International Medical Device Regulation and Harmonization

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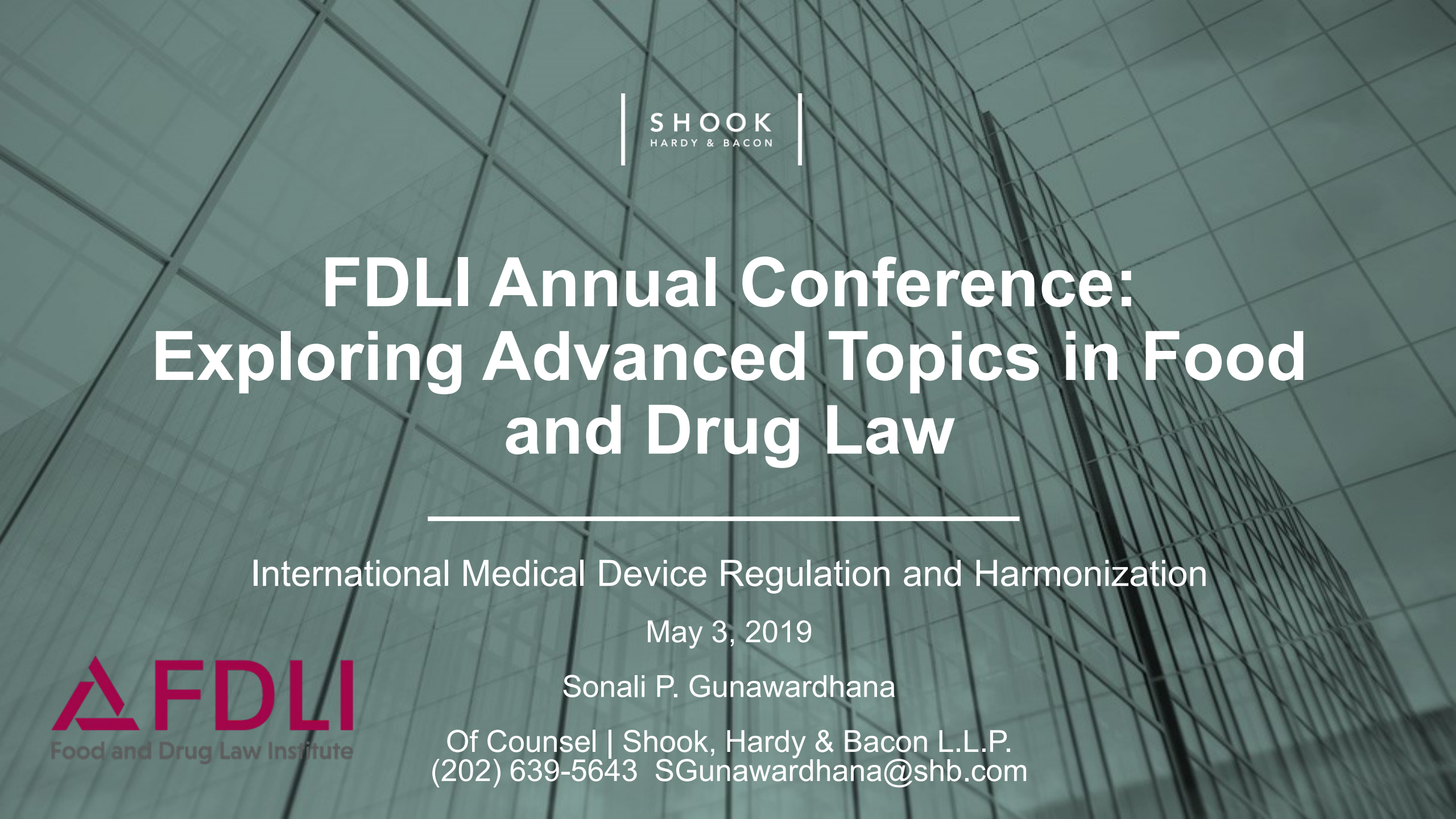

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FDLI Annual Conference: Exploring Advanced Topics in Food and Drug Law

International Medical Device Regulation and Harmonization

May 3, 2019

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Medical Device Single Audit Program

(MDSAP)

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Brief History

- The International Medical Device Regulators Forum (IMDRF) recognizes that a global approach to auditing and monitoring the manufacturing of medical devices could improve their safety and oversight on an international scale.
- The Medical Device Single Audit Program allows an MDSAP recognized Auditing Organization to conduct a single regulatory audit of a medical device manufacturer that satisfies the relevant requirements of the regulatory authorities participating in the program.

What is MDSAP?

- The Medical Device Single Audit Program (MDSAP) is a program that allows the conduct of a single regulatory audit of a medical device manufacturer's quality management system that satisfies the requirements of multiple regulatory jurisdictions. Audits are conducted by Auditing Organizations authorized by the participating Regulatory Authorities to audit under MDSAP requirements.
- International Partners:
  - US Food and Drug Administration (FDA)
  - Therapeutic Goods Administration of Australia (TGA)
  - Brazil's Agência Nacional de Vigilância Sanitária (ANVISA)
  - Health Canada
  - Japan's Ministry of Health, Labour and Welfare, and the Japanese Pharmaceuticals and Medical Devices Agency (MHLW)
  - *The World Health Organization (WHO) Prequalification of In Vitro Diagnostics (IVDs) Programme and the European Union (EU) are Official Observers

Pilot Program

- From January 2014 to December 2016, the international partners participated in the Medical Device Single Audit Program Pilot.
- On 29 June 2017, a report was generated summarizing the outcomes of prospective “proof-of-concept” criteria established to confirm the viability of the Medical Device Single Audit Program.
- The outcomes documented in the Final MDSAP Pilot Report are based on data generated during the three (3) year pilot, in which the MDSAP Regulatory Authority Council determined that the MDSAP Pilot had satisfactorily demonstrated the viability of the Medical Device Single Audit Program.

FDA's Continued Participation Today

- FDA will continue to accept MDSAP audit reports as a substitute for routine Agency inspections.
  - MDSAP routine audits are announced, scheduled by the Auditing Organization with the manufacturer, with a pre-established duration;
  - The FDA will review MDSAP audit reports with a level of scrutiny commensurate to the significance of audit findings, taking into account the review and follow-up performed by the Auditing Organization;
  - Firms have one month to provide their full response to critical nonconformities (grade 4 and 5) to the Auditing Organization (as opposed to 15 working days following and FDA inspection);
  - Certification documents issued by the Auditing Organization state compliance with applicable US regulations, which may provide a marketing advantage.
    - ***Inspections conducted "For Cause" or "Compliance Follow-up" by FDA will not be affected by this program. Moreover, this MDSAP program would not apply to any necessary pre-approval or post approval inspections for Premarket Approval applications or to decisions under section 513(f)(5) of the Act (21 U.S.C.360c(f)(5)) concerning the classification of a device.***

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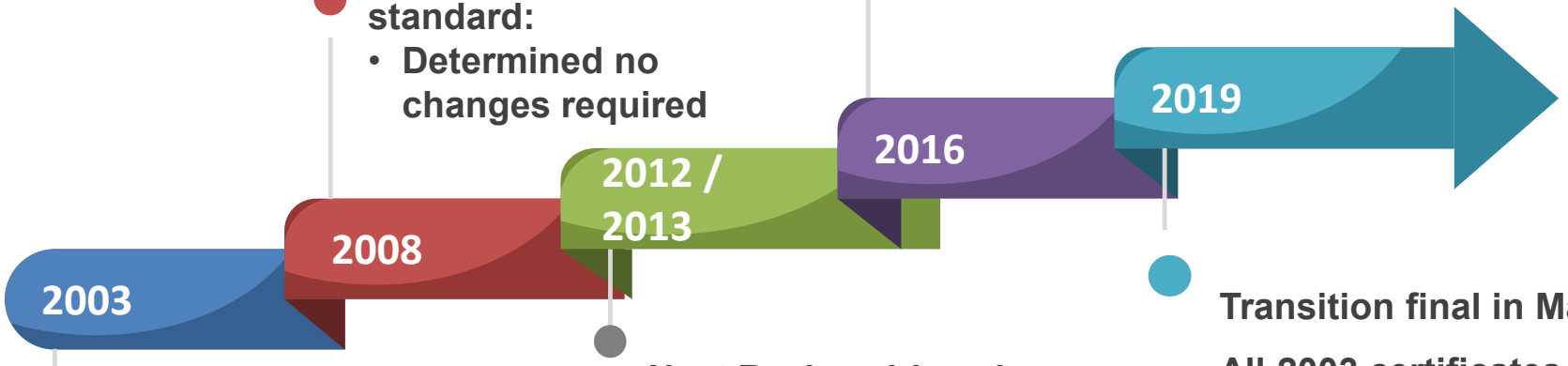
Validant

VALIDANT
Vital in healthcare

ISO 13485:2016 versus 21 CFR Part 820

- International manufacturers have long struggled to maintain compliance to both 21 CFR Part 820 for US products, and ISO 13485 for the EU market and many ROW markets
  - Requirements differences
  - Terminology differences
  - Oversight differences
- The US first signaled a change in policy by participating in the ISO 13485 Voluntary Audit Report Submission Pilot Program
- Evolved into Medical Device Single Audit Program (MDSAP)

ISO13485: A Timeline



First update to the 1996 standard

Second review of the standard:
- Determined no changes required

Next Review driven by need for:
- Clarity
- Global Harmonization
- EU Challenges

ISO13485:2016 Published March 2016

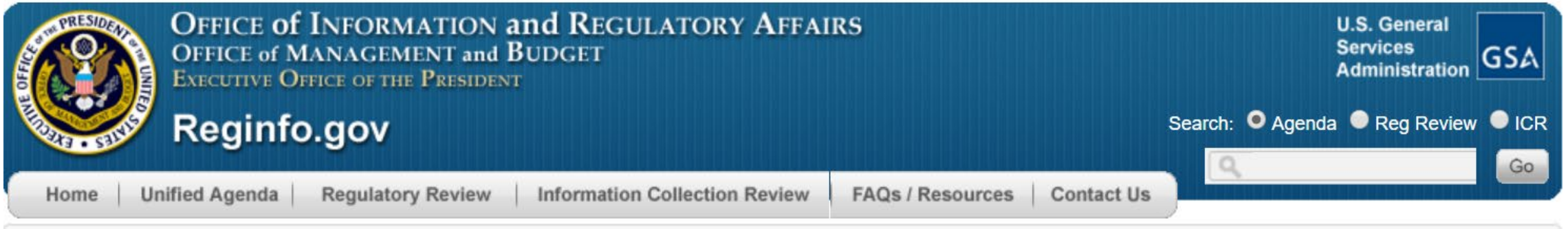
Transition final in March 2019

All 2003 certificates expired Feb 28, 2019

Backlog with some NB

Issues shipping and distributing 2003

Harmonizing and Modernizing Regulation of Medical Device Quality Systems



- "FDA intends to harmonize and modernize the Quality System regulation for medical devices. The revisions will supplant the existing requirements with the specifications of an international consensus standard for medical device manufacture, ISO 13485:2016. The revisions are intended to reduce compliance and recordkeeping burdens on device manufacturers by harmonizing domestic and international requirements. The revisions will also modernize the regulation."
- https://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201804&RIN=0910-AH99

FDA Transition to ISO 13485:2016

- Proposed rule - planned to be published in 2019
- AAMI Technical Information Report expected by mid-2019 – comparative analysis between Part 820 QSR and ISO 13485:2016
- FDA warns that transition may take several years
- Multiple challenges for implementation:
  - Training of FDA staff, investigators, and compliance officers
  - Updating guidance documents and other supplemental documentation
  - Revising the existing QSIT audit
- Drives FDA agenda for global convergence of medical device regulatory processes

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- **Medical Devices**
  - Federal Food, Drug, and Cosmetics Act
  - Regulation (EU) 2017/745
- **In Vitro Devices (IVDs)**
  - FDA Statutory Initiative
    - Diagnostic Accuracy and Innovation Act (DAIA)
    - Verifying Accurate Leading-Edge IVCT Development (VALID)
  - Regulation (EU) 2017/7456

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U.S. Medical Device Review

- Classification[1]
  - **Class I – self-designation under Part 862 - 892 regulation**
  - **Class II – § 510(k) premarket clearance as substantially equivalent to a predicate device**
  - **De novo 510(k) – product specific submission**
  - **Premarket Approval – valid scientific evidence**
- General Controls
  - **Adulteration/misbranding, standards, registration/listing, medical device adverse event reporting (MDRs), corrections/removals, recordkeeping/reports, uniform device identifiers (UDIs) in force.**
  - **Risk-based inspections**
    - Part 820 → MDSAP/IMDRF/ISO 13485

[1]Excludes certain software, special rules for re-processing, custom, and additional requirements for drug component of combination products

Regulation (EU) 2017/745 (Eff 5/26/20)

- **Notified Bodies (but EudaMed[1] for MDRs)**
  - **"Convergence" with IMDRF[2]**
- **Risk-based approach (Annex VIII Rules)**
  - **Class I – low (self-conformity with technical documentation on safety/ performance)**
  - **Class IIa – short-term invasive with body (other than wounds, surgery)**
    - **Newly-defined dossier comparable to typical nonclinical 510(k) (Annex II)**
  - **GCP clinical studies (retrospective due from 2020 through 2024)**
    - **Most Class IIb "active" (biological function/administers energy or meds)**
    - **Class III includes most long-term implantables (implant card)**
- **General Controls**
  - **Misbranding, standards, registration/devices, adverse events/deficiencies, corrections/field safety/recalls, UDIs by int'l standard starting 2021**
  - **ISO 13485 (Quality Management System including design – Annex IX)**

[1]Risk-based exemption from GDPR OJ C 358/10 7.12.2013
[2]Excludes certain software for life-style and well-being, "health institution" use, special rules for re-processing, custom, blood/tissue collection and storage devices, and collaborate with EMA on combination products with "actions" of "pharmacological, immunological or metabolic means" other than when "ancillary actions."

[2]Exemptions for "minimal eiakleft-over" specimens

IVDs – DAIA/VALID

- Definition[1]
  - Detects something in a human specimen
  - Validity requirements dependent on labeling
    - Analytical and clinical[2]
    - Highly flexible but excludes clinical utility
- General Controls (enhanced listing – CTIS)
- Categories (high-, grandfather, precert, rare, unmet)
- FDA Review

  - PMA, standards for validity, Special Rule, withdrawal

[1]Excludes certain software, analyte specific reagents ("component, part or raw material"), if also a biological products, custom, certain tests under "laboratory protocol", research/nonclinical use, additional requirements for companion diagnostics, and CLIA clarification.

[2]Exemptions for no substantial risk studies

Regulation (EU) 2017/746 (Eff 5/26/22)

- **Definition[1]**
  - "Examination of [human] specimens"
  - "Common specifications" based on int'l standards (Annex I)
    - Analytical and clinical performance[2] on ability to recognize or exclude target marker
    - Limited to "intended clinical benefit" (which could be "accurate medical information")
- **Same General Controls (UDI by November 2023)**
- **Classification (A, B, C, D in Annex VIII)**
  - A = reagents and procedural equipment (see analytic specific reagents)
  - D = transmissible agent and other blood tests
  - C = life-threatening disease, cancer, staging of disease and over-the-counter
  - B = all other
- **NB Conformity Assessment for B, C and D**
  - **Designation, D and sampling by Competent Authority**

[1]Excludes certain software for general well-being or medical records, general laboratory use, research only, single health institutions, and additional requirements for generic testing and companion diagnostics.

[2]Exemptions for studies that use "left-over" specimens