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Companion Diagnostics and Regulatory Strategies: Insights from the INNOVANCE® Antithrombin Assay

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ABSTRACT

Companion diagnostics (CDx) are vital tools in personalized medicine, enabling the safe and effective use of targeted therapies by identifying patients most likely to benefit or be at risk. This paper reviews the regulatory framework for CDx, with a focus on the U.S. Food and Drug Administration (FDA), which classifies most CDx as high-risk devices requiring premarket approval. Key regulatory components include analytical and clinical validation, labeling, and post-market surveillance. The paper also highlights global regulatory perspectives, including the European Union's IVDR, China's co-development model, and Japan's simultaneous development approach.

Statistical considerations play a vital role in CDx and drug co-development. To demonstrate they have performance characteristics and product configuration that are very similar to those of the test that was used in the clinical trial assay, as well as their accuracy, precision, and clinical utility, the candidate CDx must undergo thorough analytical and clinical. In this paper, a case study of Siemens INNOVANCE® Antithrombin assay illustrates the clinical application of CDx. Used to guide dosing of drug X in patients with hemophilia A or B, the assay helps maintain antithrombin activity within a target range. Through the clinical validation, it could be proven the assay proves reliable for monitoring AT activity to optimize drug X dosing across all hemophilia A or B patients, regardless of factor VIII or IX inhibitor status.

INTRODUCTION

Companion diagnostics (CDx) are medical devices that provide essential information for the safe and effective use of a corresponding therapeutic product. They play a crucial role in personalized medicine by helping to identify patients who are most likely to benefit from a particular therapeutic product, or those who may be at increased risk for serious side effects [1]. This paper provides an overview of the regulatory landscape for CDx, with a focus on the U.S. Food and Drug Administration (FDA) framework. It also highlights international regulatory approaches in the European Union, China, and Japan. Analytical validation and clinical validation are crucial to illustrate the clinical application and validation of CDx. Also, we present a clinical validation case study of the INNOVANCE® Antithrombin assay, developed to guide dosing of drug X in patients with hemophilia A or B. This example demonstrates how CDx can improve treatment outcomes and support regulatory approval through robust clinical evidence.

DEFINITION AND CONTEXT

The FDA defines a companion diagnostic as an in vitro diagnostic device (IVD) that provides information essential for the safe and effective use of a corresponding therapeutic product [2]. Key points about CDx include:

- They are co-developed and co-approved with the corresponding therapeutic.
- Their use is stipulated in both the assay instructions and the labeling of the therapeutic product.
- CDx testing is mandatory before prescribing the specific therapeutic product.

CDx differ from complementary diagnostics, which identify biomarker-defined subsets of patients that respond particularly well to a drug but are not prerequisites for receiving the drug.

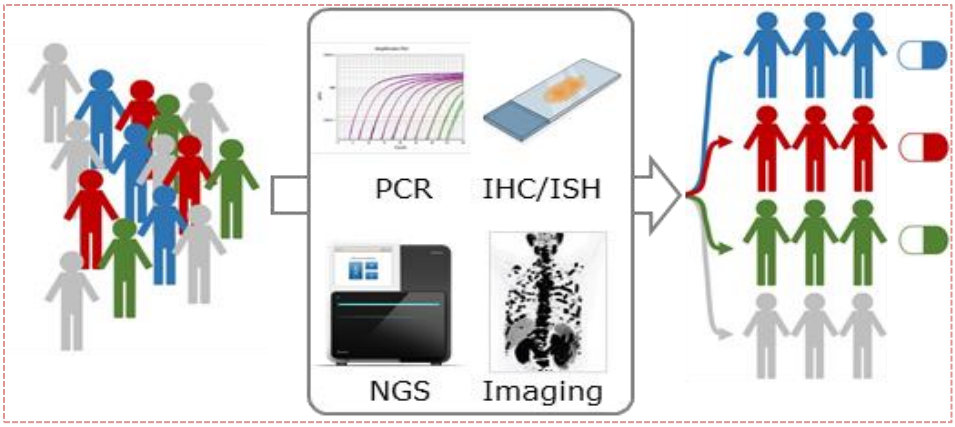

Figure 1. Companion Diagnostics in Personalized Medicine

FDA REGULATIONS

The FDA has established specific regulations for companion diagnostics to ensure their safety and effectiveness. Under the purview of the FDA's device regulations, IVDs (and all other medical devices) fall into three risk-based categories that determine their regulation: Class I (low risk); Class II (moderate risk); and Class III (high risk). Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval [3].

Key aspects of these regulations include:

1. Co-development and Co-approval

   The FDA strongly encourages simultaneous development and review of a CDx and its corresponding therapeutic product [2]. This approach ensures that the diagnostic is available at the time of drug approval and that the clinical performance of both products is well-characterized.

2. Premarket Approval (PMA)

   Most CDx are classified as high-risk (Class III) medical devices and require a PMA submission [1]. The PMA process involves a rigorous review of the device's safety and effectiveness, including:

   - Analytical validation data
   - Clinical validation data
   - Manufacturing information
   - Proposed labeling

3. Analytical and Clinical Validation

   CDx must undergo thorough analytical and clinical validation to demonstrate their accuracy, precision, and clinical utility. This includes:

   - Analytical performance studies (e.g., sensitivity, specificity, reproducibility)
   - Clinical performance studies (e.g., positive and negative predictive values)
   - Cut-off determination for biomarker levels

4. Labeling Requirements

The labeling for both the CDx and the therapeutic product must cross-reference each other and provide clear instructions for use. This ensures that healthcare providers have all necessary information to use the products correctly.

5. Post-market Surveillance

   Ongoing monitoring and reporting of device performance and safety are required after approval [4]. This may include:

   - Periodic reporting of adverse events
   - Post-approval studies to gather additional performance data
   - Updates to labeling as new information becomes available

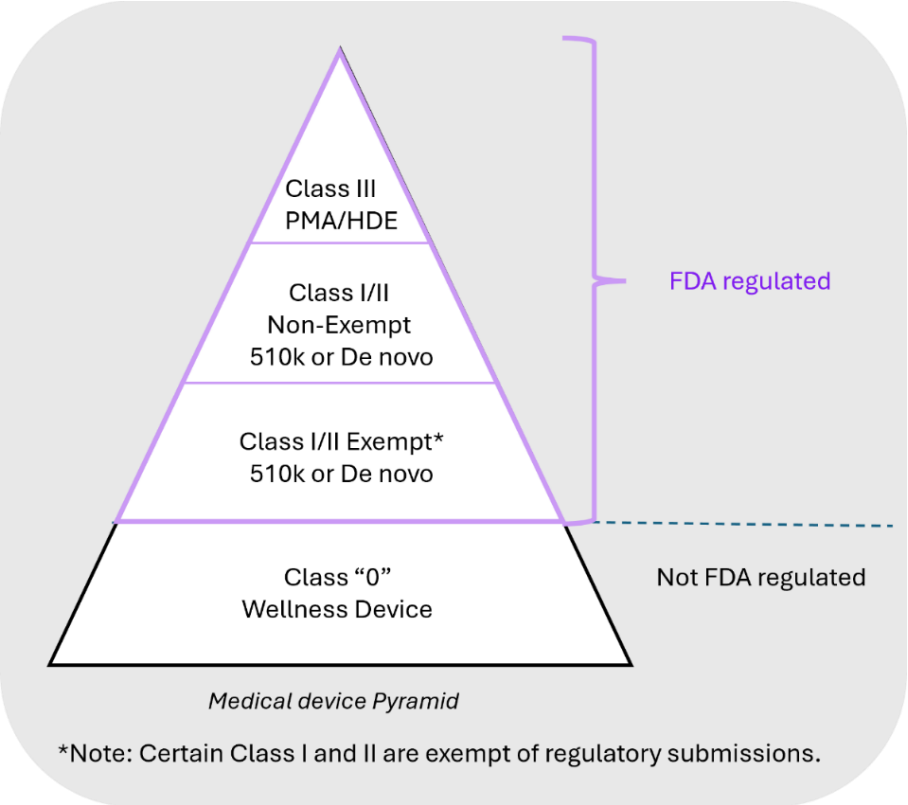

Figure 2. Different CDx regulatory

GLOBAL REGULATORY CONSIDERATIONS

While this paper focuses on FDA regulations, it's important to note that CDx regulations vary globally:

1. European Union

   The EU's In Vitro Diagnostic Regulation (IVDR) uses risk-based classification. Now, IVDs will be classified into four different classes based on risk, from class A (low) to class D (high) under IVDR. And most CDx are classified as Class C IVDs, requiring Notified Bodies reviewing [5]. Generally, the IVDR introduces stricter requirements for clinical evidence and post-market surveillance.

2. China

The National Medical Products Administration (NMPA) has been developing a regulatory framework for CDx, with a focus on oncology-related tests. The NMPA is moving towards a co-development and co-approval model similar to the FDA's approach.

3. Japan

   The Pharmaceuticals and Medical Devices Agency (PMDA) has established guidelines for CDx development and approval, emphasizing the importance of simultaneous development with the corresponding therapeutic.

ANALYTICAL VALIDATION AND CLINICAL VALIDATION

Analytical validation and clinical validation are mandatory to demonstrate that the candidate IVD CDx has performance characteristics and product configuration that are very similar to those of the test that was used in the clinical trial assay. And statistical considerations play a vital role here, such as sensitivity, specificity, accuracy (positive percent agreement, negative percent agreement, positive predictive value, negative predictive value, etc.), precision (like ANOVA), linearity, and so on.

Also, to demonstrate that the CDx reliably identifies the intended patient population and provides consistent results across different testing conditions, we need clinical validation via pivotal clinical trial(s). Following are some clinical validation study considerations.

- Drug and device are typically studied in the same clinical trial.
- Study design should support the Indications for Use.
- Device’s algorithm including the cut-off should be locked down before the initiation of analytical/clinical validation studies.
- Assure proper use of test in the trial.
- Analytical validation precedes clinical validation (recommended).

A CASE OF CLINICAL VALIDATION FOR CDX

FDA approved drug X for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A or hemophilia B, with or without factor VIII or IX inhibitors (neutralizing antibodies) this year [6].

To illustrate the process of clinical validation for a companion diagnostic, we'll examine the case of Siemens INNOVANCE® Antithrombin assay as a CDx for drug X dosing. This companion diagnostic is intended to monitor and—by informing dosing and frequency of injections—achieve antithrombin activity in the target range (15%-35%) to reduce the risk of bleeding and to reduce the risk of excessive blood clotting [6,7]. Since the most existing AT tests that diagnose AT deficiency (<80%) cannot measure the lower AT range, the INNOVANCE® Antithrombin assay can reliably measure AT activity at the clinical decision points of 15%-35% of normal and is most suitable for clinical management of patients taking drug X [8].

1. Study Design

   An antithrombin-based dose regimen for the therapeutic, aiming to maintain antithrombin (AT) activity levels between 15% and 35% [7].

2. Methods

   - Included participants who received at least one dose of drug X antithrombin-based dose regimen (AT-DR).
   - Antithrombin activity levels records from a central lab using the INNOVANCE® Antithrombin assay were taken into account.
   - AT measurements were taken at baseline and throughout the treatment period.
   - Dose adjustments were made based on AT levels to achieve the target range.

- Statistical analysis of AT measurements over time, including spaghetti plots and statistical summary tables. Also, trajectory plots of AT for individual participant with thrombotic event were provided.

Figure 3 and figure 4 below are generated by randomized dummy data, for reference only.

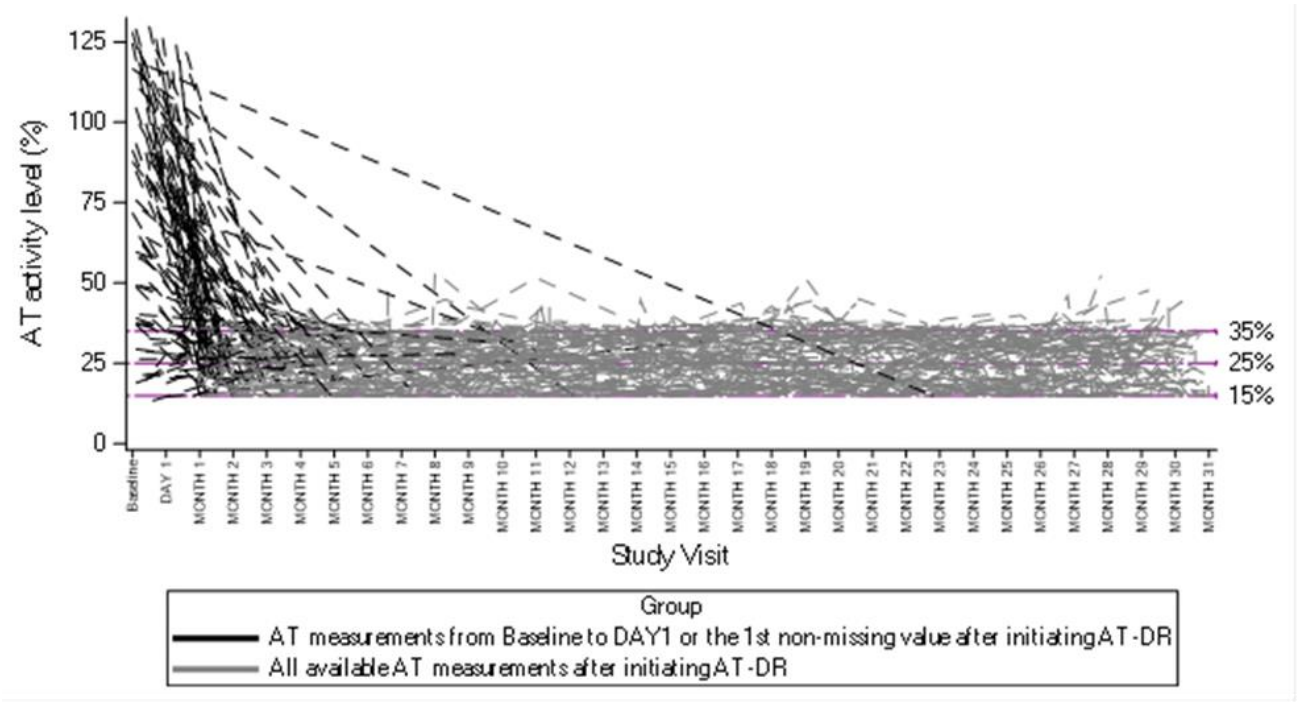

Figure 3. Spaghetti plot of antithrombin (% of norm) measurement over time

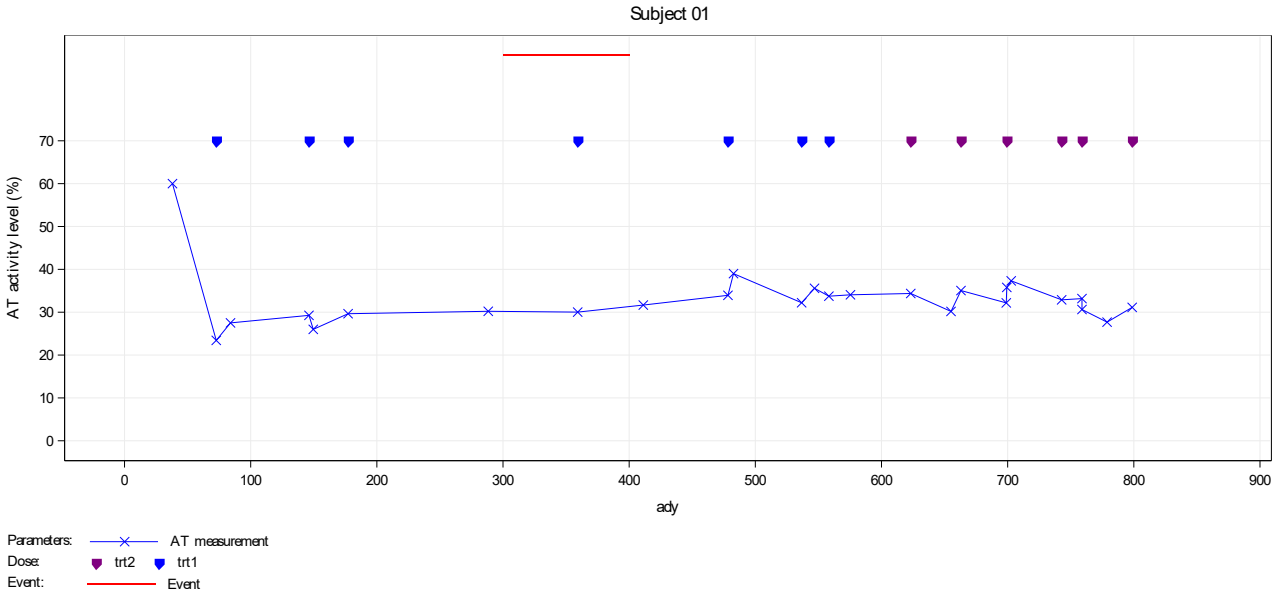

Figure 4. Trajectory plot of antithrombin measurements overtime for individual participant with thrombotic event

Category	Statistic of Antithrombin measurement					
	Number of Participants	Number of AT Measurements	Mean (SD) (%)	Median (%)	Q1 : Q3 (%)	Min : Max (%)
Total	XX	XX	XX.XX (XX.XX)	XX.XX	XX.XX ; XX.XX	XX.XX ; XX.XX
Baseline	XX	XX	XX.XX (XX.XX)	XX.XX	XX.XX ; XX.XX	XX.XX ; XX.XX
AT-DR period	XX	XX	XX.XX (XX.XX)	XX.XX	XX.XX ; XX.XX	XX.XX ; XX.XX

Table 1. Summary table of antithrombin measurements

3. Results

   The clinical experience demonstrated that drug X AT-based regimen was successful at maintaining AT activity levels within the targeted range using the INNOVANCE Antithrombin assay. And the FDA had granted 510(k) marketing clearance of the INNOVANCE Antithrombin test as a companion diagnostic for drug X to Siemens Healthcare Diagnostics GmbH [6].

CONCLUSION

The development and approval of companion diagnostics involve complex regulatory processes and rigorous clinical validation. As personalized medicine continues to advance, the importance of CDx in guiding treatment decisions is likely to grow. The FDA's evolving regulatory framework aims to ensure the safety and effectiveness of these critical devices while promoting innovation in the field.

The successful development of CDx requires close collaboration between pharmaceutical companies, diagnostic manufacturers, and regulatory agencies. As the field progresses, we can expect to see further refinements in regulatory approaches, statistical methodologies, and clinical trial designs to support the efficient development and validation of these essential tools in personalized medicine.

REFERENCES

1. U.S. Food and Drug Administration. In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff. 2014.
2. U.S. Food and Drug Administration. Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product: Draft Guidance for Industry and Food and Drug Administration Staff. 2016.
3. Overview of Device Regulation | FDA
4. U.S. Food and Drug Administration. Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry and Food and Drug Administration Staff. 2016.
5. In Vitro Diagnostic Regulation (IVDR) (EU) 2017/746 - OMC Medical
6. FDA Approves Novel Treatment for Hemophilia A or B, with or without Factor Inhibitors | FDA
7. qfitlia.pdf
8. Chhabra ES, Sadeghi-Khomami A, Liu M, Young G, Pipe SW, Ozelo MC, Camus CL, Toh ML, Demissie M, Peyvandi F. Global Comparative Antithrombin Field Study: Impact of Laboratory Assay Variability on the Assessment of Antithrombin Activity Measurement at Fitusiran Clinical Decision-Making Points. Haemophilia. 2025 Apr 20. doi: 10.1111/hae.70045. Epub ahead of print. PMID: 40254822.

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