulatory requirements for IVDs
- How the specific characteristics of an IVD impact the design of a regulatory strategy with an emphasis on U.S. regulatory requirements
- The types and number of studies – both analytical and clinical – commonly required during IVD development
- A few scenarios in which the type of IVD or regions of IVD development inform unique regulatory strategies and associated trial design considerations

Regional distinctions in IVD regulatory requirements

The challenge of determining the appropriate regulatory pathway for an IVD is compounded by an evolving and regionally dependent regulatory landscape. Navigating the regulatory requirements becomes especially demanding if one wishes to obtain approval to market an IVD in the European Union (EU), for example, in addition to the U.S.

U.S. AND EU REGULATORY OVERVIEW

In the U.S., IVDs are regulated as medical devices by the FDA under the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), and classified as Class I, II or III based on their risk to patients and to public health. Class I tests, such as a cholesterol test performed in a clinical laboratory, pose the lowest risk, while Class III tests, such as a genetic test used to stratify patients and guide cancer treatment, pose the highest risk.

IVD classification informs the level of regulatory control. Most Class I IVDs are exempt from premarket requirements in the U.S. However, most Class II and all Class III tests require premarket review through one of three pathways, depending on the risk classification and novelty of the IVD product. The three primary pathways for FDA premarket review of an IVD are as follows:

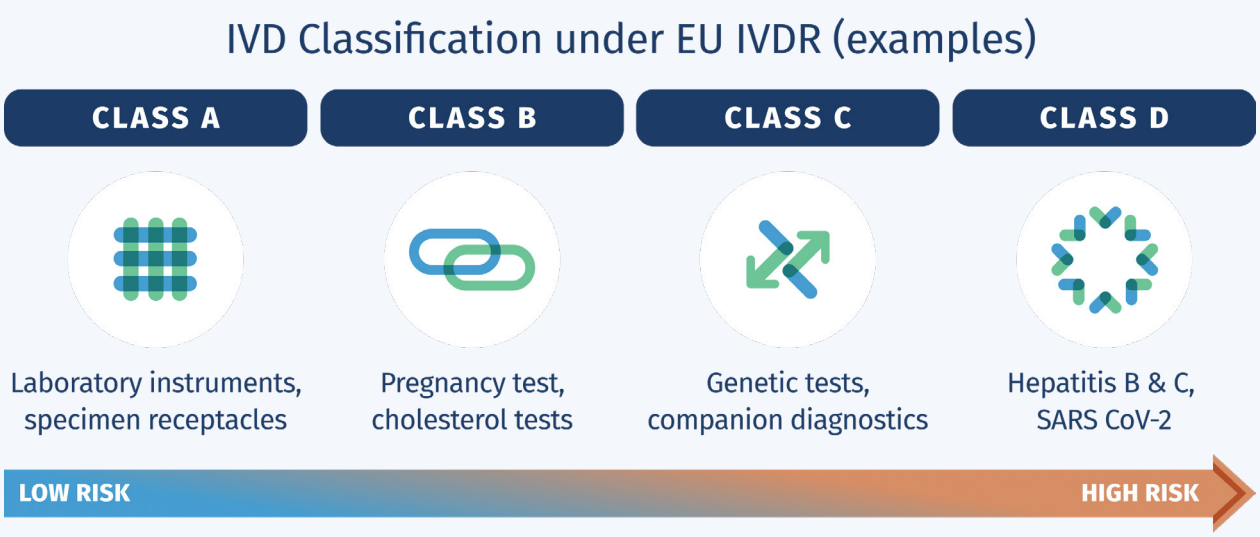
- **510(k) premarket notification**: this is the most common pathway, intended for tests that pose moderate risk and have a legally marketed predicate device. To achieve FDA clearance , applicants demonstrate their IVD is "substantially equivalent" (has comparable performance) to the predicate device.
- **Premarket approval (PMA):** this is the most stringent pathway, intended for devices, including IVDs, that present a potential unreasonable risk of illness or injury. To achieve FDA approval , applicants must demonstrate the IVD's safety and effectiveness.
- ***de novo* classification request**: for devices that are of moderate risk but are novel, this third pathway may be appropriate.

FDA OHT7 2023 Highlights

- 1,670 submissions
- 90 PMAs and PMA Supplements*
- 300 510(k)s
- 20 de Novos
- 900 pre-submissions
- 50 IDEs
- 1 CLIA Waiver by Application
- Dual Path 510(k) / CLIA Waiver
- 80 EUAs
- 240 EUA Supplements

*PMA supplements are submitted to modify a lawfully marketed PMA device.

Source: FDA Medical Device Databases



In the EU, the In Vitro Medical Devices Regulation (EU) 2017/746 (IVDR) aims to provide "a robust, transparent, predictable, and sustainable regulatory framework that ensures a high level of safety and health, while supporting innovation." Under the IVDR there are four classes of IVDs: Class A non-sterile/ Class A (sterile); Class B; Class C; Class D.

As in the U.S., IVDR classification rules are risk-based, with Class D designated as the highest risk. However, there is no one-to-one correlation with FDA risk classifications. Also, just as in the U.S., "conformity assessment procedures" vary by risk classification with certain IVDs (e.g., companion diagnostics) having specific requirements. Under the IVDR, all IVDs, except Class A non-sterile, are subject to conformity assessment by a notified body.

While the U.S. and EU require that a sponsor demonstrate IVD analytical and clinical performance, performance requirements under the IVDR have greater specificity and include the need to demonstrate scientific validity. The distinction is as follows:

- **Scientific validity** establishes the association of an analyte with a clinical condition or physiological state
- **Analytical performance** establishes the ability of an IVD to correctly detect or measure a particular analyte
- **Clinical performance** establishes the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user

Further, an additional (and new) critical component of the IVDR requires manufacturers to plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportional to the risk class and the type of IVD.

A global CRO that specializes in IVDs can provide regulatory guidance and act as a liaison with the relevant regulatory agencies to ensure that the development of an IVD product will comply with the relevant EU and FDA regulations.

GLOBAL IVD MARKETS BEYOND THE U.S. AND EU IVDR

Diverging regulatory requirements across the globe in major markets, including Great Britain (England, Wales and Scotland), China, Japan and Australia, require an in-depth understanding of evolving regulations and guidelines. For example,

the Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for regulating the Great Britain (England, Wales and Scotland) medical device market, including IVDs. As in the EU, the regulation of IVDs is changing in the UK – in this case, due to Great Britain's departure from the EU. Currently, IVDs are regulated under Part IV of the UK Medical Devices Regulations 2002 (as amended), which is based upon the EU's previous IVD legislation, Directive 98/79/EC on in vitro diagnostic medical devices (EU IVDD). Therefore, IVDs are classified as Class II List A, List B, devices for self-testing or "other." The majority of IVDs fall into this last category and are self-certified, while IVDs for self-testing, or included in Annex II, require UK Approved Body review.

Of note, the MHRA intends to implement substantial reform of the current regulatory framework, which is expected to be based on some of the same principles of the EU's IVDR (core aspects are expected to apply, beginning in July 2025). Currently, there are transitional arrangements in place, which will allow certain CE-marked IVDs (in addition to those that have the UK Conformity Assessment mark) to continue to be placed on the Great Britain market. But, it is expected that the updated regulations will begin to be introduced in the near future, with new post-market surveillance requirements expected to apply beginning in mid-2024.

In China, the National Medical Products Administration (NMPA) has oversight for regulated medical devices and IVDs. Importantly, for foreign manufacturers, proof of home country approval (e.g., U.S. FDA Certificate to Foreign Government or EU Certificate of Free Sale) is required before registration in China is permitted. Foreign manufacturers without an office in China will also need to appoint two in-country representatives – an agent and an after sales service provider – in addition to a distributor.

Since 2020, the NMPA has published a series of policies, guidelines, standards, and announcements of significance to IVD (including CDx) manufacturers that continue to significantly impact diagnostic manufacturers planning to import and sell their IVDs in China. In 2021, classification rules for in vitro diagnostic reagents

were published for the first time, and, by the end of 2022, NMPA had published 154 guidelines for IVD products that, together, established an IVD regulatory framework.

NMPA categorizes IVDs into one of three classes – Class I, II, or III – based on their risk levels. Low-risk Class I IVDs are subject to a filing application requiring submission of registration documents and Product Technical Requirements (PTR) – which consist of technical documents associated with NMPA certificates — while new Class II and III IVDs are subject to additional requirements, including product type-testing and a clinical trial or comparative study report.

In-country data may also be required in the case of patient self-testing or neonatal testing products, or in cases in which there are insufficient qualified overseas data. Though the changes to IVD regulations and requirements were intended to afford greater consistency with international standards and practices (e.g., those developed by the International Medical Device Regulators Forum), the regulatory landscape remains complex and is expected to continue to evolve.

ANTICIPATING SHIFTS AND CHALLENGES IN IVD REGULATIONS

Navigating regulatory requirements in ways that anticipate barriers and identify opportunities is critical to maintaining timelines and budgets. Beaufort has found that a combination of attendance and engagement at industry events and routine meetings with IVD regulators, such as the FDA's OHT7, is key to staying up to date on changing expectations and emerging trends.

One recent shift in the U.S. regulatory landscape is the forthcoming 180-day advanced termination notice for emergency use authorizations (EUA), an abbreviated regulatory pathway that the FDA used to authorize tests during the COVID-19 pandemic, as allowed by section 564 of the Public Health Service (PHS). This shift was triggered by the expiration of the COVID-19 public health emergency declared under section 319 of the PHS.

> **"the FDA recommends that manufacturers begin preparing for EUA termination as soon as possible."**

While, at the time of this writing, it is not yet known when the EUA declaration under section 564 of the PHS will be terminated, the FDA recommends that manufacturers begin preparing for EUA termination as soon as possible. This includes developing a transition implementation plan for all IVDs currently under distribution that were authorized by the EUA. If manufacturers wish to continue to distribute their product when the EUA declaration ends, they will also need to determine the appropriate regulatory pathway and submit an application for market authorization.

During this period of transition, Beaufort's team of regulatory, quality and clinical experts can provide a comprehensive regulatory strategy and submission support to ensure that manufacturers submit early enough to avoid the overflow of marketing submissions the FDA anticipates toward the end of the 180-day advanced notice period. In addition, Beaufort's experience with the FDA's OHT7 means that the team will be able to react quickly to any future changes in the EUA and anticipate the degree of backlogs or delays in regulatory review by the FDA.

IVD regulatory program planning

An IVD's characteristics and subsequent risk-based classification, along with the novelty of the device, inform the level of regulatory control and associated regulatory pathways required for IVD review and authorization. These IVD characteristics include how it will be used, the indications for use/intended purpose, who will conduct the test, and the risks associated with conducting the test or using the test results. Regardless of region, novel devices and those with high potential risk require more regulatory control and associated testing requirements. To prevent additional costs and delays, it is essential to understand and develop a strategy that accounts for the IVD performance testing criteria and meets the requirements for the intended submission.

After helping sponsors with the initial characterization of their IVD, a CRO experienced with IVD development, such as Beaufort, can help identify appropriate regulatory requirements from applicable regulatory pathways and ancillary regulations, which will affect the evidence requirements for their IVD's regulatory application. Following the development of an overall regulatory strategy, a CRO can help a sponsor plan the number, type, and order of studies that will result in the most efficient and cost-effective path towards commercialization.

DEFINING THE USER AND USE ENVIRONMENT

The performance of IVD products depends not only on the accuracy of a test, but also on the user performing the test and the testing environment. Because of this, defining the intended user and intended use setting of an IVD is one of the most important considerations for development, figuring into risk-based classification, test complexity, appropriate regulatory submission(s), and study design requirements.

In general, more stringent regulatory requirements are associated with tests that have a higher likelihood of error by the intended user. In cases where user error is more likely, a waived IVD may receive a higher risk classification (Class II vs. Class I), and require more regulatory oversight (e.g., a Clinical Laboratory Improvements Amendments of 1988 (CLIA) waiver application that includes additional studies) to ensure that users can reliably conduct the test and interpret it correctly.

LIKELYHOOD OF ERROR BY THE USER IS INFLUENCED BY:

- **The degree of specialized knowledge required to perform the test**
- **The degree of user training and experience for preanalytical, analytical and post-analytical phases of the testing process**
- **The degree of judgment required to perform the test and interpret the results**
- **Whether operational steps are manual or automated**
- **Whether quality control and calibration are available**
- **Whether reagents and materials are stable or require special handling**
- **Whether troubleshooting requires decision-making or is automatic**

Effect of user and use environment on regulatory pathways: A test that is intended to be used near patients (a point-of-care [POC] test) may be considered higher risk and require a more stringent regulatory pathway than one that is conducted in a laboratory setting. Consider the case of a cholesterol test, used in the diagnosis and treatment of disorders involving excess cholesterol in the blood. In the U.S., when conducted in a central laboratory, the test is classified as lowest risk, Class I, and is exempt from premarket notification procedures such as 510(k). However the exemption from premarket notification no longer applies if the same test is intended for near patient (POC) testing.

Effect on regulatory requirements: The user and use environment may also impact the "complexity" of the test, which, in turn, affects regulatory requirements. Specifically, in the U.S., an IVD's test complexity will inform whether laboratory certification by CLIA is needed, or whether manufacturers will need to submit a CLIA waiver application.

In the U.S., all facilities that perform laboratory testing on human samples for medical reasons are regulated under CLIA, which established quality standards for laboratory testing to ensure the accuracy and reliability of results in the intended use setting. On January 31, 2000, the responsibility for the categorization of commercially available IVD tests was transferred from the Centers for Disease Control and Prevention (CDC) to the FDA Center for Devices and Radiological Health (CDRH).

The FDA categorizes clinical laboratory tests by their complexity — from the least to the most complex: waived tests, moderate complexity tests, and high complexity tests. The FDA determines test complexity by reviewing the package insert test instructions in the premarket submission using the criteria listed in 42 CFR 493.17. The tests that are not waived by regulation under 42 CFR 493.15 and are not cleared or approved for home use or for over-the-counter use may be categorized either as moderate or high complexity.

In addition to submitting premarket notification, manufacturers whose tests are intended to be used for near-patient testing (POC), must also submit a CLIA Waiver by Application, which can be submitted separately from the 510(k) submission or through a dual 510(k) and CLIA Waiver by Application (Dual Submission) 510(k). In general, a CLIA waiver requires the following additional studies:

- "Flex studies" demonstrating insensitivity of the test system to environmental and usage variations under conditions of stress
- A user study demonstrating that the test is simple to perform and has an insignificant risk of erroneous results in the hands of untrained operators in CLIA-waived settings

Effect on study design: In studies, IVD testing must be conducted by the intended users of the product. Study site and personnel considerations need to be planned for IVDs that require more technical skill sets and specific equipment to ensure that these resources are available and that the location is appropriately qualified to conduct laboratory testing. Likewise, a testing-naive patient population would be required in the design of studies in which patients are intended to collect the samples or conduct the tests themselves, as in the case of IVDs designed for home use.

Additional IVD study considerations -- such as the need for informed consent or a Waiver of Informed Consent in the U.S. or General Data Protection Regulation (GDPR) disclosure in the EU – will depend on the type and nature of the patient information to be collected during the study and the type of study procedures to be performed, including study-specific sample collection, and any risks to the patient.

DEFINING THE INTENDED USE (OR INTENDED PURPOSE) AND INDICATIONS FOR USE

The IVD intended use encompasses the intended user, intended use setting, the indication for which the test will be used (e.g., oncology, sickle cell disease, infectious disease), and what the test results will be used for, such as prognosis, diagnosis, screening, monitoring, or management or prediction of treatment. Some IVDs are also intended to provide information, which guides the use of a corresponding therapy.

A properly defined intended use is critical to identifying the appropriate risk classification of an IVD, the regulatory pathway and associated study design considerations. As part of a quality management system, a sponsor should assess the risk associated with the design, manufacture, and intended use of the IVD. Based on this assessment, relevant standards, references, and regulatory requirements can be identified and studies can be designed as a means to mitigate those risks.

Of note, companion diagnostics (CDx), which are used, for example, to identify patients who are most likely to benefit from a particular therapeutic product, may have rigorous regulatory requirements and considerations that are distinct from other types of IVDs. Because CDx provide information that is essential for the safe and effective use of a corresponding drug or biological product, CDx are often classified as Class III devices in the U.S., requiring premarket approval.

In the EU, CDx are generally classified as class C, and often need to follow additional requirements for certain performance studies (Regulation [EU] 2017/746 Article 58), including preparation of an application and authorization by the EU member state(s) in which the performance study is to be conducted. Beaufort's expertise in companion diagnostics can help a sponsor develop an appropriate CDx-specific regulatory strategy – including identification of the appropriate regulatory requirements, as well as performance study planning and execution.

Identifying a predicate IVD or reference standard

The novelty of an IVD may also inform the regulatory pathways, as well as the type of evidence that should be collected to establish clinical performance. In the U.S., for example, for an IVD to be appropriate for a 510(k) premarket submission, the IVD will need to be comparable to a predicate device, which must be legally marketed and have the same intended use as the candidate IVD. However, it is not unusual for IVDs to lack a single clear predicate device. In these instances, it is important to work with an experienced IVD regulatory expert who can aid in finding and effectively using predicate devices.

> **“A predicate device must be legally marketed and have the same intended use as the candidate IVD”**

For instance, there may be limited cases in which a reference standard may be used if the appropriate statute is met. A reference standard is the best available method for establishing the presence or absence of the condition or characteristic of interest, and may be a single test or a combination of methods and techniques, including clinical follow-up. However, when a reference standard is not appropriate, other considerations may be required to determine and follow the proper regulatory strategy.

GUIDANCE AND REGULATORY ENGAGEMENT IN STRATEGIC PROGRAM PLANNING

Regulatory authorities, such as the FDA's OHT7, provide guidance documents, consensus standards and decision summaries that can help with regulatory strategy development, such as the classification of an IVD. These documents should be consulted and, in most cases, followed to avoid delays in device clearance or approval.

For new IVDs, the product code and generic device classification can be used to identify applicable guidance documents and consensus standards, which provide insight into the expectations for a specific IVD's development requirements. Additionally, a review of recent decision summaries for products in that device classification may help determine the types and objectives of studies required for similar IVDs.

Sponsors developing an IVD in the U.S. should also be engaging early and often with the FDA's OHT7, which serves as a primary source for scientific and medical expertise regarding the safety and effectiveness of IVDs throughout the total product lifecycle. The FDA's Q-Submission Program (Q-sub), provides sponsors with a number of different mechanisms to request feedback and guidance at different stages of IVD development, including informal meetings and pre-submission meetings (Pre-Sub).

Q-Sub type*	When to request	Feedback mechanism	Timeframe for feedback
Information Meeting	Used to inform the FDA about ongoing device development without a specific feedback request, useful for familiarizing the FDA with the differences between a new IVD and those currently available	Meeting	90 days
Study Risk Determination	Used when sponsor is unsure of their IVD's risk classification	Formal letter	90 days
Pre-submission (Pre-Sub)	Useful for early feedback on specific questions during submission preparation, prior to the initiation of analytical or clinical studies	Meeting with written feedback in advance **OR** Written feedback only	Typically 70-75 days for a meeting, within 70 days or 5 days prior to scheduled meeting, whichever is sooner. 70 days for written feedback only.
Agreement meeting	Used when finalizing an investigational plan, to reach agreement on study protocols	Meeting	Meeting date scheduled within 30 days
Determination meeting	Used when anticipating PMA submission, to discuss prospective clinical trial design	Meeting	Meeting date scheduled within 30 days
Submission Issue Request (SIR)	Used to discuss deficiencies identified during premarket review	Meeting **OR** Written feedback	21 days as resources permit if SIR is received within 60 days of FDA's marketing submission letter. Otherwise, 70 days as resources permit.
Informational meeting	Used to inform FDA about ongoing device development without a specific feedback request, useful for familiarizing the FDA with the differences between a new IVD and those currently avalable	Meeting	90 days
PMA Day 100 meeting	Used to discuss the review status of a PMA submission	Meeting	Within 100 days from PMA filing date

**Source*: Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program, June 2023

In early stages of IVD development, sponsors may wish to engage with the FDA to receive guidance on the following:

- Appropriate type of regulatory submission
- Prior to starting a study, to determine whether the IVD under investigation poses a significant risk to patients, and requires an approved investigational device exemption (IDE), as may be the case for companion diagnostics.
- To obtain a Breakthrough Device (BD) or a "Safer Technology Program (STeP) designation, in cases where an IVD offers significant advantages related to safety and/or effectiveness over other IVDs
- To clarify standards, guidance documents or study requirements that may apply to your IVD
- During the development of study protocols

While early and regular engagements with regulatory agencies can smooth the pathway towards regulatory clearance and approval, it is important that sponsors are well-prepared prior to requesting agency feedback. Beaufort's long-established experience working with regulators and decades of IVD expertise can help prepare for, and facilitate communications with, regulatory bodies. This engagement is especially invaluable in early clinical study design because of the great cost in time and resources associated with conducting a clinical study.

Partnering with an IVD-specialized CRO can prove advantageous to avoid costly and untimely errors in IVD study planning, protocol development, and implementation. An IVD-experienced CRO can help ensure that a sponsor's understanding of the evolving regulatory landscape is up-to-date and that conversations with regulatory bodies are comprehensive.

In the EU IVDR, notified bodies are not allowed to consult with manufacturers. Here, a CRO's understanding of evolving guidelines becomes especially critical.

IVD study planning considerations

After an overall regulatory strategy and program plan are determined with preliminary alignment from the relevant regulatory bodies, a sponsor must plan and prepare to conduct the number and type of studies needed to provide supporting evidence for the regulatory pathway.

In some cases, these studies may have regulatory requirements that must be met prior to study initiation. An IVD-specialized CRO can help identify which combination of studies will be most efficient and cost-effective for regulatory approval, guide study protocol development, and verify that all of the necessary studies are carried out appropriately

IDENTIFYING THE APPROPRIATE TYPE AND NUMBER OF IVD STUDIES

Many sponsors new to IVD development are unaccustomed to the number of discrete studies that may be needed, all with distinct study protocols. It is not unusual to have more than ten analytical studies supporting an IVD submission.

The high-level types of studies that are generally required to provide supporting evidence for an IVD are as follows:

Analytical studies – These studies are intended to confirm the analytical performance of an IVD as found in their labeling, such as the instructions for use, under controlled conditions. Often, they are performed by the sponsor within an appropriate development or verification laboratory, and are designed to follow recommendations found in FDA-recognized Clinical Laboratory Standards Institute (CLSI) test methods.

The IVD characteristics assessed by analytical studies may include sample handling and storage; limit of detection and assay measuring range; and cross-reactivity and assay interference, as well as precision and reproducibility. Generally, many different analytical studies are required to provide evidence of analytical performance, with the types and design of studies often impacted by the test results from a prior analytical study, whether quantitative or qualitative.

> **“It is not unusual to have more than ten analytical studies supporting an IVD submission”**

Clinical studies – These studies are intended to demonstrate clinical performance (i.e., that the IVD conforms to defined user needs and intended

uses). They may encompass any studies performed at a site or sites external to the sponsor, with the testing sites representative of the end-user testing (as opposed to sponsor-performed testing). In clinical studies, all investigational product(s) should be appropriately labeled for investigational use, and all studies using human specimens must have internal review board (IRB) approval.

Human factor and usability studies – These studies are intended to mitigate or eliminate risks associated with how a user interacts with an IVD, by assessing the potential for use-related errors and considering feedback from users. Human factor and usability studies may be required, in addition to analytical and clinical studies, depending on the intended use, user, and environment for an IVD

In the U.S., the types of studies needed for market clearance or approval should be extensively reviewed by experienced regulatory professionals. Additional insight may be gathered during meetings or feedback from regulatory bodies.

IVD EVIDENCE REQUIREMENTS IN STUDY DESIGN

In the U.S., all IVD regulatory submissions require analytical studies and most require clinical studies. However, the evidence requirements for analytical and clinical studies can vary, depending on the regulatory pathway and the specific IVD characteristics.

For a PMA submission, determining clinical performance typically requires a prospective clinical trial that establishes the safety and effectiveness of an IVD, while 510(k) submissions establish an IVD's clinical performance by demonstrating substantial equivalence to a predicate device, for example, in method comparison studies. That said, some 510(k) submissions may require prospectively collected samples , instead of relying on previously collected samples (e.g., "leftover" or "banked" samples), necessitating a prospective clinical trial.

To clarify the cases where prospective clinical data is necessary, the FDA published a draft guidance in September 2023, outlining scenarios in which prospective data may be needed for a 510(k) submission. They include the following:

1. If there are differences in the technological characteristics, or indications for use, between a new and predicate device
2. If there have been newly identified risks associated with the predicate device
3. When analytical testing is not appropriate for demonstrating substantial equivalence. For example, a POC IVD, in which the predicate device was not intended for POC use, may require prospective clinical data. This is because the testing environments and the diverse populations that perform POC testing can affect device performance

While guidance documents contain non-binding recommendations and draft guidance documents are not for implementation, guidance documents represent FDA's current thinking on a topic and the recommendations therein can be beneficial when planning.

While method comparison studies for 510(k) submissions have been performed at sites internal to the sponsor previously, revisions to the CLSI guidelines now strongly recommend that method comparison studies be conducted at multiple external laboratory testing sites (CLSI EP09).

Unlike in the U.S., there are some cases in the EU under the IVDR where the evidence used in a regulatory submission may not need to come from a performance study at all. For higher-risk class IVDs and novel devices, a direct demonstration of clinical performance from studies using previously collected samples or prospectively collected samples is necessary. But, for devices of lower risk classes, an indirect demonstration with data based on scientific peer-reviewed literature or published experience gained by routine diagnostic testing with the subject IVD may be permissible. However, per the IVDR, the expectation is that studies evaluating IVD performance are generally carried out, unless justification is provided for relying on other sources of data.

REQUIRED REGULATORY APPROVALS PRIOR TO STUDY INITIATION

In the U.S., the FDA requires IRB review for all IVD studies that involve human subjects, including those that use leftover, de-identified human specimens in FDA-regulated studies. While sponsors are generally aware that IRB review is required for clinical studies, the requirement extends to analytical studies using human specimens as well.

Additionally, when clinical studies are conducted to support a PMA or 510(k) submission, study sponsors need to determine whether their IVD is subject to IDE regulations specified in 21 CFR 812. Often IVD clinical studies do not require IDEs. But, sponsors should review regulatory guidance to determine whether the IVD meets the requirements to be exempt from an IDE submission during the clinical study design, as well as consult with their regulatory experts. If an IDE is required, sponsors will need FDA IDE approval, in addition to IRB approval, before the initiation of a study that uses the investigational device.

ACHIEVING ALIGNMENT WITH REGULATORS

Engaging with the FDA through the Q-Submission Program's Pre-Submission ("Pre-Sub") meetings are important to gain alignment on planned study protocols and study designs prior to study initiation.

It's important to note that the FDA will not design study protocols at Pre-Sub meetings, and Pre-Subs are not for general questions, or interactive review of an active submission. Instead, appropriate questions at a Pre-Sub meeting may include the following:

- Are the proposed analytical study designs and acceptance criteria appropriate?
- Is the proposed predicate device appropriate for determining substantial equivalence?
- Is the proposed clinical study design, statistical analysis and acceptance criteria adequate to support a future 510(k)?
- Is the planned real-world data collected using SARS-CoV-2 EUA of sufficient quality to support a future 510(k)?

Early FDA alignment is the best way to avoid a Refuse to Accept (RTA) letter or a substantial request for additional information during submission review, requiring collection of additional performance data.

Use of real-world data: Early engagement with the FDA through the Q-Submission program is highly recommended prior to 510(k) submission if the sponsor wishes to use real-world evidence instead of a clinical study to gain alignment with the FDA on the acceptability of the evidence. Real-world evidence can be appropriate if the device is already marketed, either in a different market or for a different intended use. However, in this case, the evidence is often of variable quality, and is at higher risk of being rejected by the FDA if there is no alignment ahead of submission.

IVDs with unique regulatory strategies and study design considerations

Some IVDs, including CDx and POC diagnostics, have unique regulatory requirements and associated study design considerations. In addition, special considerations need to be made for global studies. Beaufort is strategically positioned to provide regulatory strategy for these especially complex IVD cases, and help manufacturers make the transition from developing their regulatory strategy to designing and implementing efficient studies.

CONSIDERATIONS FOR GLOBAL STUDIES

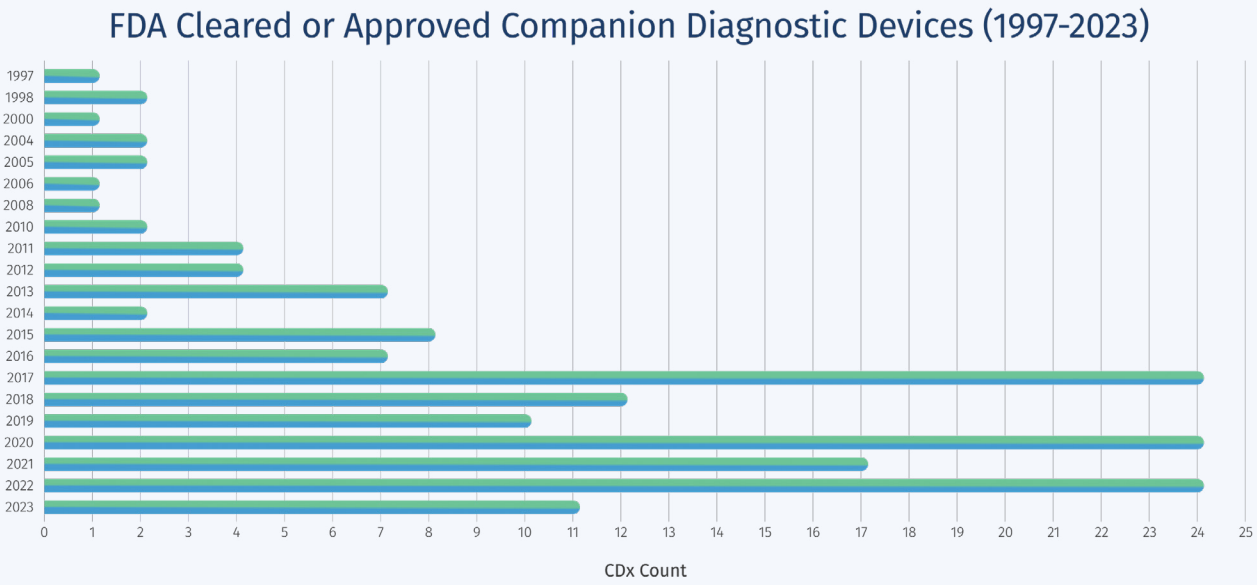
In global studies, the sponsor will need to account for regional regulatory requirement differences that may impact the acceptance of data collected out of country. When designing global studies, it is also critical to consider regional population differences where studies are being conducted, as the data may not be representative of the intended use population in the country for which a submission is intended. Some potential differences for which to account include:

- Differences in the definition and prevalence of disease
- Differences in underlying comorbidities
- Differences in the standard of care
- Differences in clinical practice, including where the patient may be treated
- Differences in demographic factors and genetic variants associated with a disease

Some of these population differences may be permitted if the sponsor can provide an explanation and justification for any limitations or omissions, and propose post-market mitigation, for example, a post-market study. In addition, bridging studies may be of use to mitigate risks introduced by differences in populations, but would require the availability of banked samples representative of the missing population's characteristics.

CONSIDERATIONS FOR COMPANION DIAGNOSTICS (CDx)

While the number of CDx cleared in the U.S. as a percentage of all submissions remains relatively small, the CDx landscape is expanding to areas beyond oncology, such as gene therapy. In part, this is due to a growing marketplace for personalized medicine and targeted therapeutics primarily in the U.S., Europe, and Japan. However, CDx present unique regulatory strategy challenges. The regulatory landscape is especially complex for CDx because the development process typically requires coordination between pharmaceutical and diagnostic companies, often with little regulatory guidance for how this coordination should occur.



Source: List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) | FDA | *Current as of October 2023*

This has been especially problematic in the EU, where several factors have made it difficult to initiate clinical trials of investigational medicinal products (CTIMPs) that rely on a CDx for medical management decisions.

While the European Medicines Agency (EMA) offers scientific and protocol assistance to developers of investigational medicinal products through multiple pathways — including the Simultaneous National Scientific Advice pilot, which has been successfully used by CDx developers in conjunction with their pharma partners — currently, there is no process for structured dialog among all stakeholders (e.g., medicinal product developer, diagnostics manufacturer, notified bodies and the EMA) prior to, or during, the conformity assessment of the CDx and the medicinal product authorization.

This lack of guidance puts at risk the simultaneous approval of the medicinal product, alongside certification of the CDx, potentially delaying timely access for patients to both. As a result, the feasibility, development and ultimate approval of a CDx relies heavily on a CRO's ability to understand and manage the relationship between pharma and diagnostic companies in the context of the evolving regulatory landscape and their familiarity with CDx development.

In Beaufort's experience, one key consideration when developing a program strategy for a CDx is that establishing the performance of the CDx — that it can, for example, identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product — may not always be enough to garner acceptance of clinical utility from healthcare payers or physicians. This is especially true for molecular diagnostics, where clinical utility hinges on a complex sequence of actions that transform a test result into a potential improvement in healthcare outcomes based on test interpretation, treatment selection, treatment efficacy, and patient adherence.

Unless evidence linking treatment to outcomes already exists, it may be necessary to conduct a prospective clinical trial collecting new patient outcomes data. However, it may not be feasible to link the results of an investigational diagnostic to an improved clinical outcome - especially if that outcome is long-term. In this case, sponsors may be able to use an accepted surrogate endpoint to demonstrate clinical utility more quickly.

CONSIDERATIONS FOR NEAR-PATIENT/ POINT OF CARE (POC) AND HOME-USE IVDS

POC, or near-patient testing, devices used in a clinical use setting often require specific study considerations related to who is performing the test. For example, the test users and the testing environment must meet qualifications specified by the IVD's CLIA certification, which may impact site selection to ensure study personnel and testing locations meet the requirements. Additionally, analytical and clinical studies for POC tests in clinical use settings will need to take into account if and when the study is performed by a personnel representative of the intended end user.

Further, when designing analytical studies for POC tests, sponsors should pay special attention to pre-analytical and analytical processes that may impact the sample (e.g., specimen collection, handling, processing, transportation, and storage until time of analysis), from collecting the sample to obtaining results and consider whether additional studies may be required to provide additional data, for example, sample stability data to support regulatory submissions.

Meanwhile, home-use IVDs may require additional clinical and analytical studies to receive a CLIA waiver, which can add additional months to an IVD development timeline. As discussed above, CLIA waiver status allows for the test to be conducted at sites (including the home) that do not have CLIA certification because the test has established a low risk associated with an incorrect result and is accurate in the hands of the intended user.

Often, to receive a CLIA waiver for a home-use test, sponsors will conduct two clinical studies, first with trained test operators and then with untrained users. Trained test operators will first perform a clinical study for regulatory clearance. This provides some assurance that the test performs appropriately before moving forward with a second clinical validation study with untrained users for the CLIA Waiver by Application submission.

However, this two-step process incurs the cost of a second clinical study and extends the regulatory approval timeline of a CLIA-waived test. Instead, sponsors may consider a dual submission, an optional approach offered by the FDA, in which a 510(k) submission and a CLIA Waiver by Application are submitted concurrently using one set of clinical studies, in addition to the required analytical studies. This offers the potential for a faster approach to achieve a CLIA waiver determination. However, it also poses some unique challenges, including the need for sites to have staff who would be considered "naïve" per the FDA's definition.

Partner with experience, prepare with confidence

Sponsors face many regulatory strategy options when planning to place their IVD on one or more markets. There are a wide range of interconnected considerations that can impact both timelines and budget. Ensuring that the product development and study designs are aligned with the regulatory strategy and requirements is critical.

Companies planning to commercialize an IVD should consider all applicable regulatory requirements as early as possible in the development process. In our experience, sponsors benefit from partnering with a full-service CRO with IVD-specific experience to ensure (1) a thorough understanding of all the regulatory requirements; (2) the proper design for the appropriate number and type of studies; and (3) the effective implementation of study protocols.

BEAUFORT

About Beaufort

Beaufort is a global contract research organization (CRO) built around one purpose — ensuring your IVD successfully reaches the market. Our team is composed of diagnostics-focused experts who have guided hundreds of sponsors through every step of the regulatory, clinical, and quality control process. Further information is available at beaufortcro.com, or contact us today at info@beaufortcro.com for a consultation.

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