

Getting ready for the new European Medical Device Regulation

Paul Brooks, Executive Director, RAPS

RAPS Overview

- Established in 1976
- Non-political, independently funded, not-for-profit
- Headquartered in metro Washington, DC
- Chapters and affiliates throughout North America, Europe, Asia and Latin America

RAPS Mission

Develop and sustain a competent global regulatory workforce that drives good regulatory practice and policy to advance public health.

RAPS Members

- 24,000 individual members in 82 countries
- From industry, government, research, academic and clinical organizations
- Involved with medical devices, drugs, biologics, IVDs and other regulated healthcare products

EU MDR Context

- Directives in place since early 90s needed review
 - Some inconsistency in implementation of MDD
- Almost record length negotiations on MDR
- New regulations are demanding, but, not as dramatic as they could have been
- Brexit introduces potential complexity and duplication

EU MDR Current Status

- 30,000-foot view
 - Current practices and guidance
- Known knowns, known unknowns, unknown unknowns *(Donald Rumsfeld)*
- Stakeholders working together
- Identifying key challenges
- Many questions don't have all the answers
- No grandfathering

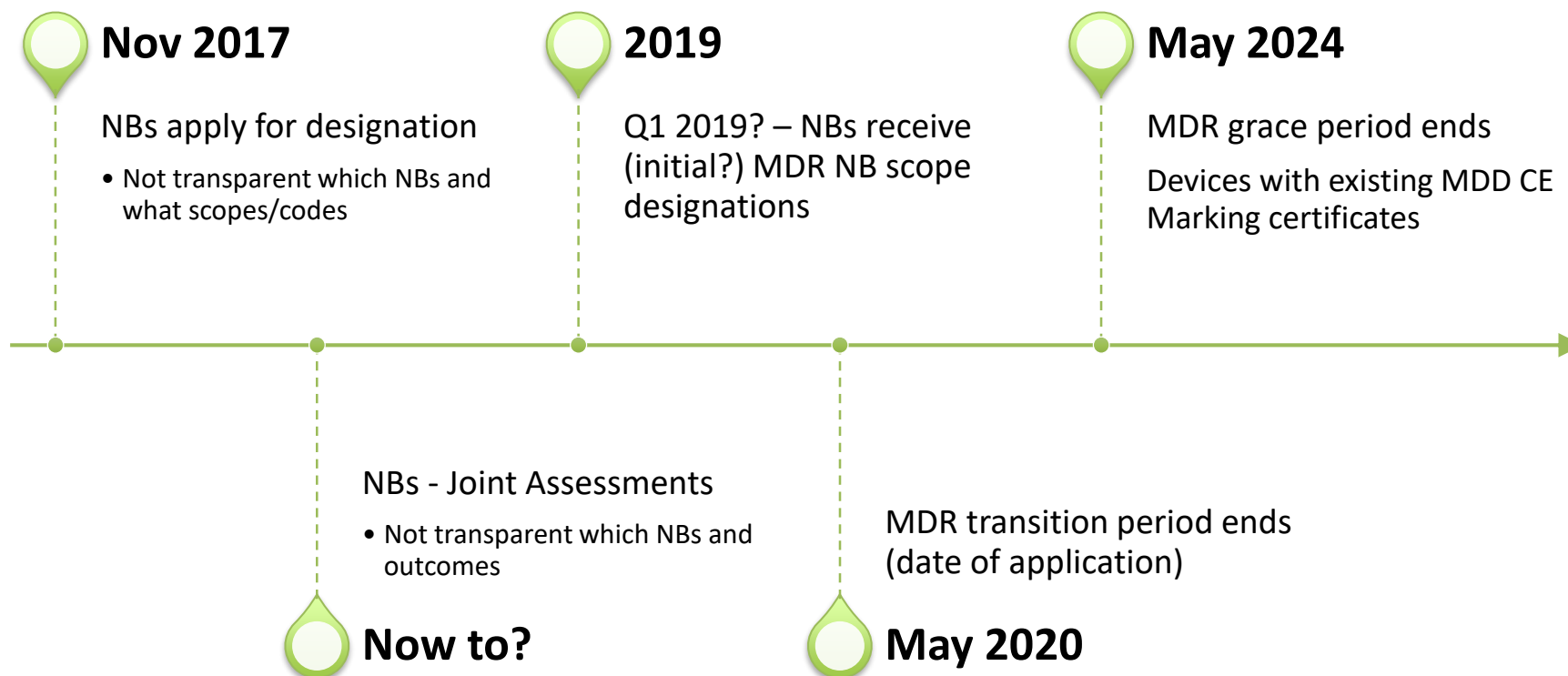
EC Implementation Priorities

- Designation of notified bodies
- Governance (MDCG, WGs, expert panels)
- EUDAMED
 - Very ambitious requirements
 - Significant concern about design and development in time (for now focus on the essentials)
 - Unique and challenging to build/run
- UDI
 - Taking account of US experience, IMDRF and other RAs
 - Seeking a more harmonized approach
- Communication (including third countries)

Transitional Provisions

- From date of application of MDR, all existing NB designations under MDD and AIMD become void
- Certificates issued under MDD and AIMD before and during the transition (between MDR entry into force and date of application) become void at latest four years after date of application
 - Entry into force Q2 2017
 - Date of application Q2 2020
- Some requirements apply to all manufacturers at date of application
 - PMS, vigilance, registration requirements

Key MDR Dates – Notified Bodies



Notified Bodies

- Notified Body Applications
 - Many have applied (EC does not have direct oversight)
 - Some NBs leaving, some new NBs applying
- Some have had initial joint assessments
 - Non-conformities may have been raised
 - Two are designation some others may occur soon
- Concern about transparency on applied designation scopes and adequate coverage

Timeline

- Deadlines in place now very tight required by EU stakeholders (including the EP)
- Challenging to meet for EC, MS, NB and manufacturers
- No extensions possible unless there is strong evidence that the system is not working
 - Parliamentary elections in May 2019?

High-level MDR CE Marking Process

Confirm it is a <i>Medical Device</i>	(Article 2)
Determine the <i>Classification</i>	(Article 51, Annex VIII)
Identify the <i>Conformity Assessment Procedure</i>	(Section 2 Article 52)
Address <i>General Safety and Performance Requirements</i>	(Article 5, Annex I)
Prepare <i>Technical Documentation</i>	(Annex II, Annex III)
Complete <i>Conformity Assessment</i>	(Annexes VIII, IX, X, XI)
Sign <i>Declaration of Conformity</i>	(Article 19, Annex IV)
Affix <i>CE Marking</i>	(Article 20, Annex V)
Conduct <i>Post-Market Surveillance</i> and <i>Vigilance</i>	(Article 83 & 87, Annex XIV)

High-level looks similar to the Medical Device Directive

Interpretation of EU Regulations

Manufacturer interprets/implements MDR

Advice/input from experts, consultants, CAs, NBs* (NB* - must maintain independence/objectivity)

Notified body assesses/evaluates the manufacturers solutions

Competent authority/EC audit the notified body reviews/assessments

Courts can provide interpretation (rarely needed)

CAMD



- Competent Authority for Medical Devices network
 - Best practice, consistency across CA's
 - Improving inter-CA cooperation/collaboration
- EU will remain a decentralized regulators
 - Requires confidence in CE Marking
 - Confidence in other CAs and NBs

Examples of WG Questions

Certificate Validity	Scenarios – place on-market pre-MDR/IVDR, certified during transition period
Certificates of Free Sale	Length of validity during transition
Implant cards	Content, symbols, language
Vigilance	Timeframes and parallel systems
Systems	Eudamed, UDI and national databases Parallel systems in place during the transition
Governance	Resources, expertise, establishing expert panels
NB bottlenecks	Joint assessments, application process, scheduling JAs, Brexit
Clinical	<u>Sufficient clinical evidence, equivalence, summary of safety & clinical performance (SSCP)</u> , templates and formats

Obligations of Manufacturer

- Products are in accordance with the MDR
- Risk management system
- Clinical evaluation including post-market clinical follow-up (PMCF)
- Technical documentation (maintained for 10 years, implants 15 years after last device being placed on market)
- Comply with UDI requirements
- Changes to harmonized standards/common specifications
- Quality management system (more prescriptive – ISO 13485)
- Post-market surveillance systems
- Provide access to documentation to Competent Authorities
- Identify significant subcontractors (design and manufacturer)
- Liability coverage

Identification & Traceability

- Traceability of devices between economic operators and healthcare institutions
- Medical device nomenclature (CND not GMDN)
- UDI system
- Registration of devices and economic operators
- Single Registration Number (SRN) process
- Summary of safety and clinical performance (implantable and class III)—validated by Notified Body, then uploaded to Eudamed
- European databank
 - Devices, UDI, economic operators, certificates, clinical investigations, vigilance
- Transparency of system

EUDAMED

- EC expect to be ready by Spring 2020
- In event that Eudamed is not fully functional: Article 123(3)(d) specifies which Articles are postponed
- Use of Eudamed system that is postponed (upload) not the obligations
- Eudamed is a ‘monster’ or ‘bit of a beast’
 - A lot has been done, focused on meeting minimum needs

Clinical Evidence

Clinical Evidence

- Clinical data and clinical evaluation results pertaining to a device
- Sufficient amount and quality to allow a qualified assessment of whether device is safe and achieves the intended clinical benefit(s)

Clinical Evaluation

- Methodologically sound/systematic and planned process to contiguously generate, collect, analyze and assess clinical data from a device
- To verify safety and performance, including clinical performance of device when used as intended

Clinical Data

- Clinical investigation of a device
- Clinical investigation reported in scientific literature of a device where equivalence can be demonstrated
- Peer reviewed scientific literature on clinical experience of device or equivalent device
- Clinically relevant information coming from PMS (in particular PMCF)

Clinical Evaluation and Investigation

- Conformity with Annex I shall be based on clinical data providing sufficient clinical evidence
- Manufacturers shall plan, conduct and document a clinical evaluation
- Manufacturer may request clinical strategy review from EC expert panel
- Class III and implantable devices normally require clinical investigation
 - Exceptions – device already CE marked (MDR or MDD – CS CE compliance) by same manufacturer or equivalent to marketed device and acceptable clinical evaluation (sufficient to demonstrate conformity with GSPR)
 - Class III and implantable devices can rely on equivalency data from another manufacturer's device where manufacturer has contractual access to data of equivalent device and clinical evaluation was conducted under MDR
- PCMF required – class III and implantable devices updated at least annually
- Clinical investigation documentation detailed precisely
- EUDAMED
- Consistent EU processes

Clinical Evaluation

A clinical evaluation shall follow a defined and methodologically sound procedure based on the following:

(a) a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where the following conditions are satisfied:

- it is demonstrated that the device subject to clinical evaluation for the intended purpose is equivalent to the device to which the data relate
- the data adequately demonstrate compliance with the relevant general safety and performance requirements

(b) a critical evaluation of the results of all available clinical investigations, taking duly into consideration whether the investigations were performed under MDR requirements

(c) a consideration of currently available alternative treatment options for that purpose, if any

Clinical Evaluation Consultation Procedure

- Class III implantable devices
- Class IIb rule 12 devices
- Clinical evaluation consultation process
- EC expert panel review

Not required for devices when:

- renewal of a certificate issued under this Regulation
- device has been designed by modifying a device already marketed by the same manufacturer for the same intended purpose (notified body agrees no adverse affect on the benefit-risk ratio of the device)
- clinical evaluation of the device type or category have been addressed in a CS (notified body confirms that the clinical evaluation is in compliance with CS)

Post-Market Surveillance (PMS)

- For each device, manufacturers shall plan, establish, document, maintain and update a PMS system proportionate to the risk of the device – integral part of QMS
- PMS suitable to analyze data on quality, performance and safety through the product lifecycle
 - Update risk/benefit determination, clinical evaluation, summary of safety & clinical performance, identify preventive/corrective action, usability, safety etc.
- PMS plan incorporated into technical documentation
- Class IIa, IIb and III shall prepare periodic safety update report (PSUR): PMCF findings, volume of sales, population of users, and frequency of use
 - Class III and IIb PSUR updated at least annually
 - Class III and implantable PSUR submitted to NB
- Vigilance in line with new MEDDEV – note maximum timelines
- Annual surveillance plans from authorities, including announced and unannounced

Changes in Clinical Expectations

	Clinical Evaluation (CE)	Clinical Investigation	Summary Safety & Clinical Performance	Post-Market Clinical Follow-up	Post-Market Surveillance	Periodic Safety Update Report
Class I	Clinical Evaluation Plan	Clinical Development Plan		Justification on Clinical Evaluation/Risk Management	Required	
Class IIa	Clinical Evaluation Plan	Clinical Development Plan		Justification on Clinical Evaluation/Risk Management	Required	<2 Years
Class IIb	Clinical Evaluation Plan	Clinical Development Plan		Justification on Clinical Evaluation/Risk Management	Required	Annually
Class III	Clinical Evaluation Plan	Clinical Development Plan	Required	Justification on Clinical Evaluation/Risk Management	Required	Annually

EC Implementing/Delegated Acts

- Potentially 80 empowerments, unlikely that all will be needed (18 are mandatory, but, will not necessarily be in place for the date of application)
- MEDDEV-like guidance is useful, consensus documents (new MDR much more prescriptive, but, still gray areas regarding guidance)
 - 30 years to put in place what we have against MDD, will take time for MDR

Preparing for the Changes

Manufacturers update technical documentation, systems and processes

- Product portfolio review
- Prepare supply-chain
- General safety and performance requirements
 - Including labelling requirements e.g. SRN, UDI, CMR substances etc.
 - Technical documentation and technical documentation on PMS

Notified Bodies conduct conformity assessment & assessment of technical documentation

- Assessing legacy devices – gaps to be addressed – new requirements and PMS
- CE Certificates issued against MDR

Aligning expectations with new MDR realities

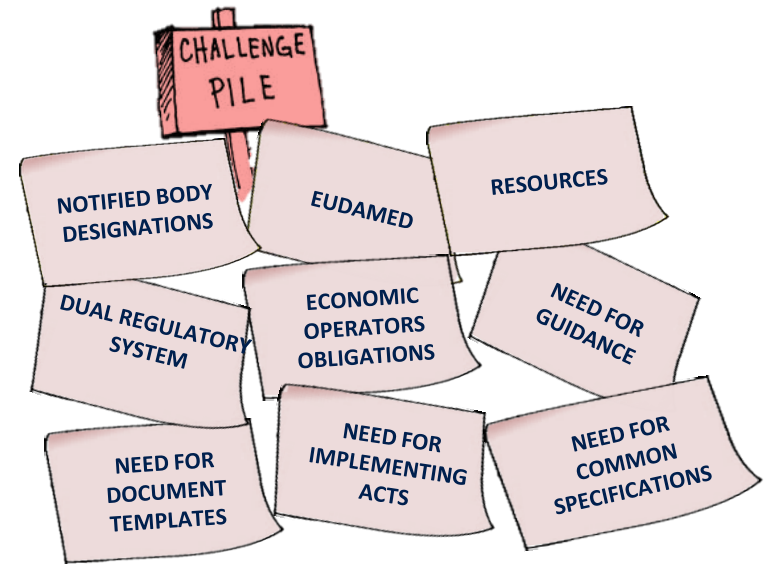
- Pre-market scrutiny/clinical/performance expectations
- Resources to achieve and maintain compliance

Key Manufacturer Concerns

- Brexit
- Managing economic operators – contract revisions
- Designation of notified bodies
- Notified bodies being restricted in sharing expectations (until designation) and best practice (clinical strategy services)
- Legacy devices (particularly clinical evidence)
- Understanding the CAMD roadmap and arrival times
- Regulation extension – business decisions made now cannot easily be reversed
- Impact on registrations elsewhere
- Clinical evidence – consistent understanding of ‘sufficient’ & ‘equivalent’ – how much data is enough?
- ‘Combination’ devices

Work Outstanding

- 80 implementing and delegating acts
- 58 Notified Bodies to re-designate (2 designated – ~30-40 in progress)
- Numerous guidance documents required
- Standards and common specifications
- Unknown number of new stakeholders – economic operators
- Database
- ~500,000 devices to re-CE Mark



Final Thoughts

- Lots of uncertainty, ambiguity, lack of guidance, changing requirements, NB expectations
- Lots of expert opinions, but, no-one has done it
- No time to wait
- Some apprehension about making mistakes
- We will make mistakes
- Best foot forwards!

Navigating the Gray

- We can't wait until we have all the answers
- We won't get everything perfect
- Sometimes we'll do more than was strictly necessary; sometimes less than what's required
- We'll need to recalibrate and adjust along the way
- We will learn, grow, continually improve

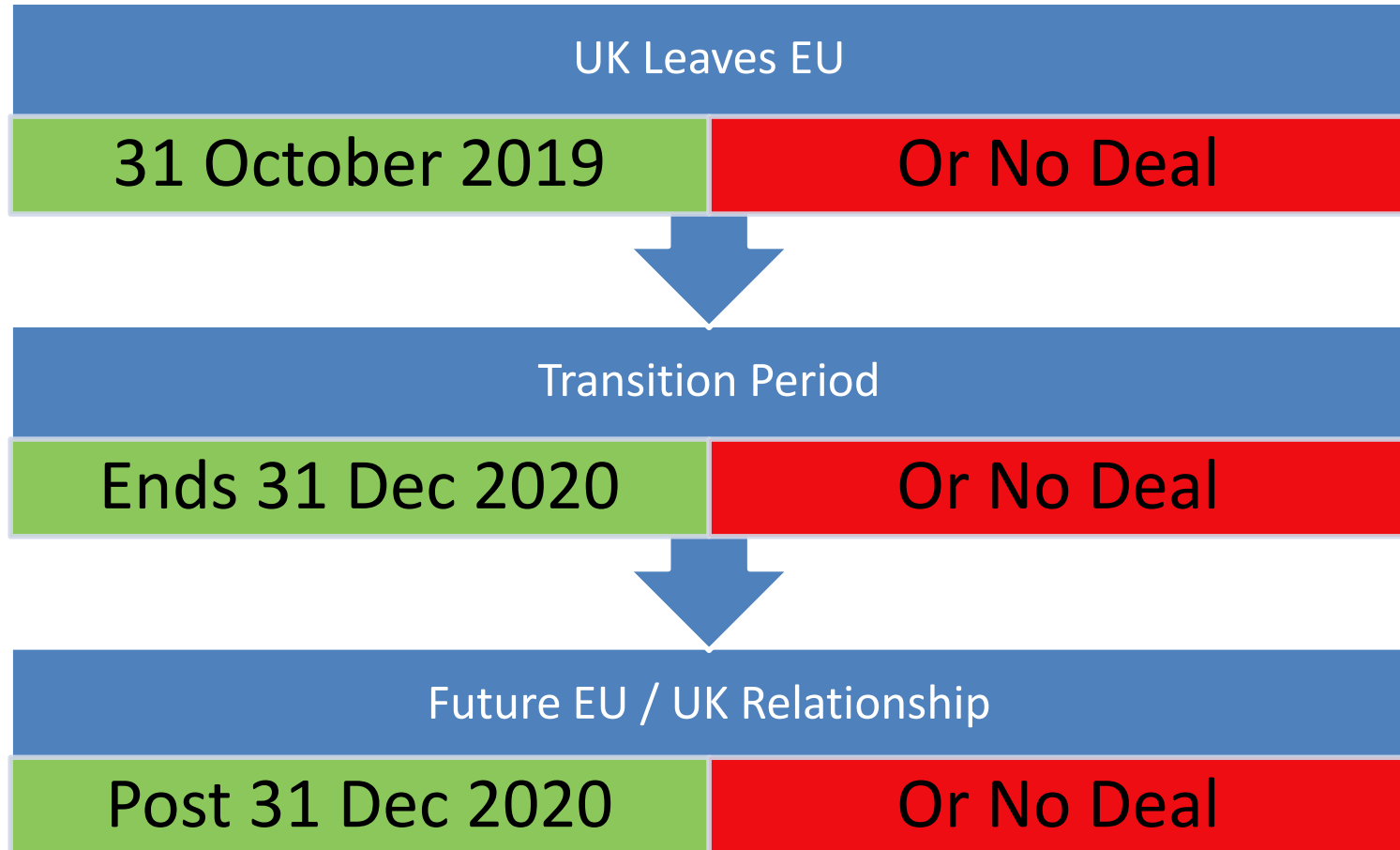
Current Brexit Timeline

- June 2016 UK referendum
- March 2017 Article 50
- March 29 2019 – Due to leave
- April 12 2019 – First extension
- October 31st 2019 – Latest extension
- 31 December 2020 – End of transition period

Transition and Brexit

- Draft Agreement on the withdrawal of the United Kingdom from the European Union as agreed at negotiators' level on 14 November 2018
- Outlines transition of UK from EU membership to full withdrawal. This transition starts on March 29, 2019 (now delayed) and ends on December 31, 2020.
- Article 127 Scope of the transition
 - Unless otherwise provide in this Agreement, Union law shall be applicable to and in the United Kingdom during the transition period.
- UK is still currently a full EU Member State (although Article 50 is in progress)

Brexit Roadmap



The background of the slide is a composite image. The left side shows a wide view of the Philadelphia skyline across the Schuylkill River at sunset, with the Comcast Center and other skyscrapers visible. The right side shows a close-up, perspective view of the Betsy Ross Bridge, with its steel structure and illuminated walkway leading towards the city. The text is centered over the skyline portion.

RAPS Regulatory **CONVERGENCE**

21-24 September 2019
Philadelphia

Paul Brooks,
Executive Director

Regulatory Affairs Professionals Society (RAPS)
Rockville, MD USA

+1 301 770 2920
pbrooks@raps.org
RAPS.org

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