Influence of CE-IVD on R&D processes

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Associate Director, MDx Assay Development

28th November 2013

Overview

- Introduction
- Value of CE IVD process
- Influence on R&D process
- Impact on Assay workflow and quality
- Impact on reliability of patient results
- Outlook change in directive

QIAGEN Manchester

- Acquisition of DxS in 2009
- Personalised Healthcare assay development in partnership with pharmaceutical companies
- Develop regulated PCR & RT-PCR assays
  - *therascreen* KRAS RGQ PCR Kit
    - PMA approval July 2012
  - *therascreen* EGFR RGQ PCR Kit
    - PMA approval July 2013
  - *therascreen* products also distributed in other regulated territories including:
    - CE
    - Australia
    - Japan

Manchester Science Park

Manchester Site Development Update 26.07.13

G2- Class 2 lab Electrical and flooring well advanced

26th July 2013

Manchester Site Development Update 27.09.13

27th Sept 2013

G2- Development Lab

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Value of CE IVD process

- The In Vitro Diagnostics Directive (IVDD) 98/79/EC is a set of regulatory requirements that medical device manufacturers must comply with in order to affix a CE marking to their product

- **Safeguard the health and safety of patients, users and third parties** ensuring that the manufacturer meets quality standards and demonstrates their products are effective and perform as intended.

- The CE marking allows the company to gain access to the 30 member states that comprise the European Economic Area (EEA) which was formed as a single market to promote free trade.

Value of CE IVD process

A. General Requirements

The device must be **designed** and **manufactured** in such a way that, when used under the conditions and for **the purposes intended**, they will not compromise, directly or indirectly, the clinical condition of the safety of the patients, the safety or health of users or, where applicable, other persons, or the safety of property. Any **risks** which may be associated with their use must be acceptable when weighed against the benefits to the patient and be compatible with a high level of protection of health and safety.

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Influence on R&D process

- The Directive lists “Essential Requirements” to which all IVDs must comply before being placed on the market
- Each IVD requires establishment of technical file
- The technical file is the basis for the CE-marking and the manufacturers declaration of conformity
- Higher risk devices require a Notified Body to assess compliance before placing the device on the European market
- Manufactures can demonstrate that they have met the Essential Requirements by complying with relevant harmonised standards
  - ISO13485 for Quality Management Systems
  - ISO 14971 for Risk Management

} Central to QIAGEN procedures

Influence on R&D process for assays

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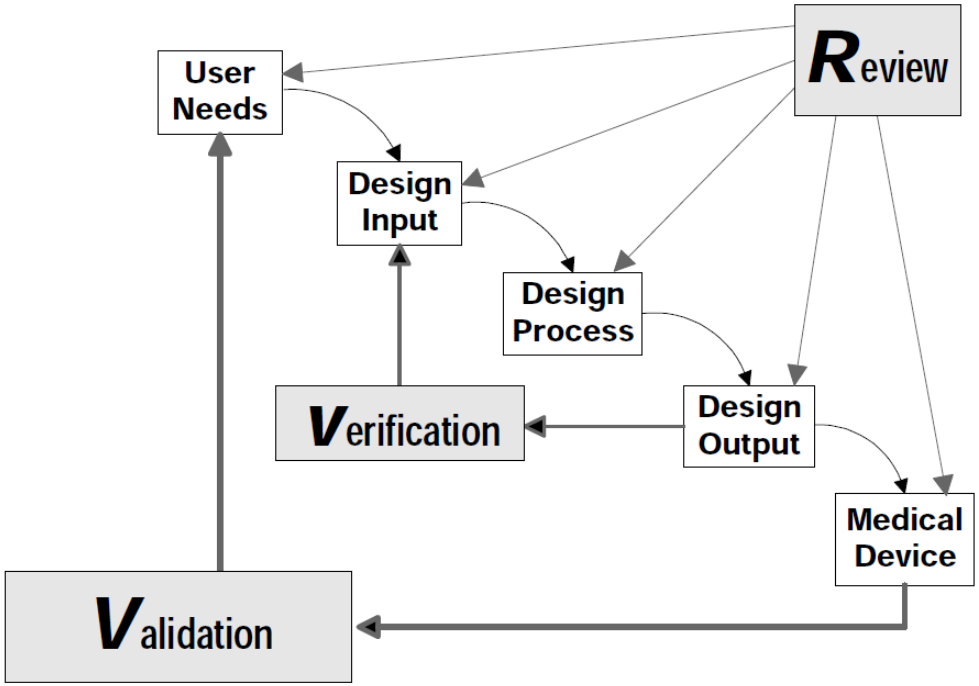
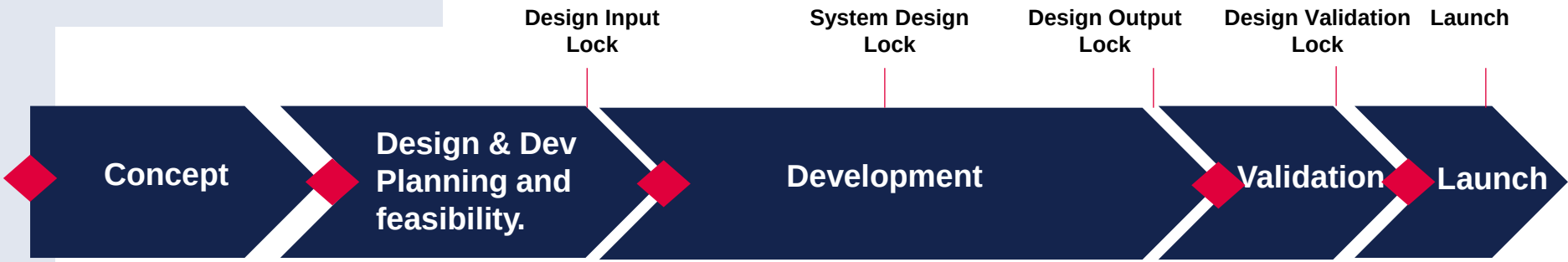


Influence on R&D process for assays



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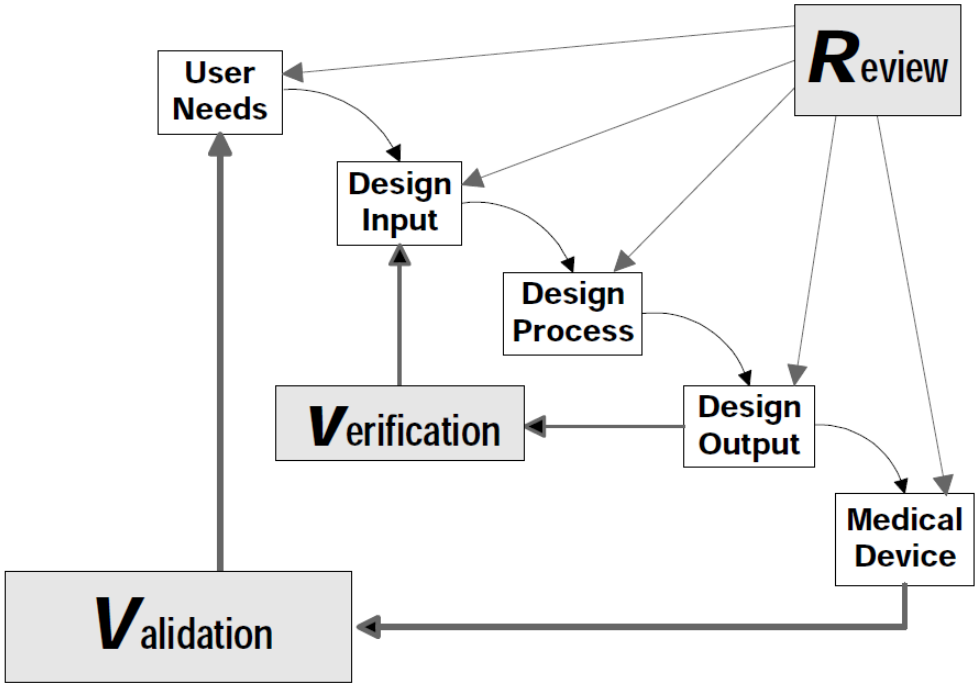
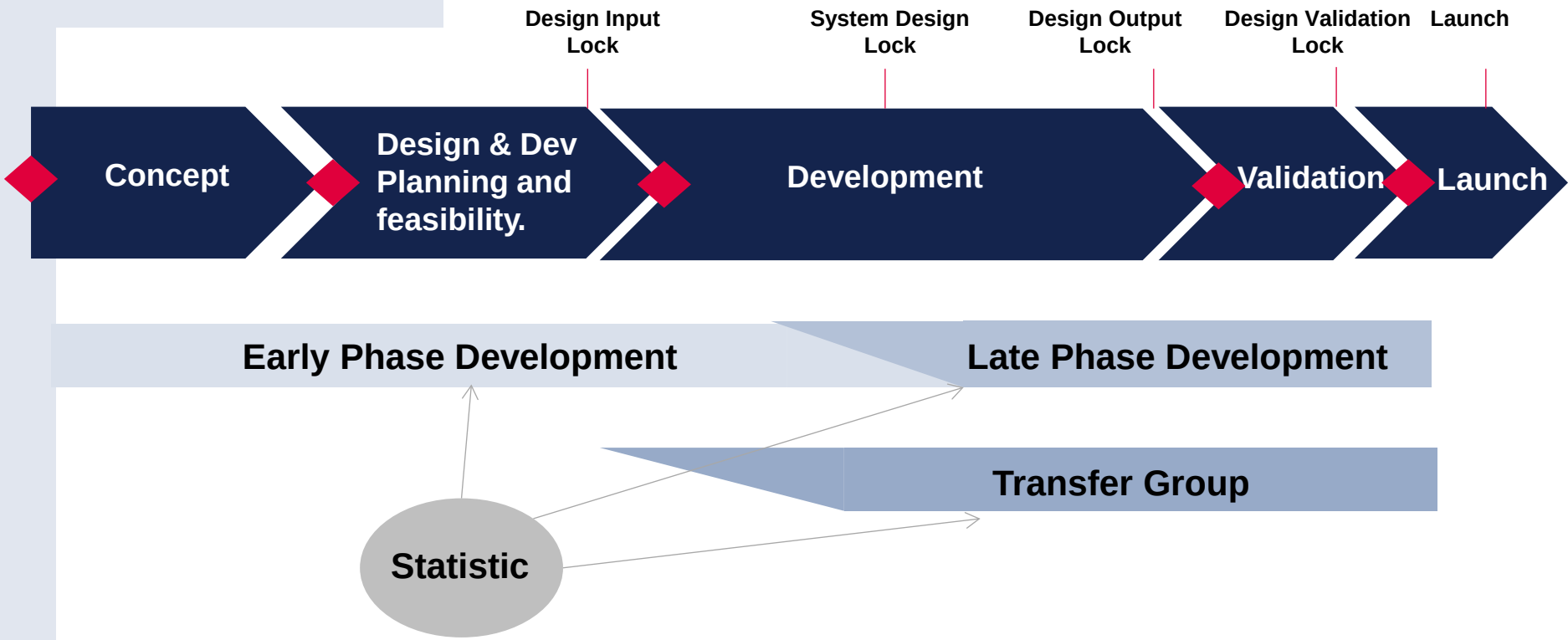


Influence on R&D process



PD Lead (core): Project 1

PD Lead (core): Project 2

PD Lead (core): Project 3 etc

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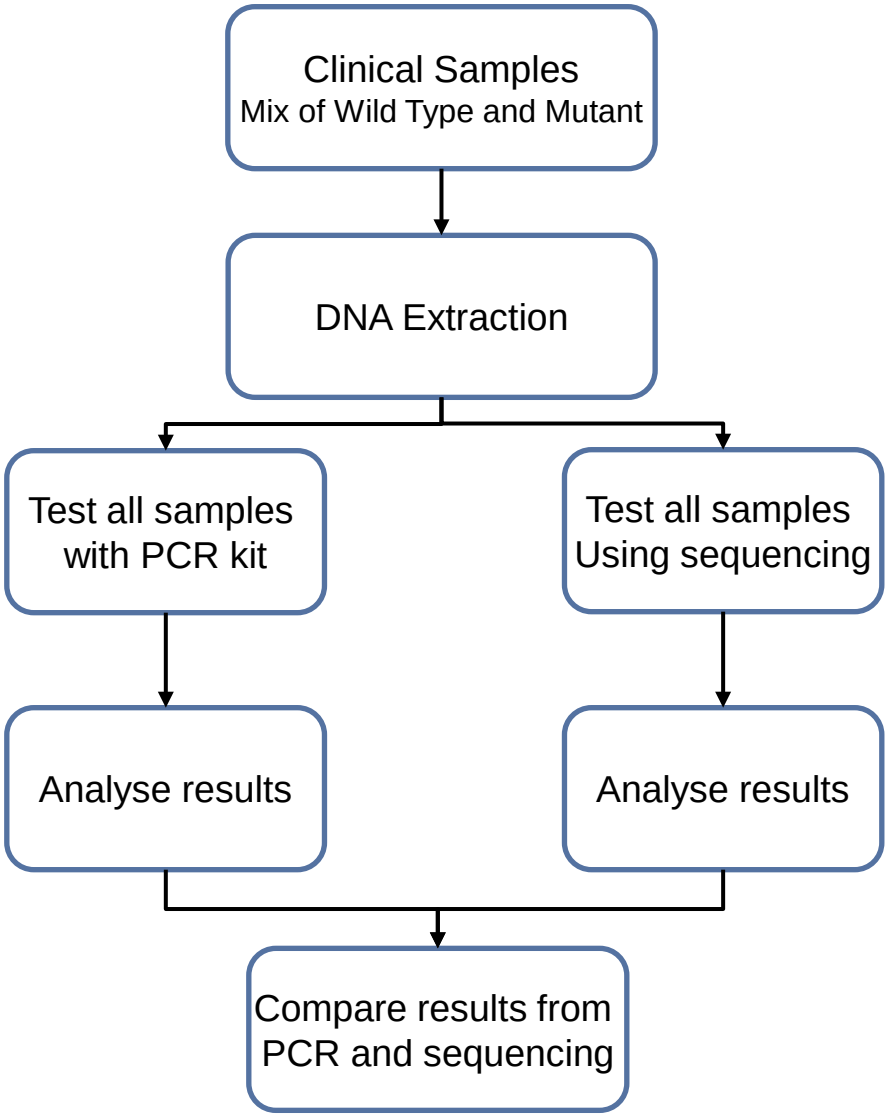
Feasibility: Clinical sample testing

Design & Dev Planning and feasibility.



- Confirmation of mutation detection capability of the kit using Clinical Samples on completion of feasibility
- PCR kit vs bi-directional sequencing (gold standard)
- >95% concordance achievable
- Non-concordant samples can be sequenced using Next Generation Sequencing to confirm that PCR kit is more sensitive than bi-directional sequencing

PCR kit vs Bi-directional Sequencing

Design & Dev Planning and feasibility.

Sample	PCR Kit	Bi-directional Sequencing	Next Generation Sequencing
1	Mutation Negative	✓	
2	Mutation Negative	✓	
3	Mutation Positive	✓	
4	Mutation Positive	✗	✓
5	Mutation Positive	✓	
6	Mutation Positive	✓	
7	Mutation Positive	✓	
8	Mutation Positive	✓	
9	Mutation Positive	✓	
10	Mutation Positive	✓	
11	Mutation Positive	Invalid	
12	Mutation Negative	✓	
13	Mutation Positive	✓	
14	Mutation Positive	✓	
15	Mutation Positive	Invalid	
16	Mutation Negative	✓	
17	Mutation Negative	✓	
18	Mutation Negative	✓	
19	Mutation Negative	✓	
20	Mutation Negative	✓	

- Valid bi-directional sequencing data obtained for 17 of 18 samples

Robustness – Concentration of Critical Raw Material

Development

Part 1
Concentration of Critical Raw Materials

Part 2
Manufacturing Robustness

Objective:

- To finalise assay composition to ensure that it is robust to changes in concentration of critical raw materials

Inputs:

- Nominal concentrations of raw materials identified in Feasibility

Design:

- Full or fractional factorial design to test multiple raw material combinations

Outputs:

- Final assay composition and define raw material specification range

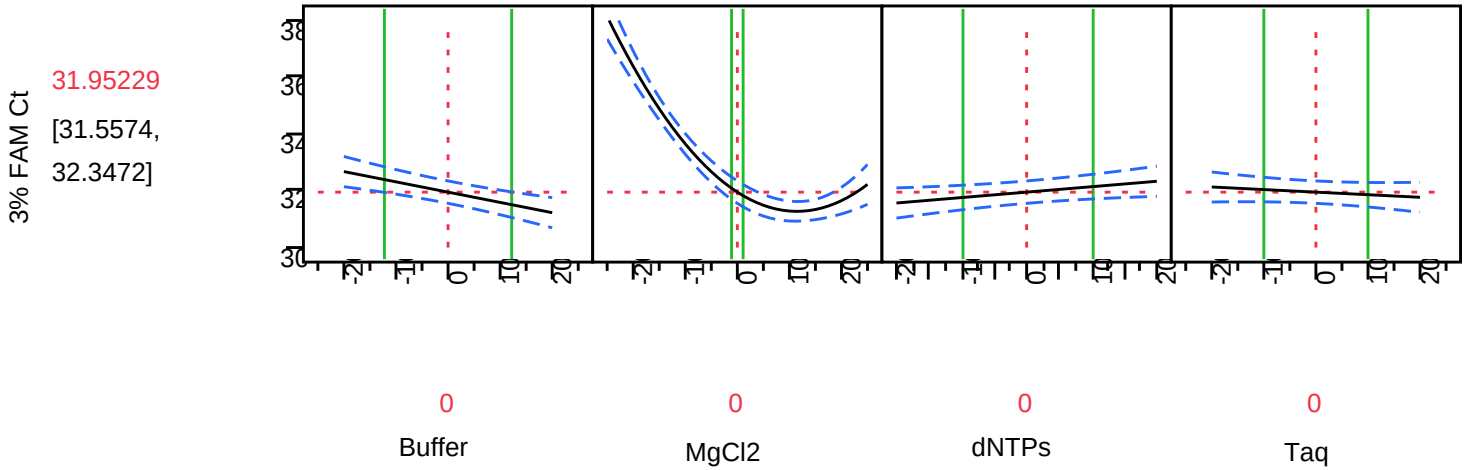
DOE for Robustness

Development

Kit Number	Operator	Taq	Buffer	$MgCl_2$	dNTPs
1	1	1	-1	1	1
2	1	-1	-1	-1	1
3	1	0	0	0	0
4	1	1	1	-1	1
5	1	-1	1	-1	-1
6	1	1	-1	-1	-1
7	1	1	1	1	-1
8	1	-1	1	1	1
9	1	0	0	0	0
10	1	-1	-1	1	-1
11	2	0	0	0	0
12	2	1	1	1	1
13	2	1	-1	-1	1
14	2	-1	1	-1	1
15	2	-1	-1	1	1
16	2	1	1	-1	-1
17	2	0	0	0	0
18	2	-1	1	1	-1
19	2	1	-1	1	-1
20	2	-1	-1	-1	-1
21	3	0	0	0	1
22	3	0	0	-1	0
23	3	0	0	0	0
24	3	0	0	1	0
25	3	0	-1	0	0
26	3	-1	0	0	0
27	3	0	0	0	-1
28	3	1	0	0	0
29	3	0	1	0	0
30	3	0	0	0	0

Robustness

Development



- All the critical parameters are investigated at ±20% of nominal concentration.
- Nominal concentrations of critical raw materials from Feasibility.
- Green lines specify manufacturer's concentration limits:

Buffer: ±12%

$MgCl_2$: ±1%

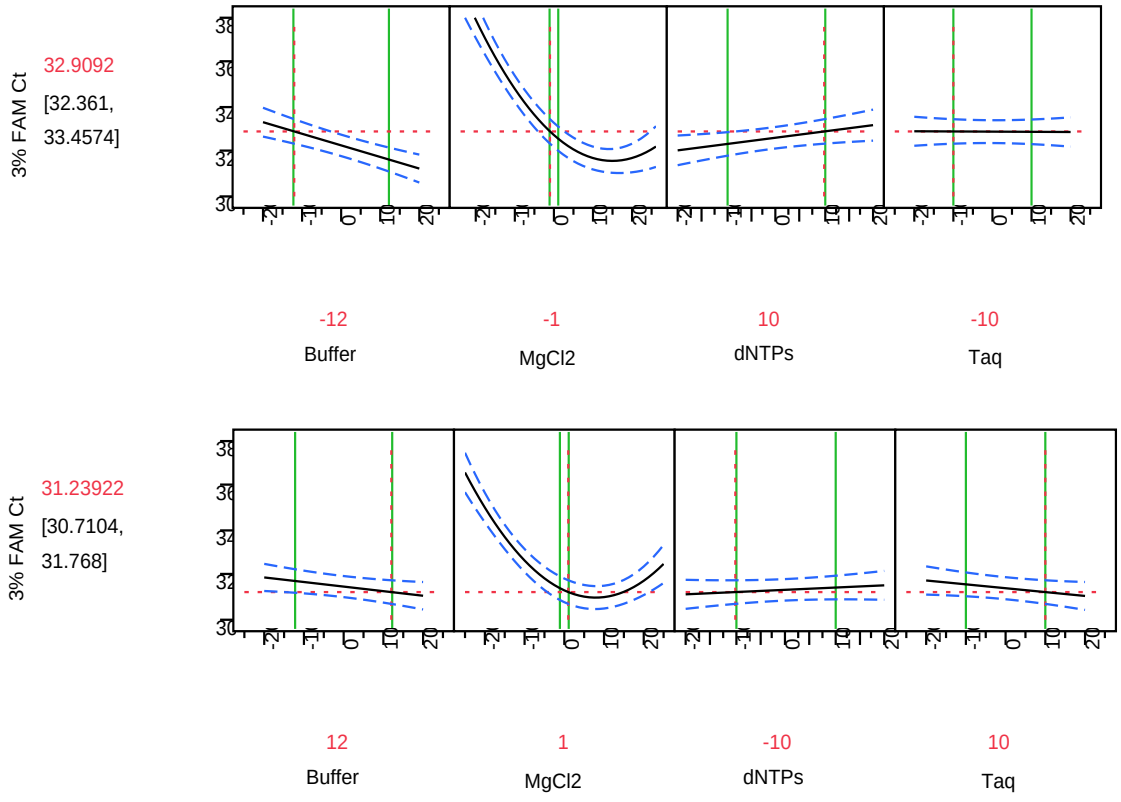
dNTPs: ±10%

Taq: ±10%

Robustness

Development

Ct at the extreme concentrations within manufacturer's range:

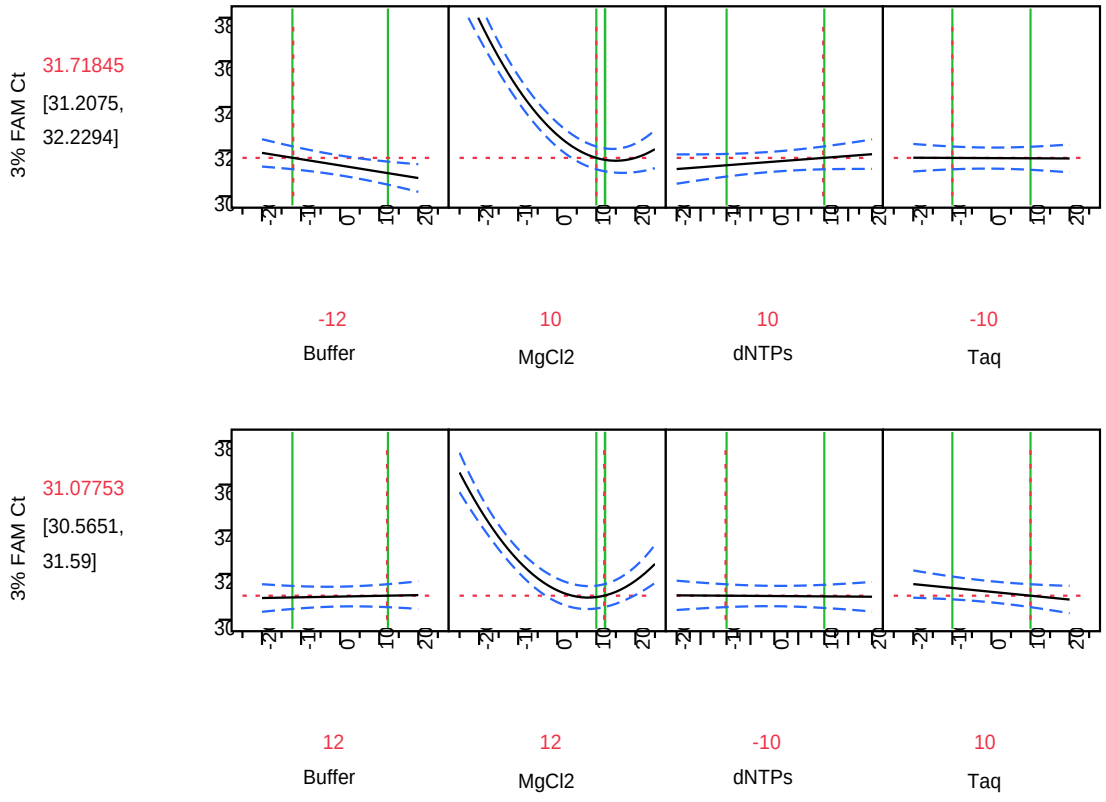


- Change in material concentrations within the manufacture's range will lead to a Ct change
- Ct could vary from 32.91 – 31.24
- Ct range of 1.67 depending on the lot-specific concentration of each material used within the manufacturers specs

Robustness

Development

Ct at the extreme concentrations within manufacturer's range increased $MgCl_2$ concentration:



- Increase $MgCl_2$ concentration by 11%
- Reduces the Ct range to 0.64, when changes in the raw material concentrations are within the manufacture's range
- Increasing the $MgCl_2$ concentration in this case yields a more robust assay
- Outcomes are confirmed experimentally

Robustness

Development

Part 1
Concentration of Critical Raw Materials

Part 2
Manufacturing Robustness

Objective:

- To ensure that kit manufacture is robust

Inputs:

- Final assay composition from Part 1

Design:

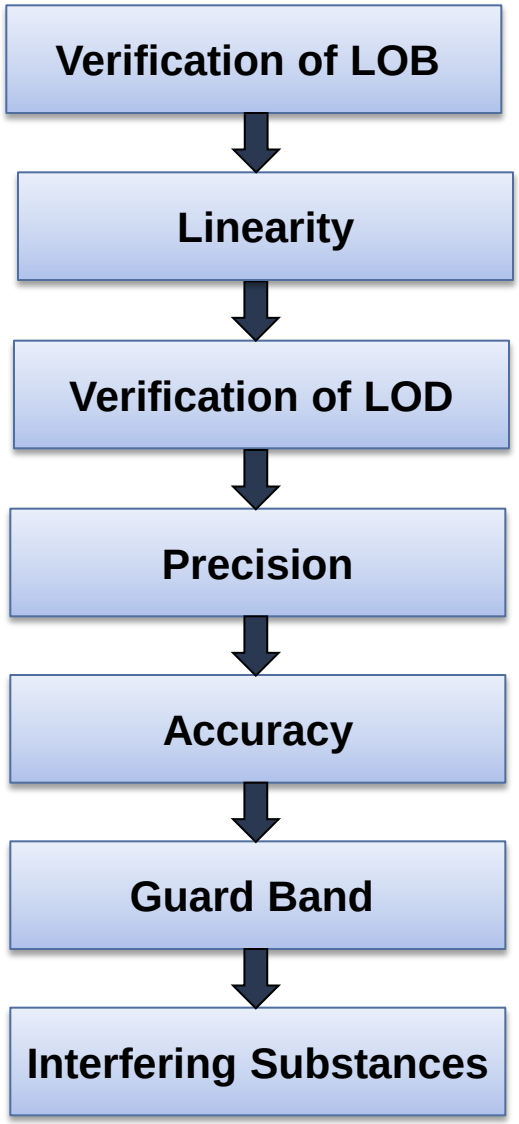
- Manufacture of multiple kits by several operators, tested by several operators on 2 RGQs over 3 days

Outputs:

- Demonstration of robust manufacture
- Interim measure of precision

Example Verification

Development



Overall Objective:

- To verify the assay performance

Verification of LOB:

- If LOB equal to the clinical cut off
- Linearity - Defined RNA or DNA working range for the kit is within linear working range

Precision:

- Lot interchangeability – lot to lot precision using different reagent lots
- Reproducibility – evaluate variation between laboratories

Accuracy:

- Demonstrate accuracy of kit to reference method when testing clinical samples

Guard Band:

- Demonstrates kits robustness within “Safe Ranges”
- Includes all crucial steps and critical specifications (e.g. sample preparation procedures, reagent thawing time, freeze thaw cycles, PCR set up time)

Interfering Substances:

- Evaluate impact of potential interfering substances

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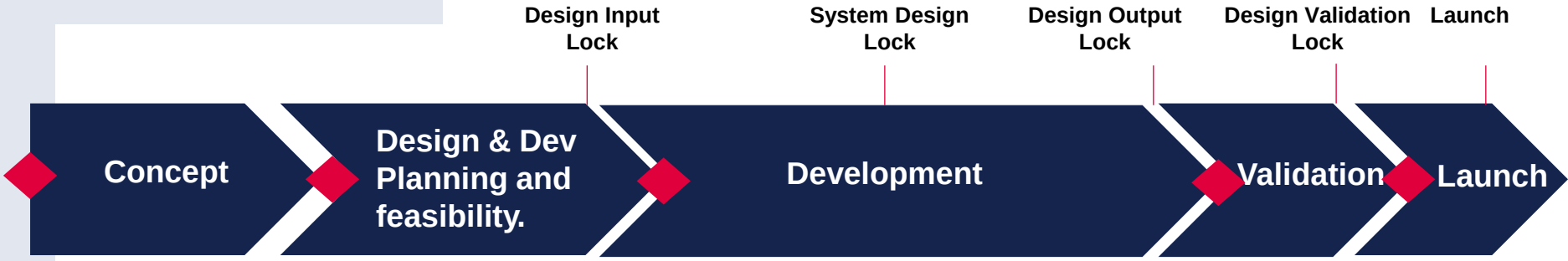
Impact on reliability of patient results



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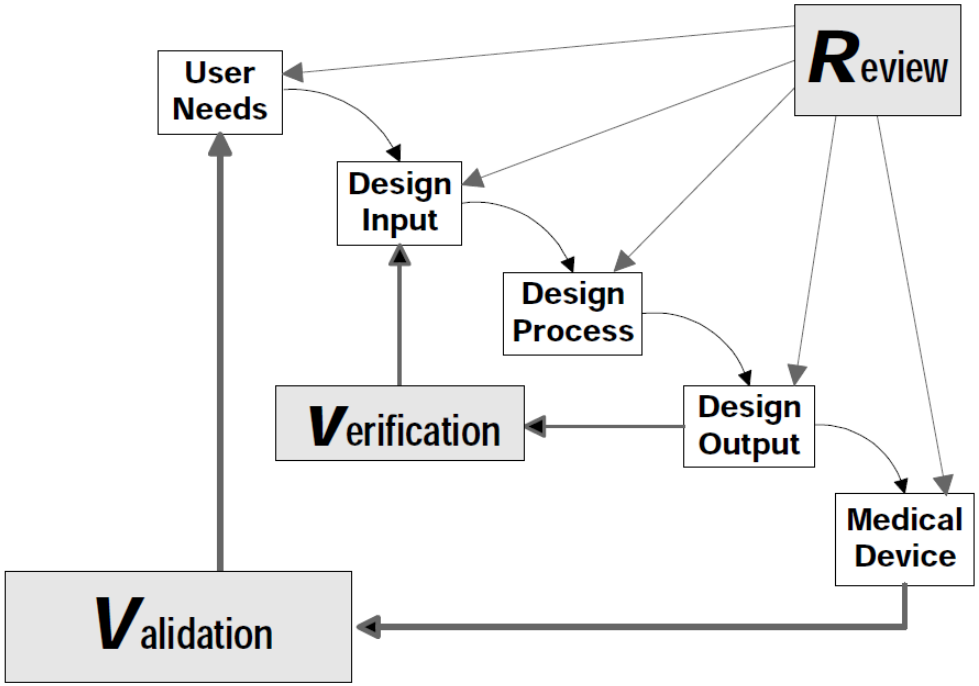

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Outlook change in directive

Main issues expected to be addressed

- Classification
- Conformity assessment procedure
- Scope
- Clinical evidence
- Other topics

Questions

Thank You