IVDD to IVDR Transition of Two Prenatal FISH Probe Kits (LPA 001 & LPF 001): Completion of Design and Development Files to Support Submission

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What binds us, makes us.

Introduction

Implementation of In Vitro Diagnostic Regulation (IVDR) has increased expectations for lifecycle documentation, traceability, risk management integration, and performance justification for in vitro diagnostic medical devices. While most legacy assays developed under IVDD are scientifically and analytically robust, supporting design and development documentation is not always fully structured or traceable within frameworks aligned to current IVDR expectations.

This work demonstrates part of the transition process for two established prenatal FISH probe kits:

CytoCell® CE-LPA 001 – overnight hybridisation

CytoCell® CE-LPF 001 – 2-hour FAST FISH (Fig.1)

Both kits are intended for the detection of chromosomal aneuploidies, including:

- trisomy 13 (Patau syndrome)
- trisomy 18 (Edwards syndrome)
- trisomy 21 (Down syndrome)
- sex chromosome aneuploidies (Turner syndrome)

Transition to IVDR required reconstruction of design history, traceability, and linkage of performance evidence within an IVDR-compliant framework, without changing assay performance and intended purpose. This work highlights practical lessons from retrospective design remediation and traceability reconstruction from a Research and Development (R&D) perspective.

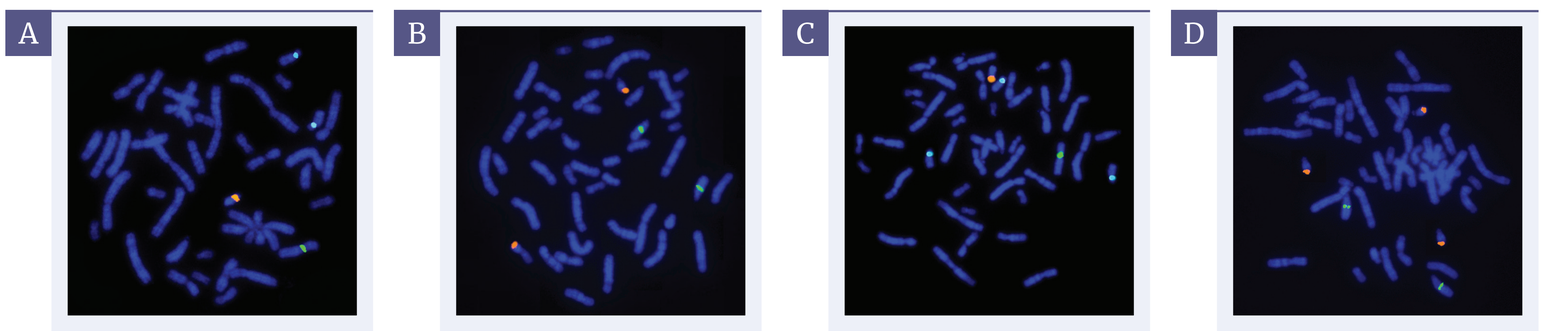

Figure 1: Representative fluorescence microscopy images generated using CE-LPF 001. A Normal male sample demonstrating one chromosome X signal (green), one chromosome Y signal (orange), and two chromosomes 18 signals (aqua). B Normal sample demonstrating two chromosome 13 signals (green) and two chromosome 21 signals (orange). C Abnormal male sample demonstrating one chromosome X signal (green), one chromosome Y signal (orange), and trisomy 18 (three aqua signals), consistent with Edwards syndrome. D Abnormal sample demonstrating two chromosome 13 signals (green) and trisomy 21 (three orange signals), consistent with Down syndrome.

Methods

A methodical, stepwise approach to documentation enhancement was implemented (Fig 2). This began with a cross-functional IVDR gap assessment against Annex I, II, and XIII with focus on retrospective remediation of design and development documentation. The outcome of this assessment informed the scope and prioritisation of downstream documentation activities, enabling a structured and sequential redevelopment of the design history file in alignment with IVDR requirements (Fig. 2).

Traceability Reconstruction

To meet IVDR traceability requirements, bidirectional traceability matrices were developed linking:

- User needs
- Design inputs
- Design outputs
- Verification activities

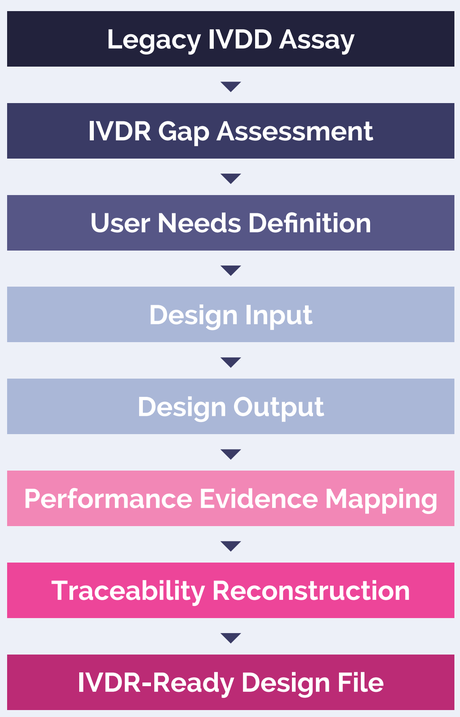

Figure 2. Retrospective IVDR design remediation workflow.

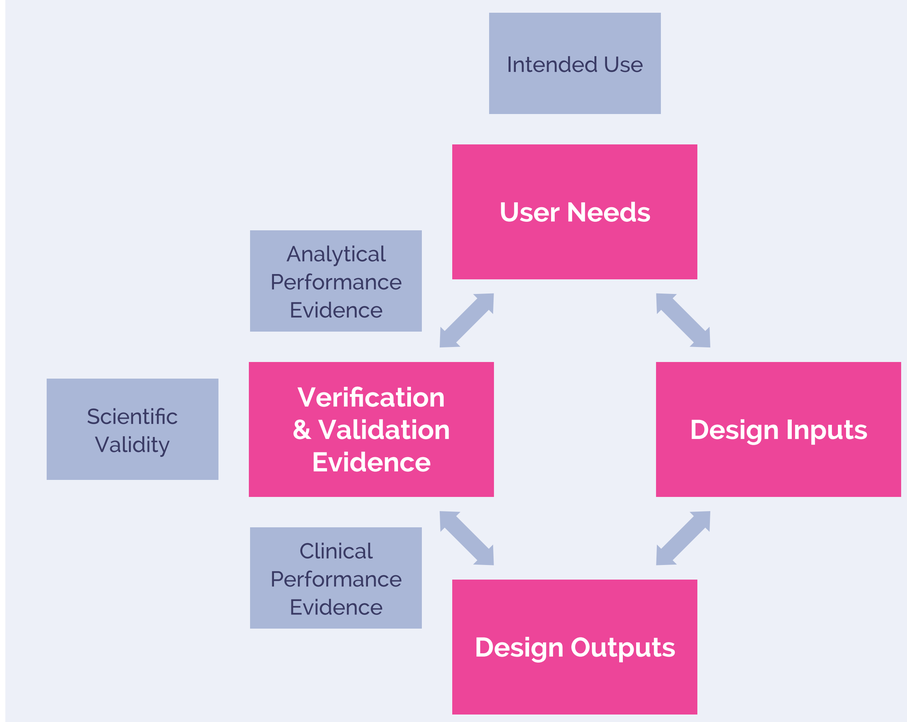

Figure 3. Bidirectional traceability framework for IVDR design remediation.

Results

Complete IVDR-aligned design and development documentation packages were successfully generated for both prenatal FISH probe kits.

Retrospective remediation enabled reconstruction of traceability between user needs, design inputs, design outputs, verification and performance evidence.

Examples of reconstructed traceability mapping are shown in Table 1.

User Need	Design Input	Design Output
Target Definition Detection of chromosomes X, Y, 13, 18 and 21	**Probe Design** Probe design and fluorophore allocation • Example- Chr 13 specific region labelled in Green	**Confirmed assay is suitable for detection by FISH of chromosome 13q14.2** **Design Review Instruction For Use (IFU)**
	Definition of abnormal signal pattern Defined expected signal criteria • Example- in a cell with trisomy 13, the expected signal pattern will be three green signals and two oranges (3G2O)	**Achieved the required high clinical sensitivity & specificity** **Design Review Instruction For Use (IFU)**
FISH technology Enumeration FISH workflow	**Probe in solution** Probe formulation in the hybridisation solution	**Probe premixed in hybridisation solution and ready to use** **Device Master Record**
	Analytical Specificity Acceptance criteria 100% specificity	**100% specificity achieved** **Design Review Instruction For Use (IFU)**
	Analytical Sensitivity Acceptance criteria ≥95% sensitivity	**>96% sensitivity achieved** **Design Review Instruction For Use (IFU)**

Table 1. Non-exhaustive traceability reconstruction examples for CE-LPA 001.

Key Outcomes

- Improved connection between legacy design documentation and performance evidence
- Enhanced traceability and documentation consistency
- Alignment of historical evidence with IVDR expectations
- No modification to assay chemistry, workflow, or intended claims

Conclusions

Strong assay performance shown by robust analytical and clinical evidence underpins the ease of transitioning a large number of probes, demonstrating the quality and reliability of products.

Retrospective reconstruction of design documentation translated existing technical knowledge into structured, traceable, and auditable evidence, providing a practical pathway for IVDR transition without modification to assay chemistry, workflow, intended use, or performance claims.

Building on our first to market IVDR FISH products, expansion using this established framework will allow for significant efficiencies, with larger and accelerated conversion to IVDR status.

References

Regulation (EU) 2017/746 of the European Parliament and of the Council on in vitro diagnostic medical devices

International Organisation for Standardisation. ISO 13485:2016 medical devices: Quality management systems

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