Bedeutung von präanalytischen ISO und CEN Standards aus Sicht eines IVD Entwicklers und Herstellers

LISAvienna Konferenz: In-vitro Diagnostika & IVDR
21. Oktober 2020

Dr. Uwe Oelmueller, SPIDIA4P Coordinator, QIAGEN GmbH

www.spidia.eu

New Technologies and Standards for Pre-analytical Workflows

SPIDIA – FP7 (2008 – 2013)

- ⇨ 16 Partners
- New technologies for sample collection, stabilization, processing, transport, storage (Blood, Tissues)
- 9 EU CEN Standards

SPIDIA4P – H2020 (2017 – 2020)

- ⇨ 19 Partners
- ⇨ 14 associated consortia & stakeholder organizations
- 13 additional new CEN & ISO Standards
- EQAs
- European and International implementation
- ⇨ **Project has received several awards**

www.spidia.eu ⇨ **Subscribe the Newsletter!**

The SPIDIA project has received funding under the Seventh Research Framework Program of the European Union, FP7-HEALTH-2007-1.2.5, under grant agreement no. 222916. The SPIDIA4P project receives funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 733112.

Deficiencies in Routine Healthcare and Research demand for Improvements

- Diagnostic errors cause about 10% of all patient deaths and about 17% of adverse events

  Institute of Medicine (IOM) Report Sept. 2015

- Pre-analytical phase accounts for 46% to 68% of clinical laboratory errors

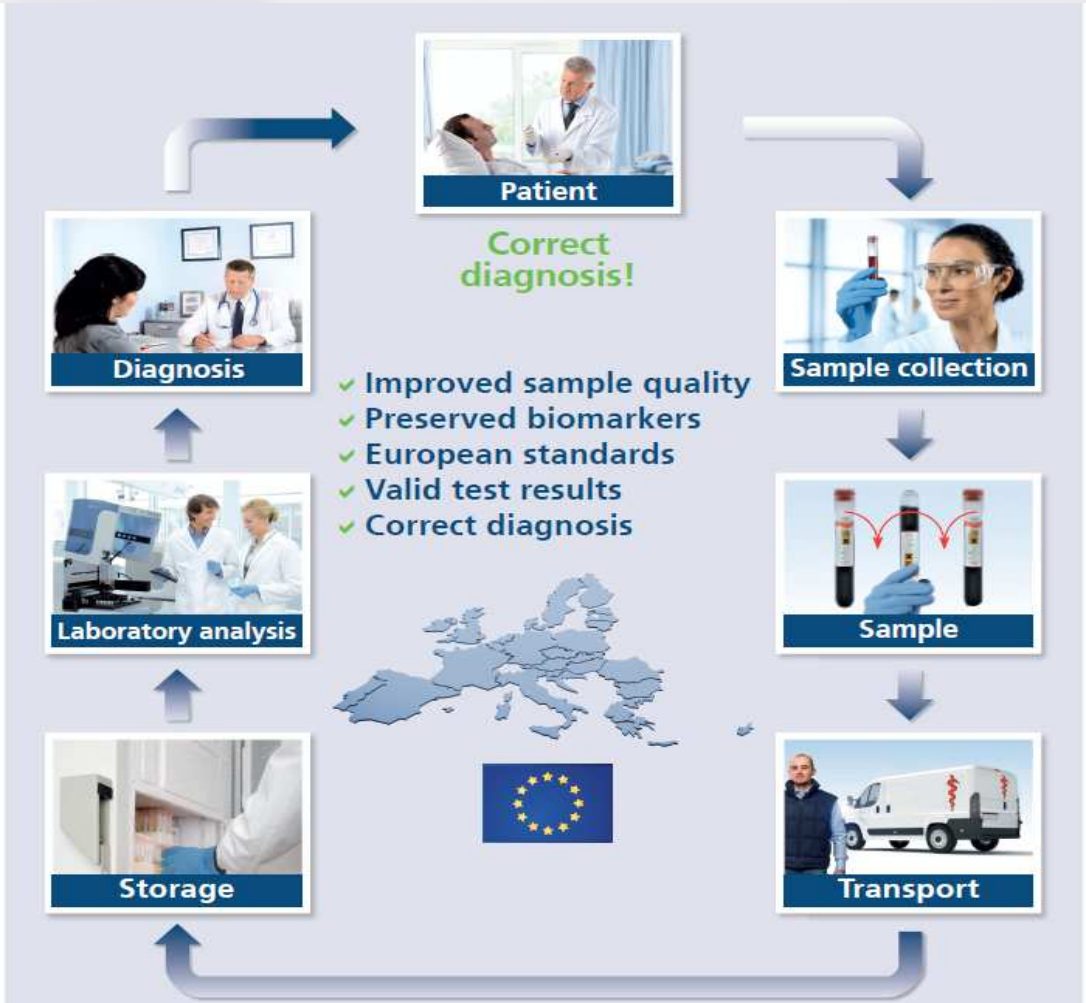
  Medical Laboratory Observer, May 2014

- Irreproducible preclinical research exceeds 50%, US $28B / year spent on preclinical research that is not reproducible - in the US

  Freedman LP, Cockburn IM, Simcoe TS (2015) PLoS Biol 13(6): e1002165.doi:10.1371/journal.pbio.1002165

SPIDIA4P

An Analytical Test Result is the Result of an Entire Workflow

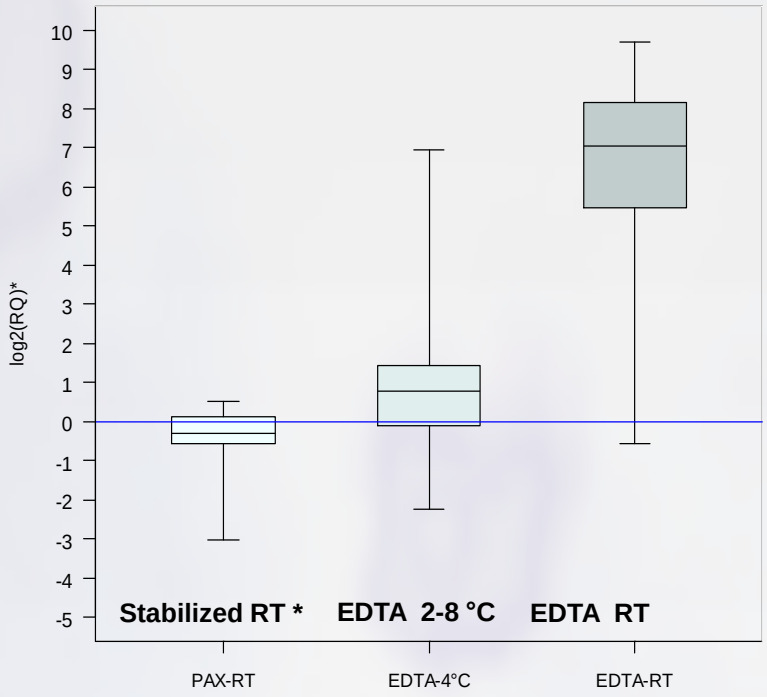


Specifying, developing and verifying preanalytical workflows is an essential part of analytical test development

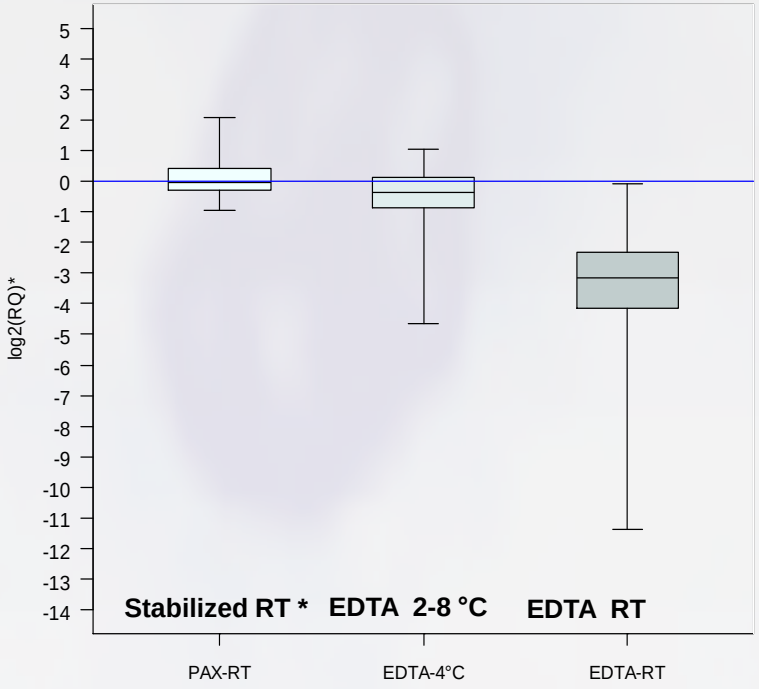
European Conference. Standards: Your Innovation Bridge. Brussels (2014). SPIDIA Booth.

Pan-European Ring Trial
Changes of Blood Cellular RNA Profile: 48 Hours After Collection

Up-regulated FOSB mRNA level



Down-regulated TNFRS mRNA level

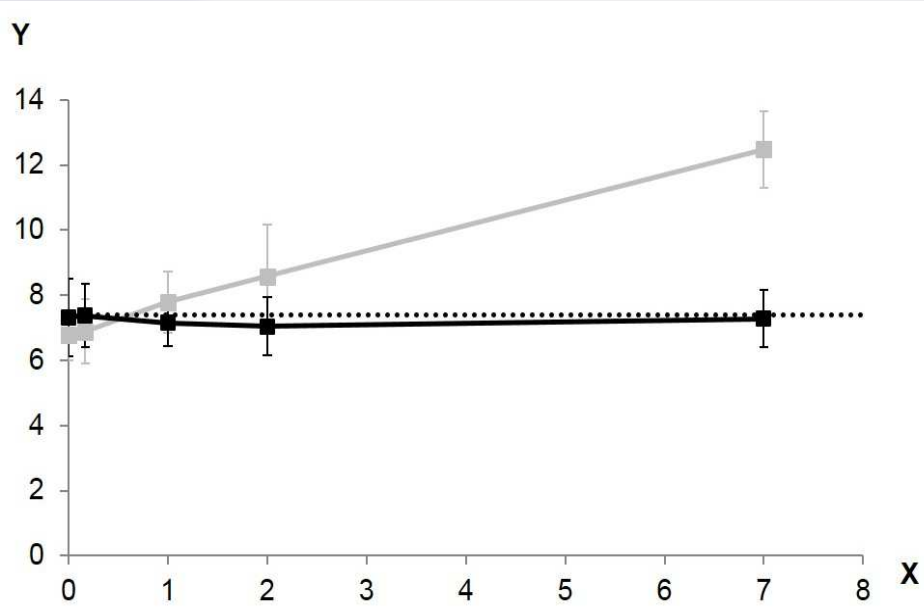


* PAXgene Blood RNA Tube

Malentacchi F et al. (2014). SPIDIA-RNA: Second External Quality Assessment for the Pre-Analytical Phase of Blood Samples Used for RNA Based Analyses. PLoS ONE 9(11): e112293.

Zhan H et al. (2014). Biomarkers for Monitoring Pre-Analytical Quality Variation of mRNA in Blood Samples. . PLoS ONE 9(11): e111644.

Post Blood Collection ccfDNA Profile Changes - Impact on EGFR Test



X venous whole blood storage duration (in days) before plasma preparation

Y ΔCT = CT (mutant) - CT (wildtype control)

EDTA Blood

Stabilized Blood

Threshold (given by the examination provider)

The average of 8 donors is shown

- Spiked restriction enzyme treated EGFR DNA with mutation T790M, equivalent to 200 copies
- ccfDNA tested with the commercially available EGFR Plasma PCR Kit (RUO)

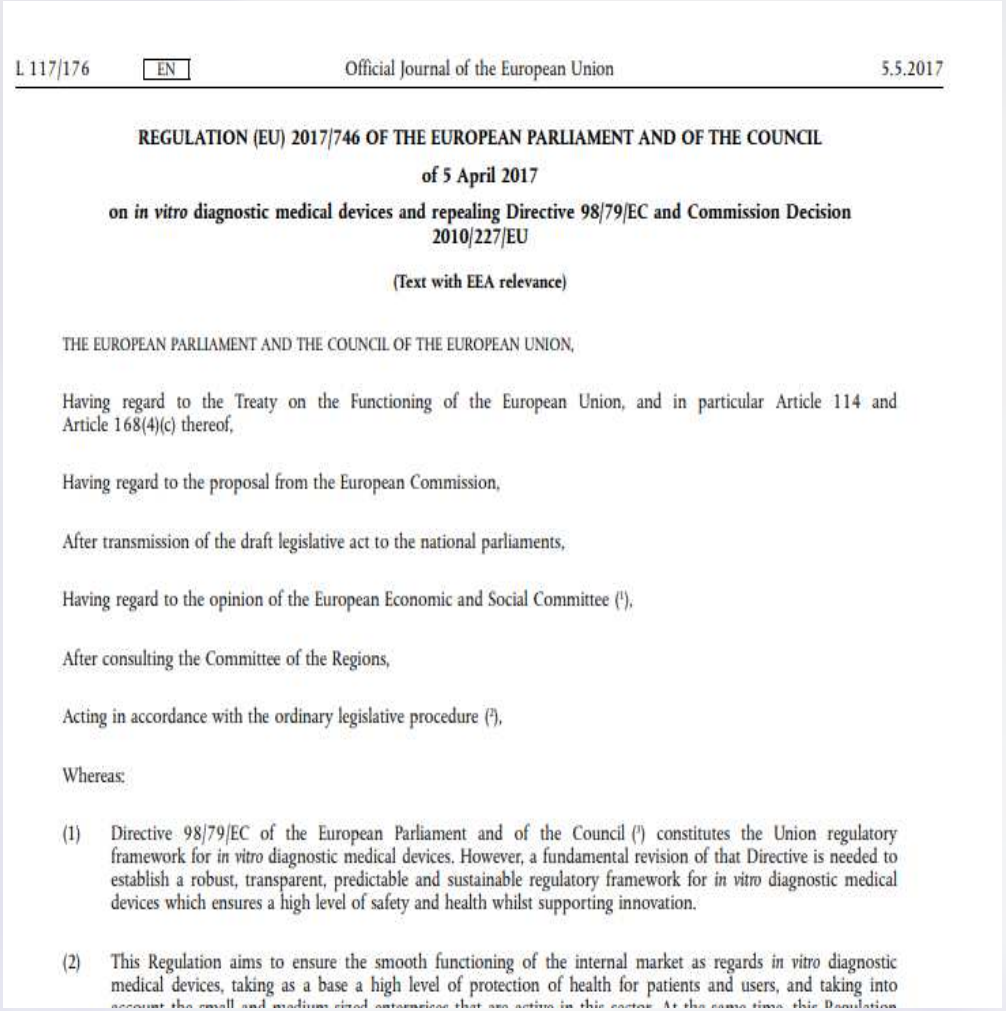
ISO 20186-3:2019
Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 3: Isolated circulating cell free DNA from plasma. Annex A.

German Public Service TV SRW: Varying Test Results between Laboratories Causing Wrong Diagnosis and Treatment

https://www.swr.de/wissen/odysso/Blut-Untersuchung-Missstand-bei-Bluttests,aexavarticle-swr-77780.html

SWR - Juni 2019

New EU In Vitro Diagnostic Medical Device Regulation (IVDR)



L 117/176 EN Official Journal of the European Union 5.5.2017

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee [1],

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure [2],

Whereas:

(1) Directive 98/79/EC of the European Parliament and of the Council [3] constitutes the Union regulatory framework for *in vitro* diagnostic medical devices. However, a fundamental revision of that Directive is needed to establish a robust, transparent, predictable and sustainable regulatory framework for *in vitro* diagnostic medical devices which ensures a high level of safety and health whilst supporting innovation.

(2) This Regulation aims to ensure the smooth functioning of the internal market as regards *in vitro* diagnostic medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the small and medium sized enterprises that are active in this sector. At the same time, this Regulation

- entered into force on 26 May 2017
- will replace the EU's current Directive on in vitro diagnostic medical devices (98/79/EC)
- transition period until 26 May 2022

New EU IVDR – Preanalytical Workflow Requirements

⇨ New pre-analytical workflow requirements are backed-up by strong scientific evidence

➢ Pre-analytical workflow parameters in several sections

- 6. PRODUCT VERIFICATION AND VALIDATION (Annex II)
- 6.1. Information on analytical performance of the device
- 6.1.1. Specimen type

This Section shall describe the different specimen types that can be analysed, including their stability such as storage, where applicable specimen transport conditions and, with a view to time-critical analysis methods, information on the timeframe between taking the specimen and its analysis and storage conditions such as duration, temperature limits and freeze/thaw cycles

QIAGEN *therascreen*® PIK3CA RGQ PCR Assay – FDA cleared

May 2019

therascreen® PIK3CA RGQ PCR Kit Instructions for Use (Handbook)

Σ 24

Version 1

IVD

For in vitro diagnostic use

Rx only (For prescription use only)

For use with Rotor-Gene® Q MDx (US) instrument

For use with QIAamp® DSP DNA FFPE Tissue Kit

For use with QIAamp® Circulating Nucleic Acid Kit

REF 873121

QIAGEN GmbH, QIAGEN Strasse 1, 40724 Hilden, Germany

R1 MAT 1115877EN

Sample to Insight

QIAGEN

- FDA approved in 2019: CDx test

  Presence of PIK3CA mutations in cancer tissue or plasma from patients with breast cancer is linked with response to treatment with Piqray® (alpelisib) / Novartis

➢ Preanalytical workflow parameters are specified and verified as part of the cleared test

⇨ Example: Collection and storage duration:

Whole peripheral venous blood collected in K_2EDTA blood collection tubes must be processed to obtain plasma within four hours of blood collection. Failure to do so may result in genomic DNA contamination of the sample. For further information on the isolation of plasma from whole blood, refer to Appendix A of the *QIAamp DSP Circulating Nucleic Acid Kit Handbook*.

Good Quality Specimen are a Prerequisite for Reliable Diagnostic Industry Research and Product Development

- Specimen with unbiased bioanalyte profiles
- Specimen pre-analytical parameter documentation required
  - o specimens suitability for research, verification and validation studies including clinical trials
- Specimen collection and pre-analytical processing according to ISO and CEN standards ⇨ broad international consensus

⇨ specimen with well documented pre-analytical parameters difficult to get

- o force industry to own prospective collections

Highly Consensus Driven Process for Developing Standards

- **CEN**
  - Recognized by the EU and the European Free Trade Association (EFTA) as being **responsible for developing standards at European level**
  - Development of a European Standard (EN) or International Standard (ISO) is governed by the principles of **consensus, openness, transparency, national commitment** and **technical coherence**

- **CEN/TC 140** (Committee for in vitro diagnostic medical devices)
  - **34 EU countries National Standards Bodies** ⇨ One European Standard replaces 34 national standards
  - **11 Stakeholder organizations in liaison**

- **ISO/TC 212** (Committee for Clinical Laboratory Testing and in vitro Diagnostic Test Systems)
  - **44 member countries, 23 observing members,**
  - **23 organizations in liaison (incl. WHO, OECD, IFCC, ILAC, European Commission . . .)**

Pre-analytical Workflow - Same Standards for all Segments and the entire Innovation & Development Chain

- **Biobanks**
  - Source for good quality samples ⇨ required for biomarker & analytical test development
- **Biomedical & Translational Research**
  - Academia
  - Pharma industry
  - Diagnostic Industry
- **Diagnostics**
  - High sample quality is the safe way
  - Analytical assay might tolerate lower quality or not ⇨ Verification studies

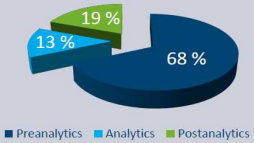
SPIDIA's Road to Standardization

under Vienna Agreement (1991)

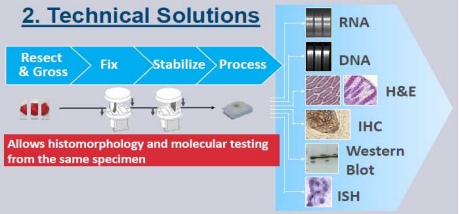
- 2019: 8 ISO/International Standards
- 2014: 8 new projects for ISO Standards approved in ISO/TC 212 „*Clinical laboratory testing and in vitro diagnostic test systems*"

- 2015: 9 CEN Technical Specifications published
- 2013: 9 new projects approved in CEN/TC 140 „*In vitro diagnostic medical devices*"
- 2010: Start of standardization work

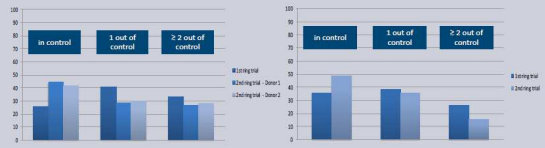
1. Problem - Errors in Diagnostics



2. Technical Solutions



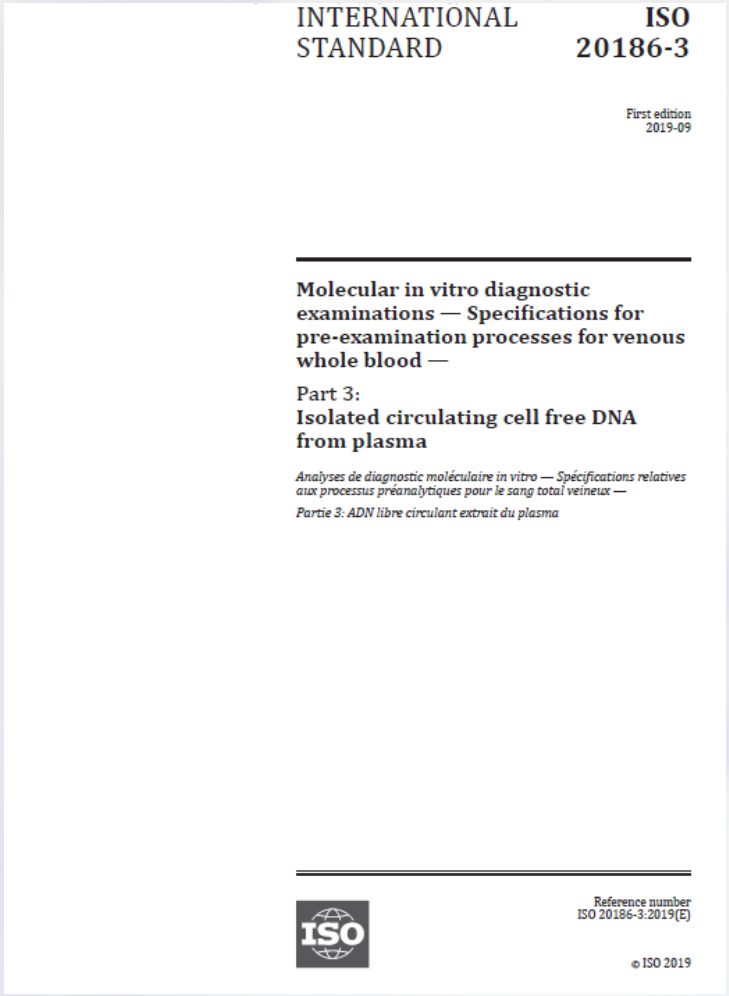
3. Ring-Trials – Blood RNA (l.) and DNA (r.)



SEVENTH FRAMEWORK PROGRAMME

European Conference. Standards: Your Innovation Bridge. Brussels (2014). SPIDIA Booth.

22 CEN & ISO Standard Documents and EQAs by 2021



INTERNATIONAL STANDARD **ISO 20186-3**

First edition
2019-09

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood —

Part 3:
Isolated circulating cell free DNA from plasma

Analyses de diagnostic moléculaire in vitro — Spécifications relatives aux processus préanalytiques pour le sang total veineux —

Partie 3: ADN libre circulant extrait du plasma

Reference number
ISO 20186-3:2019(E)

© ISO 2019

- Molecular in-vitro diagnostic examinations - Specifications for **pre-examination processes** for
  - **Blood** — Cellular RNA, gDNA, ccfDNA, ccfRNA
  - **Blood** – Exosomes, ccfRNA
  - **Blood Tumor Cells** – DNA, RNA, staining
  - **Tissue** (FFPE) — DNA, RNA, Proteins
  - **Tissue** (Frozen) – RNA, Proteins, DNA
  - **Tissue** (FFPE) – in situe staining
  - **Fine Needle Aspirates** – DNA, RNA, Proteins
  - **Saliva** – DNA
  - **Urine & Body Fluids** – cfDNA
  - **Metabolomics** – Urine, Serum, Plasma
  - **Microbiome** – Stool, Saliva etc.

published CEN published ISO in development

ISO 20186-3 – Pre-examination Processes for Blood ccfDNA

Contents

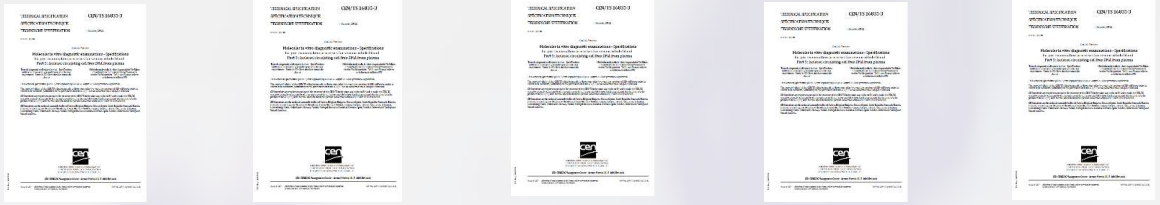
Example:

ISO 20186-3:2019 - Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 3: Isolated circulating cell free DNA from plasma

Role of Legislation, Standards, SOPs and Technologies

New EU IVDR – in-vitro Diagnostic Device Regulation 2017

Pre-analytical workflow parameters



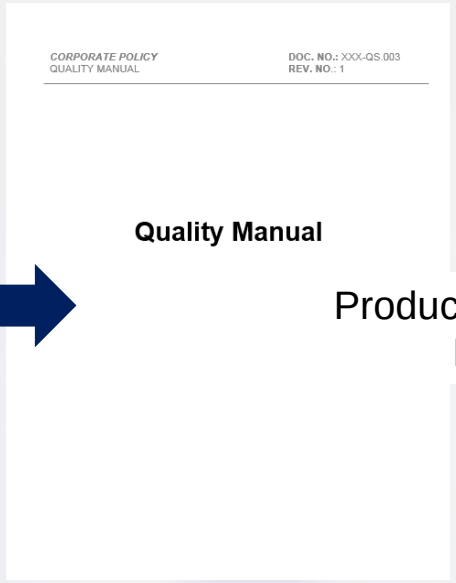
EN ISO & CEN Standards

SOPs

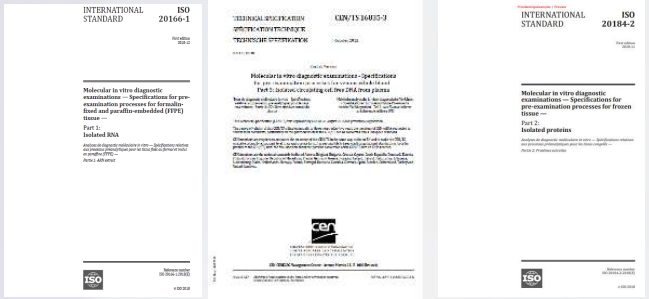
Technologies & Products

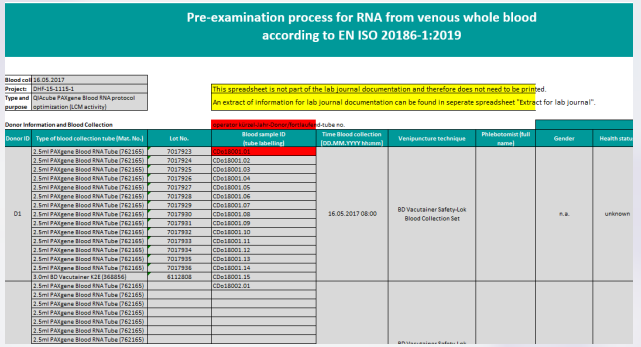
Implementation of Preanalytical Standards

Example: QIAGEN and PreAnalytiX (QIAGEN/BD Company)



Product Development Process





Certification according to ISO 13485

Company Quality Manual: Process Landscape

Global Process SOPs incl. legal requirements

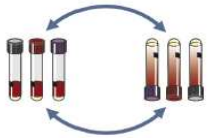
Technical SOPs for pre-analytical workflows based on ISO & CEN standards

PreAnalytiX and QIAGEN: Own Blood Collections for R&D Projects according to ISO 20186 series

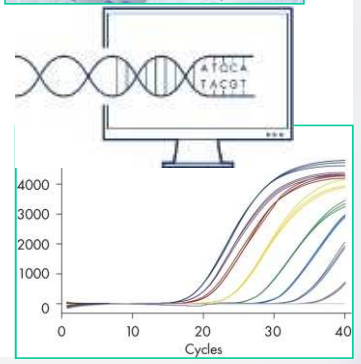
- ISO 20186:2019 parts 1-3 implemented and translated into SOPs in MasterControl System (change control)
  - *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood - . . .*
    - *. . . Part 1: Blood Cellular RNA*
    - *. . . Part 2: Blood Genomic DNA*
    - *. . . Part 3: Blood ccfDNA*
- Physicians, laboratory staff and other relevant functions trained
- Blood specimen for R&D projects including verification and validation for IVDs are collected according to ISO 20186

Pre-analytical Steps: Part of a Whole Diagnostic Test Workflow

Tube

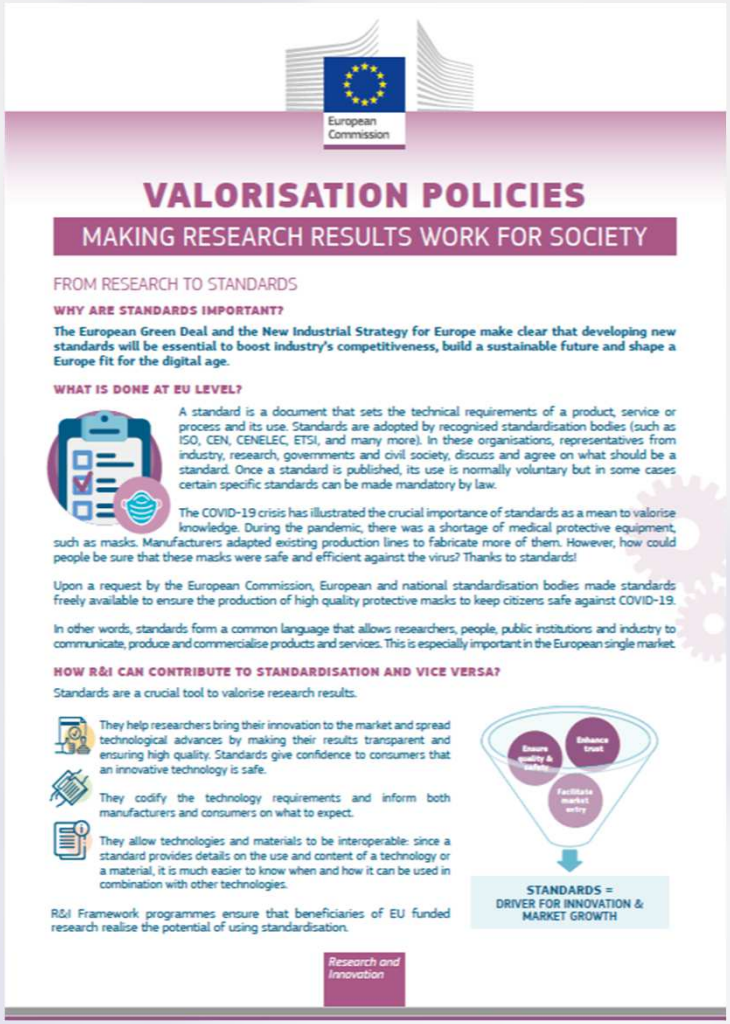


Kit



Specimen Collection & Stabilization → Storage Transport → Sample Processing → Analyte Isolation → Analytical Test → Data Analysis

Standards ensure Quality & Safety, Facilitate Market Entry and Enhance Trust



European Commission

VALORISATION POLICIES

MAKING RESEARCH RESULTS WORK FOR SOCIETY

FROM RESEARCH TO STANDARDS

WHY ARE STANDARDS IMPORTANT?

The European Green Deal and the New Industrial Strategy for Europe make clear that developing new standards will be essential to boost industry's competitiveness, build a sustainable future and shape a Europe fit for the digital age.

WHAT IS DONE AT EU LEVEL?

A standard is a document that sets the technical requirements of a product, service or process and its use. Standards are adopted by recognised standardisation bodies (such as ISO, CEN, CENELEC, ETSI, and many more). In these organisations, representatives from industry, research, governments and civil society, discuss and agree on what should be a standard. Once a standard is published, its use is normally voluntary but in some cases certain specific standards can be made mandatory by law.

The COVID-19 crisis has illustrated the crucial importance of standards as a mean to valorise knowledge. During the pandemic, there was a shortage of medical protective equipment, such as masks. Manufacturers adapted existing production lines to fabricate more of them. However, how could people be sure that these masks were safe and efficient against the virus? Thanks to standards!

Upon a request by the European Commission, European and national standardisation bodies made standards freely available to ensure the production of high quality protective masks to keep citizens safe against COVID-19.

In other words, standards form a common language that allows researchers, people, public institutions and industry to communicate, produce and commercialise products and services. This is especially important in the European single market.

HOW R&I CAN CONTRIBUTE TO STANDARDISATION AND VICE VERSA?

Standards are a crucial tool to valorise research results.

They help researchers bring their innovation to the market and spread technological advances by making their results transparent and ensuring high quality. Standards give confidence to consumers that an innovative technology is safe.

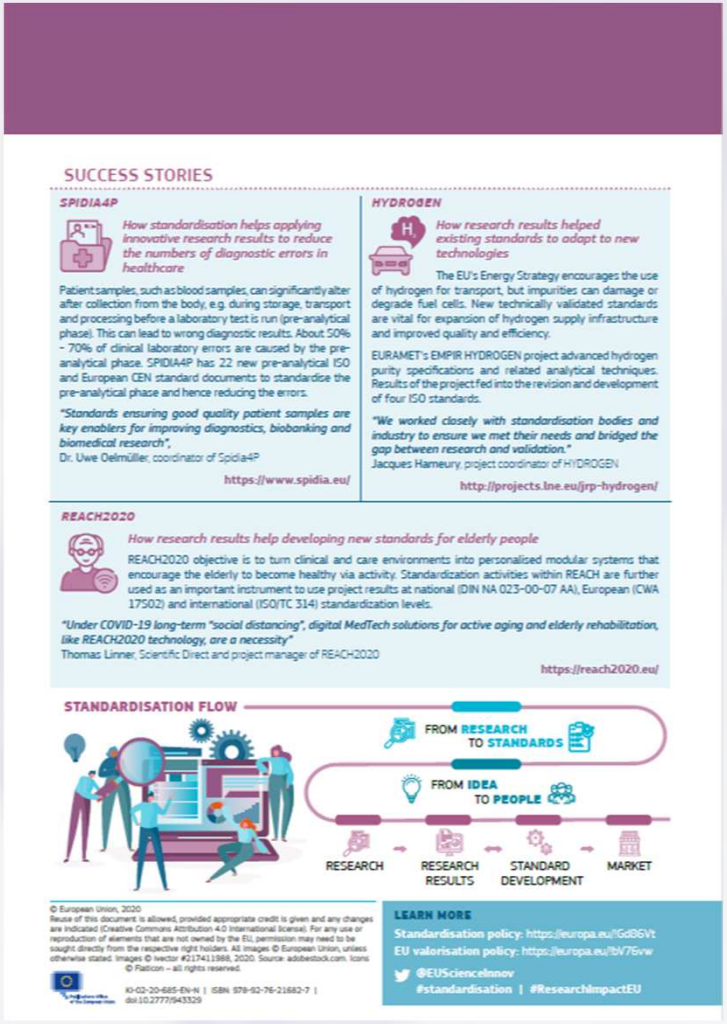
They codify the technology requirements and inform both manufacturers and consumers on what to expect.

They allow technologies and materials to be interoperable: since a standard provides details on the use and content of a technology or a material, it is much easier to know when and how it can be used in combination with other technologies.

R&I Framework programmes ensure that beneficiaries of EU funded research realise the potential of using standardisation.

STANDARDS = DRIVER FOR INNOVATION & MARKET GROWTH

Research and Innovation



SUCCESS STORIES

SPIDIA4P

How standardisation helps applying innovative research results to reduce the numbers of diagnostic errors in healthcare

Patient samples, such as blood samples, can significantly alter after collection from the body, e.g. during storage, transport and processing before a laboratory test is run (pre-analytical phase). This can lead to wrong diagnostic results. About 50% - 70% of clinical laboratory errors are caused by the pre-analytical phase. SPIDIA4P has 22 new pre-analytical ISO and European CEN standard documents to standardise the pre-analytical phase and hence reducing the errors.

"Standards ensuring good quality patient samples are key enablers for improving diagnostics, biobanking and biomedical research",
Dr. Uwe Oelmüller, coordinator of Spidia4P

https://www.spidia.eu/

HYDROGEN

How research results helped existing standards to adapt to new technologies

The EU's Energy Strategy encourages the use of hydrogen for transport, but impurities can damage or degrade fuel cells. New technically validated standards are vital for expansion of hydrogen supply infrastructure and improved quality and efficiency.

EURAMET's EMPIR HYDROGEN project advanced hydrogen purity specifications and related analytical techniques. Results of the project fed into the revision and development of four ISO standards.

"We worked closely with standardisation bodies and industry to ensure we met their needs and bridged the gap between research and validation."
Jacques Hameury, project coordinator of HYDROGEN

http://projects.lne.eu/jrp-hydrogen/

REACH2020

How research results help developing new standards for elderly people

REACH2020 objective is to turn clinical and care environments into personalised modular systems that encourage the elderly to become healthy via activity. Standardization activities within REACH are further used as an important instrument to use project results at national (DIN NA 023-00-07 AA), European (CWA 17502) and international (ISO/TC 314) standardization levels.

"Under COVID-19 long-term "social distancing", digital MedTech solutions for active aging and elderly rehabilitation, like REACH2020 technology, are a necessity"
Thomas Linner, Scientific Direct and project manager of REACH2020

https://reach2020.eu/

STANDARDISATION FLOW

KI-02-20-685-EN-N | ISBN 978-92-76-21682-7 | doi:10.2777/943329

LEARN MORE

Standardisation policy: https://europa.eu/!Gd86Vt
EU valorisation policy: https://europa.eu/!bV76vw

@EUScienceInnov
#standardisation | #ResearchImpactEU

Fact Sheet on Standards published by the European Commission on World Standards Day on 14th October

SPIDIA4P as one the EC's 3 success stories.

https://ec.europa.eu/info/sites/info/files/research_and_innovation/strategy_on_research_and_innovation/documents/ec_rtd_valorisation-policies_factsheet.pdf

A big Thank You goes to . . .

. . . to the SPIDIA & SPIDIA4P Consortium Members, CEN/TC 140, ISO/TC 212 and all European and International Partners!

www.spidia.eu **- New Website**

SPIDIA4P

Thank you!

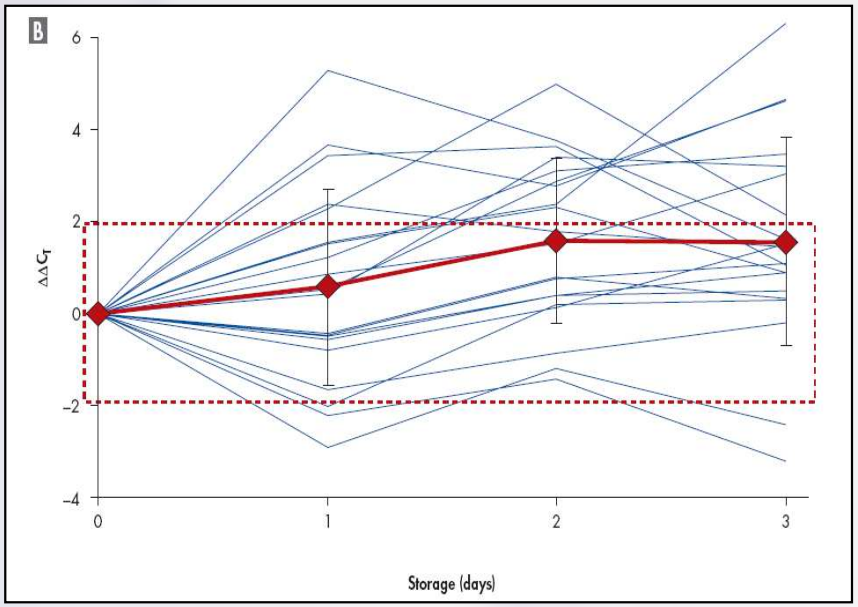
Questions ?

Back Up Slides

Blood RNA Quality Marker Discovery

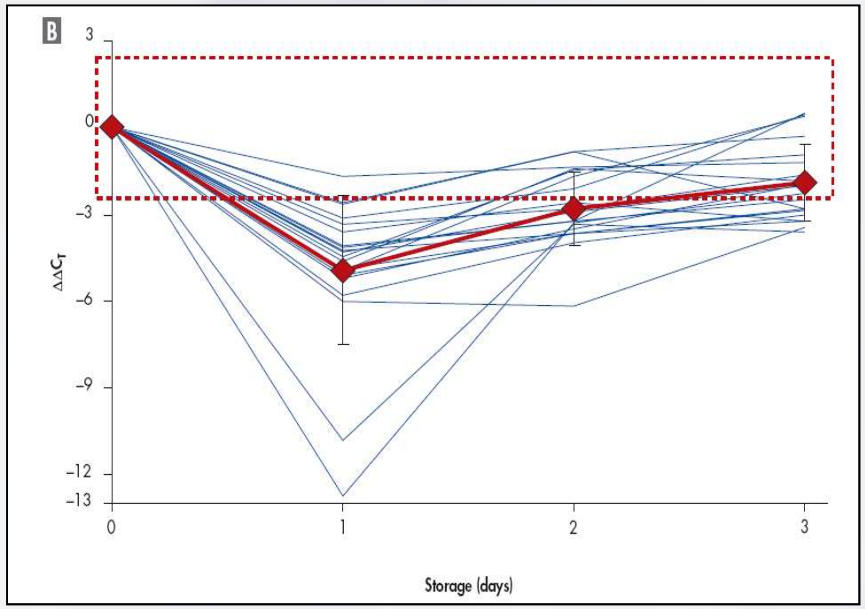
Challenge are Individual Sample Kinetics

Human EDTA Blood stored at Room Temperature over 3 days



IL-1β **mRNA**

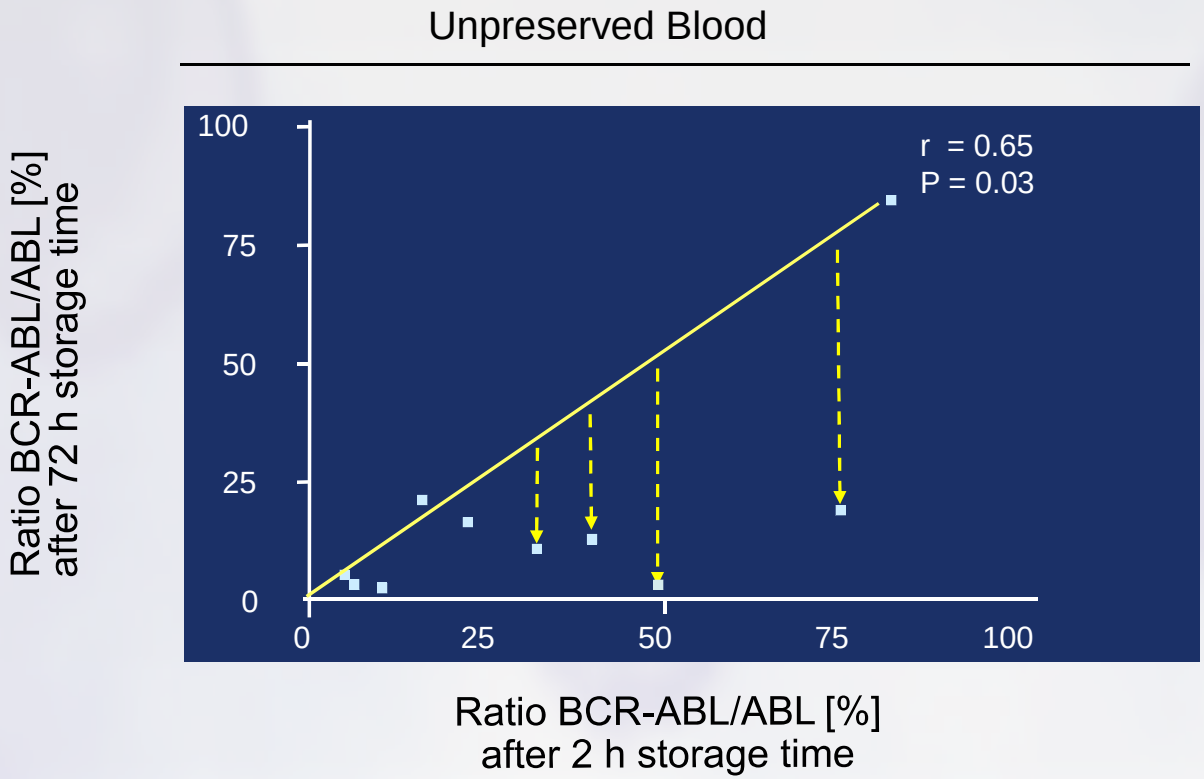
Guenther K. et al.. AMP Poster (2005)



c-fos mRNA

Guenther K. et al..CLI 5, 26-28 (2008)

Leukemia Therapy Monitoring Research Study
Blood Transcripts BCR-ABL / ABL Ratio in EDTA Tubes



Transcripts Ratio
BCR-ABL / ABL
significantly changed after 72 h of
room temperature shipment / storage

Source: Mueller et al. (2002). Leukemia 16 (12), pp. 2395-9.

Highly Consensus Driven Process for Developing Standards

CEN

- Recognized by the EU and the European Free Trade Association (EFTA) as being **responsible for developing standards at European level**
- Development of a European Standard (EN) or International Standard (ISO) is governed by the principles of **consensus, openness, transparency, national commitment** and **technical coherence**
- One European Standard replaces 34 national standards

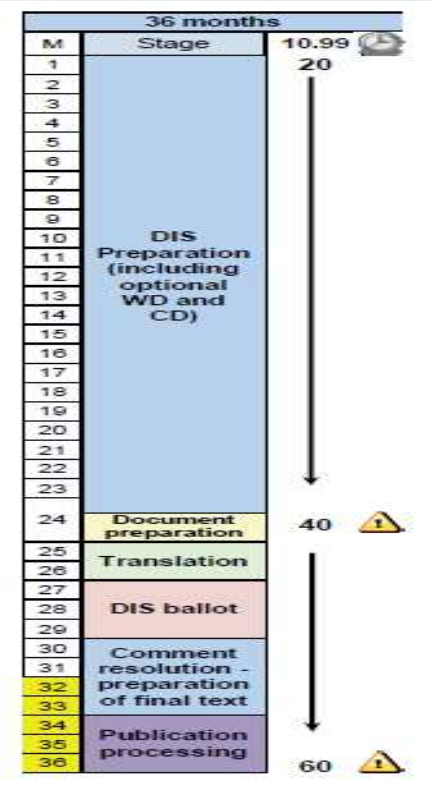
CEN/TC 140 (Committee for in vitro diagnostic medical devices)

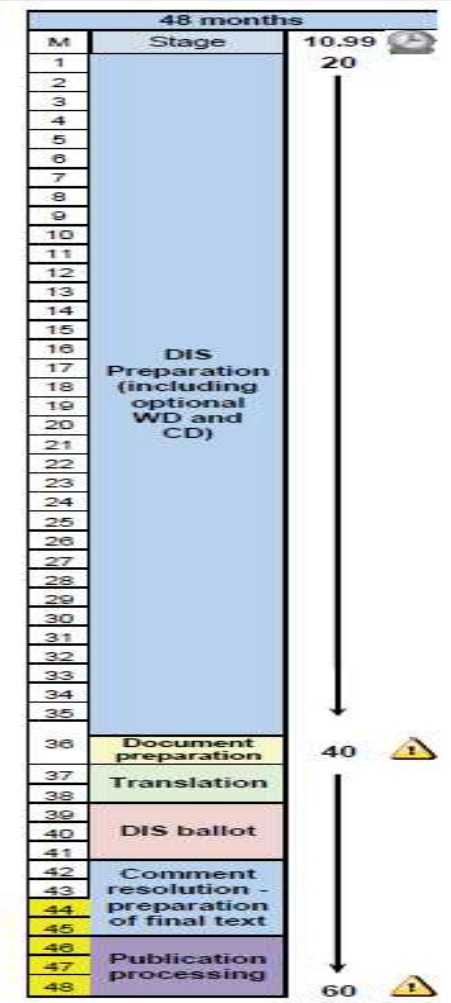
- **34 EU countries National Standards Bodies (NSB)**
- **Stakeholders in liaison & cooperations**
  - **European Commission** (EC), **ESP** (European Society of Pathology), **EFLM** (European Federation of Laboratory Medicine), **IFCC** (Int. Federation of Clinical Chemistry and Laboratory Medicine), **JISC** (Japanese Industrial Standards Committee), **MedTech Europe** (Alliance of European medical technology industry associations), **EPBS** (European Association for Professions in Biomedical Science), **BBMRI-ERIC** (Biobanking and BioMolecular resources Research Infrastructure - European Research Infrastructure Consortium), **ISO/TC 212** (Clinical laboratory testing and in vitro diagnostic test systems), **ISO/TC 276** Biotechnology

ISO/IS Development – Usually a 36 to 48 Months Period

ISO/TC 212

- Technical Committee for Clinical Laboratory Testing and in vitro Diagnostic Test Systems
- 44 member countries, 23 observing members, 23 organizations in liaison (incl. WHO, OECD, IFCC, ILAC, European Commission . . .)





Source: https://www.iso.org/files/live/sites/iso org/files/developing_standards/docs/ en/Target_date_planner_4_ISO_stan dards_development_tracks_2017.pdf

Twofold Role of Standardization

Traditional Role of Standards

- Source of technical know-how
- Trade facilitation and opening of markets
- Providing a scientific basis for legislation in the health, safety and environment sectors

Valued-added role for research and innovation

- Speeding up innovation by providing the requisite knowledge base (technology transfer)

➢ New ideas, technologies and products benefit from standardization to get into the marketplace and to be successful

Source: Gindele 2013
http://www.iso.org/iso/home/about/conformity-assessment.htm

Largest Consortia Network for Pre-analytics in Community

⇨ Tech Developments, Standards, EQAs, Implentation, Consulting, Education