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Regulatory Considerations for Co-Development Activities for a Therapeutic and an *In Vitro* or Companion Diagnostic within a Pharmaceutical or Biotech Company

Watson AD* and Saiz RT

Sanofi Inc, Cambridge Massachusetts, USA

***Corresponding author:** Watson AD, Sanofi Inc, Cambridge Massachusetts, Boston, USA, Email: Anthony.Watson2@sanofi.com

Perspective

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Abstract

The regulatory and research landscape for therapeutics is continually evolving globally. These changes are influenced by factors such as requirements by the regulatory agencies and health authorities, or strategic positioning of the product in the marketplace. Challenges also arise from the necessity to develop a therapeutic product in conjunction with an assay. The therapeutic company finds itself in unfamiliar territory and might not fully appreciate unforeseen challenges that could delay and even potentially derail a development program. Choosing the right partner to develop the assay and strategic choices regarding the source of regulatory expertise can be the difference between failure and success. This article provides considerations for regulatory professionals working within pharmaceutical or biotech companies that are actively pursuing *In Vitro* or companion diagnostics to accompany the products in their therapeutic portfolio.

Keywords: Regulatory; *In Vitro*; Companion Diagnostic; Pharmaceutical; Biotech

Abbreviations: IVDs: In Vitro Diagnostics; CDx: Companion Diagnostics; LDTs: Laboratory Developed Tests; CTA: Clinical Trial Assay; CLIA: Clinical Laboratory Improvement Amendments; CMS: Centers for Medicare & Medicaid Services.

Introduction

In Vitro Diagnostics and Companion Diagnostics

The landscape for therapeutics is continually evolving in the US as well as globally. Changes to the landscape are influenced by factors such as requirements by the regulatory agencies and health authorities, or strategic positioning of the product in the marketplace. Various articles have been published addressing the topic of *In Vitro* diagnostics and companion diagnostics; from the viewpoint of the manufacturer developing the diagnostic assays to the pharmaceutical companies strategically collaborating with the Contract Research Organizations. In 2010, an article was published describing the development of novel IVDs from a manufacturer's perspective [1]. Cotter et al., proposed a new paradigm for personalized medicine and companion diagnostics, which introduced the concept of a Contract Diagnostic Organization, a new concept designed to aid pharmaceutical companies in addressing challenges in companion diagnostics development [2]. The

pharmaceutical company Merck published a CDx guide that poses critical questions at each stage of the pipeline, and provides access to the resources needed to address these questions [3]. This article provides considerations for regulatory professionals working within pharmaceutical or biotech companies that are actively pursuing *In Vitro* or companion diagnostics to accompany the products in their therapeutic portfolio.

With the increasing focus on personalized medicine, many biopharmaceutical companies find themselves needing to target for or exclude specific patient populations for their therapies and are turning to medical device *In Vitro* diagnostics (IVDs) for assistance. *In Vitro* diagnostics offer the potential of predictability needed to ensure patients get the correct treatment and avoid harmful treatment. This endeavor is not as simple as it sounds; the biopharmaceutical (pharma) and *In Vitro* diagnostic companies approach the personalized medicine problem from complimentary, yet very different perspectives. Understanding and leveraging these differences can help avoid derailing progress in a therapeutic area and maximize development of innovative therapies.

In Vitro Diagnostics (IVD), Companion Diagnostics (CDx), and Laboratory Developed Tests (LDTs) Defined

Medical device and drug worlds typically converge in the space of combination products. *In Vitro* diagnostics are playing a prominent role in bringing innovative therapeutics to market. One particular barrier that pharma companies face, which can provide a significant amount of drag on the road to success, is one simply of terminology. A noticeable learning curve can be attributed to the words used to describe the products, as medical devices and IVDs share some terminology, but IVDs add an additional dimension of complexity. Fortunately, most of the definitions we will discuss here have been globally harmonized, if not identical, thanks to the work of international organizations (i.e. International Medical Device Regulators Forum). Speaking the same language is important to ensure the pharma and IVD companies focus in on the same goals. With that in mind, a review of some common terms is in order.

***In Vitro* diagnostic**: IVD medical device is defined as a medical device, whether used alone or in combination, intended by the manufacturer for the *in-vitro* examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. IVD medical devices may include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status [4].

Companion Diagnostic (CDx): An IVD companion diagnostic device is an IVD medical device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD-CDx device with a therapeutic product is outlined in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product [5].

Laboratory Developed Test: A laboratory developed test (LDT) is an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory and is subject to the Clinical Laboratory Improvement Amendments (CLIA '88) of 1988 [6].

Companion diagnostics and LDTs are subsets of IVDs. It is important to remember that they have different implications in terms of their quality and regulatory requirements. In the U.S., companion diagnostics are regulated by the FDA and LDTs are regulated by the Centers for Medicare & Medicaid Services (CMS) through CLIA. Although the LDT and IVD development requirements are relatively consistent globally, the regulatory requirements, prior to entering the clinical validation stage, are not completely aligned. This will be discussed later. In an ideal scenario the development of companion diagnostics is performed in parallel to the development of the therapeutic product.

Background on IVD medical device differences and why they are important to pharma and biotech

In Vitro Diagnostics

Looking at the general category of IVDs, we find a wide array of products from reagents to bioassays. IVDs usually have broad uses and are not typically tied to a specific therapeutic; however, the information provided by the IVD coupled with clinical presentation of the patient symptoms can assist physicians in making informed decisions about whether or not any course of treatment is necessary. These IVDs are the fundamental revenue-

driving technologies upon which the IVD companies base their businesses. This also affords independent regulatory review of the IVD separate from the treatment. Conversely, pharma companies are looking to pursue an IVD or IVD-based medical device that is directly tied to a therapeutic product, in order to provide their therapeutic product a strategic market advantage over competitors operating in the same therapeutic space or to meet the requirements set forth by the regulatory agencies or health authorities.

Companion Diagnostics

Companion diagnostics pose a different challenge to pharma companies as they are typically developed contemporaneously with an associated therapeutic. Although growing relevance of companion diagnostics is recognized within the industry, many emerging markets (e.g. India, Russia, and Africa) have not specifically called out these devices as independent entities. Most of these emerging markets have not produced specific guidance on the regulatory expectations for these products. In 2014 and 2016, the FDA had previously published two different draft guidance documents directed at helping industry understand the agency's current thinking regarding how they will regulate these products and their expectations for co-development with a therapeutic [5,7]. In 2017, the European Parliament approved the new *In Vitro* Diagnostics Regulation (IVDR), which tightened the regulation of IVDs in the EU, and by association, companion diagnostics have been delineated as part of the IVD organizational structure. As stated previously, although companion diagnostics are a subset of IVDS, what sets them apart from many IVDs is the use of the diagnostic test in conjunction with the therapeutic product. The distinguishing factor is the close connection between the clinical development of the diagnostic and the therapeutic product. Although the two are reviewed and approved separately, they are typically clinically evaluated during the same clinical trial.

Pharma and IVD companies engaged in a strategic partnership for the development of a CDx, face the challenge of coordinating the clinical trials to ensure the appropriate data is available at the right time for both products to be approved contemporaneously. The pharma company is faced with a dilemma: at what point in the development of the therapeutic product should they invest in the development of the diagnostic, when the viability of their therapeutic has yet to be confirmed. Although there is no single correct answer, it is generally accepted that some risk will have to be assumed, and investment in developing a prototype of the diagnostic test for the therapeutic product will be needed. These prototype assays are subsequently used during the Clinical Phases 1 and 2 in order to determine the predictive potential of the biomarker(s) assessed in the diagnostic test [8]. Delaying the development of the diagnostic until Phase 3 increases the risk of delaying the therapeutic product approval and can bring into question the validity of data collected at previous phases. Of course, using bridging and cross-over strategies can reduce the risks to delayed approval. Therefore, it is better to plan for the upfront cost to invest in the development of a prototype of the diagnostic, if Phase 1 data for the therapeutic shows promise, and the company anticipates the need to select or exclude patients in their clinical trials. It is also worth pointing out that there is a significant amount of work (due diligence and establishing infrastructure) to prepare an analytically validated diagnostic test for Phase 3, so strategic planning and a financial commitment to the early development stages of the identified CDx program, is the key to later success.

Laboratory Developed Tests (LDTs)

As discussed earlier, LDTs are designed and manufactured for use within a single laboratory (US or International) and are subject to the CLIA regulations. Some companies will rationalize the use of a CLIA-certified laboratory for development of the Clinical Trial Assay (CTA) as support for the validity of the assay to move forward with the clinical trial. Although CLIA-certified laboratories have advantages over non-CLIA-certified laboratories, that point might not suffice for producing a ready-for-use CTA, depending upon how the laboratory validates the CTA and documents its development.

The CLIA certification does not cover certain quality system requirements for medical devices that IVDs must meet. In the US, the specific requirements that apply are the provision of 21 CFR Part 820.30, the design control provisions. The international standard for medical device quality systems, ISO 13485 also contains similar requirements. These requirements ensure that the development follows traceable good development and engineering processes. One of the major stages of design controls is design validation, which establishes that the product meets the needs of its users. In the case of FDA regulated diagnostics, this means that the diagnostic actually measures what it is supposed to measure at the right level, repeatedly and reliably. In short, you have to ensure your measuring tool is calibrated before you begin measuring.

A significant amount of work is required to achieve a completely-validated diagnostic test, as there is no middle ground as far as validation is concerned. The good news is that the hard work is not effort wasted if the therapeutic proceeds. The validation data developed for the CTA can be used as the basis for the final validation of the near-commercial (GMP manufactured) assay to be used in the Phase 3 clinical trial. The Phase 3 assay should be the planned, commercially viable assay, validated on commercially available platforms.

When considering IVDs, Companion Diagnostics, or LDTs; several factors, such as the business case or intended use of the device, will influence the strategy and final outcome for determining which regulatory pathway (FDA or CLIA) is most suitable for the diagnostic. An example of this would be after completion of the Phase 1 and Phase 2 trials, it is determined that there is no correlation between the biomarker and the clinical outcome. Lack of biomarker correlation would determine that the diagnostic would not be required for use in the Phase 3 trial. However, the early phase trial data may demonstrate the diagnostic test does in fact have some utility, such as an increased likelihood of improved outcomes from use of the test, and the pharma and IVD companies will need to determine if it is commercially advantageous to pursue the diagnostic as an LDT or to pursue it further as a cleared/approved IVD medical device.

Different from Traditional Medical Device Expertise

One important consideration when developing a therapeutic that requires a companion diagnostic is whether or not the pharma company has internal expertise for development and regulatory activities for the diagnostic. Typically, this expertise is either non-existent or sparsely dispersed throughout the company. The business decision is then whether to hire this expertise or outsource it. Diagnostic development expertise is almost always outsourced due to the significant resources needed to develop and validate an assay for clinical trial use. Acquiring the necessary regulatory expertise does not require as much of an investment but still requires appropriate planning. We will focus on the considerations for this business decision.

If internal regulatory expertise is lacking, the first business decision is whether to engage a consultant, contractor, or allocate a full-time internal resource to assist in development and commercialization of the diagnostic. An overall strategy based on the regulatory issues associated with the IVD or companion diagnostic should also be developed.

Therapeutic companies, depending upon their size and product portfolio, might have an internal regulatory group with specific medical device expertise. Although some medical device regulatory groups can cover some projects themselves for intermittent or a small number of projects that involve a companion diagnostic, these groups are typically not experienced with handling the technical (i.e., diagnostic assay threshold/cutoff, CMC, etc.) details that arise in Phase 1 trials or consistent development of therapeutics that require a companion diagnostic. But is this regulatory expertise for the development and regulation of IVDs really different than traditional medical device expertise? The short answer is, yes.

IVDs are composed of reagents, laboratory equipment, antibodies, and other substances, making them very different from traditional medical devices. These components are typically combined and then transferred onto a specific technology platform, which is integral to the success of the assay. Some of the technology platforms have associated software with intricate algorithms used for delivering the final test result once the patient specimen has been completely processed. In addition, concepts such as accuracy, reliability, repeatability, and precision are expectations for all IVDs and mirror those of traditional devices, with some added levels of intricacy for the IVDs. Making changes during the development and validation process for the IVD will require the IVDs to undergo re-validation. Changing the platform upon which the assay is tested will require a subsequent regulatory submission for clearance or supplemental application for pre-market approval. The expertise required to understand the nuanced differences associated with the various technology platforms (e.g. IHC, FISH, Real-Time PCR, etc.) adds an additional dimension to the complexity of the IVDs not necessarily present of traditional devices and may be challenging for the biopharmaceutical company's ability to successfully navigate the development and regulatory approval process.

Pharmaceutical or Biotechnology companies who are looking to enhance their product portfolios with an *In Vitro* diagnostic or companion diagnostic, must assess and take into consideration the influencing factors, the type of diagnostic test that provides the best fit for their therapeutic program, the regulatory expertise available within the organization, and the capabilities of establishing and managing a strategic external

partnership with an organization that specializes in developing and commercializing diagnostic tests. The first step is having a solid but basic foundation of where the company stands now with its therapeutic strategy and where it plans to be in the future. This regulatory primer on *In Vitro* diagnostics and related products was intended to set the stage for further in-depth examination of these and related topics. Hopefully, this article will also begin a dialog within companies venturing into the companion diagnostics area by giving some ideas as to early considerations for planning.

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