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PREDICTABLE AND SUSTAINABLE IMPLEMENTATION OF NATIONAL CARDIOVASCULAR REGISTRIES (PASSION CVR)

PART IV: Registry-Supported Prospective Trials Part IV: Working Group Deliverables: Consolidating 2022, Envisioning 2023

Global Regulatory Acceptance Working Group

Think Tank IV – October 28, 2022

Co-chairs

FDA: *Kenneth Cavanaugh, U.S. Food and Drug Administration*

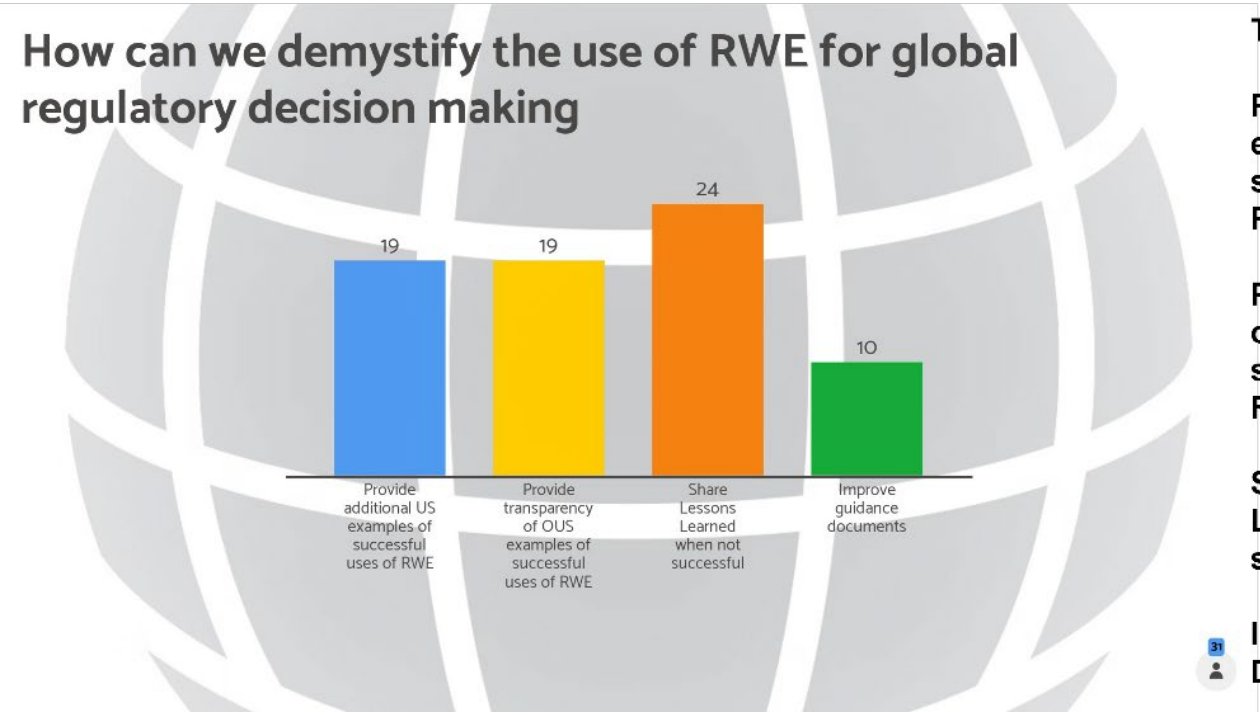
Academic: *Aaron Lottes, Purdue University*

Industry: *Melanie Raska, Boston Scientific*

DISCUSSION TOPICS

- Overview of WG Activities to date
- Survey Results
- Review Proposed 2023 Goals
- Questions

WORKING GROUP ACTIVITIES (PAST AND CURRENT)



Total Participants = 31

Provide additional US examples of successful uses of RWE = 19 [26%]

Provide transparency of OUS examples of successful uses of RWE = 19 [26%]

Share Lessons Learned when not successful = 24 [33%]

Improve Guidance Documents = 10 [14%]

- Review of Regulatory Decisions based on Real-World Evidence (May 2022 Think Tank)
- Determined that more information about Successful and Unsuccessful RWE experiences was needed
- Developed and Conducted a Survey (September 7 – October 14, 2022)
- Results To Date (Today's presentation focuses on the **37** RWE Experiences findings)
- Final Report will be delivered with Survey Findings (survey will remain open after the Think Tank for additional feedback)

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SUCCESSFUL/UNSUCCESSFUL

Successful

- 31 RWE Experiences were Successful
- $500K – 20M Cost Savings
- Less than 12 months saved in 14 submissions; 12 – 24 months saved in 7 submissions ; 2+ Years saved in 5 submissions [Only 26/31 responses to this question]

Unsuccessful

- 6 RWE Experiences were Not Successful
- Data Quality, Data Completeness and Access to Data cited as issues raised by Regulator
- Most submissions sought official communication with Regulators prior to submission of RWE

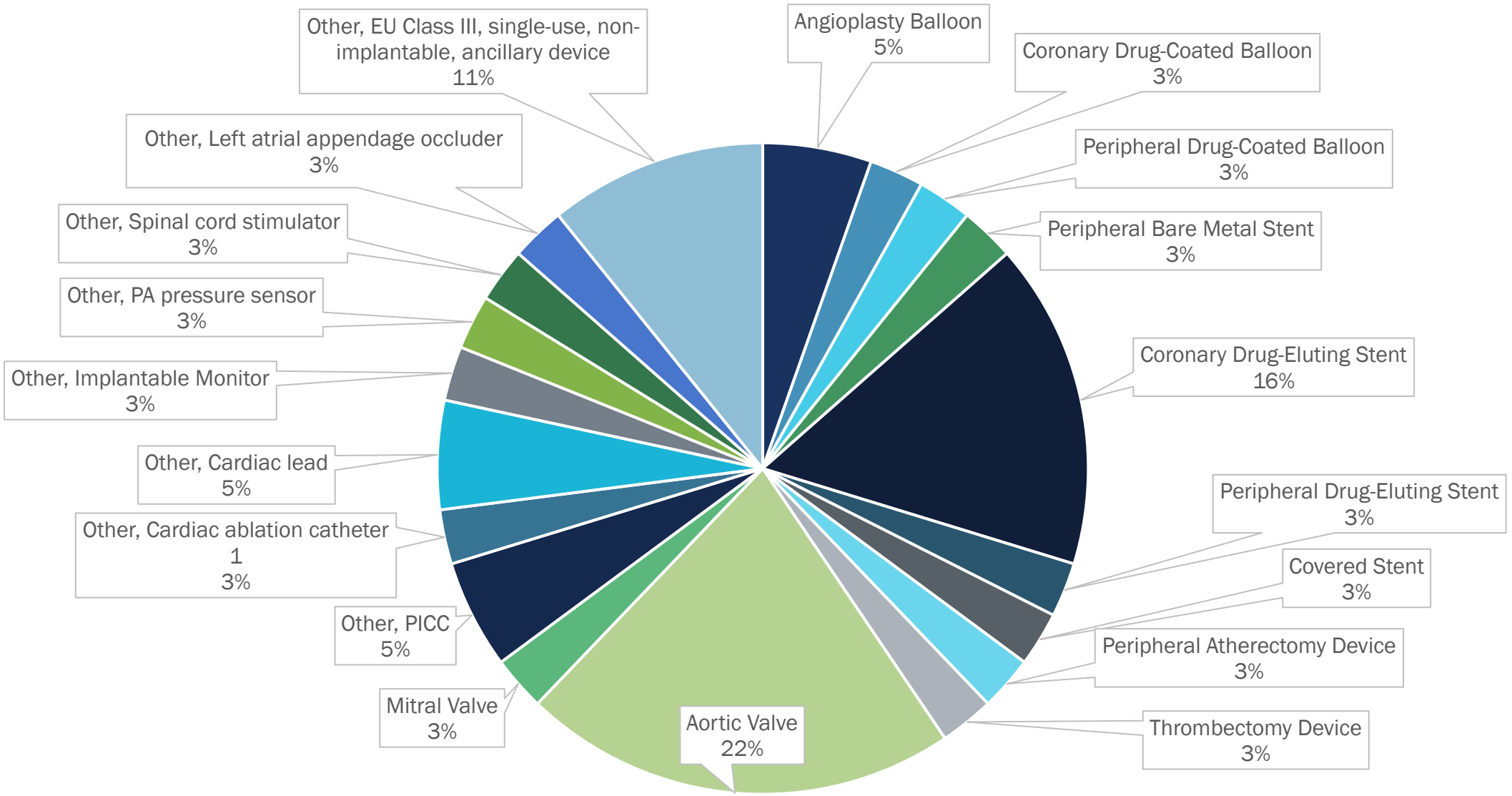
Summary Totals
Successful/Unsuccessful (Total)

US – 18/5 (23)
EU – 7/0 (7)
JP – 4/1 (5)
CA - 1/0 (1)
CN – 1/0 (1)

All 31/6 (37)

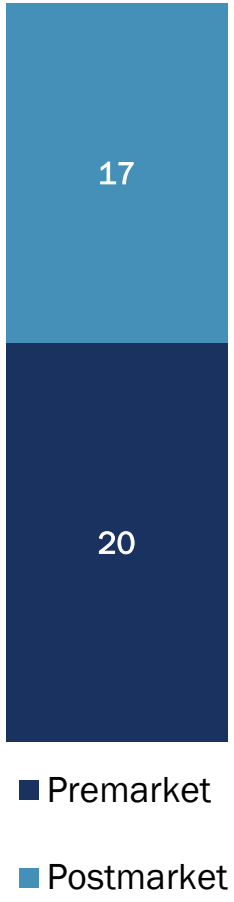
No Experiences reported in the following Regions:
AUS – 0/0 (0)
UK – 0/0 (0)
KR - 0/0 (0)
Other - 0/0 (0)

DEVICE TYPE

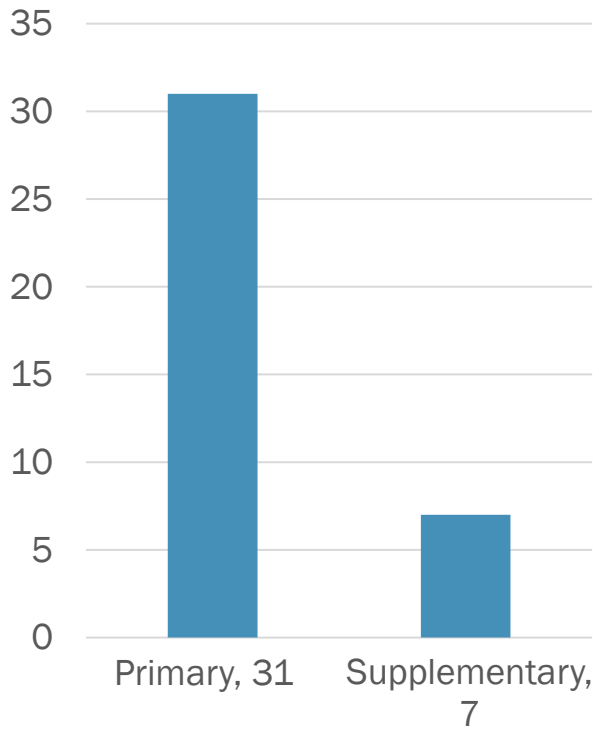

Other, EU Class III, single-use, non-implantable, ancillary device 11%
Angioplasty Balloon 5%
Coronary Drug-Coated Balloon 3%
Other, Left atrial appendage occluder 3%
Peripheral Drug-Coated Balloon 3%
Other, Spinal cord stimulator 3%
Peripheral Bare Metal Stent 3%
Other, PA pressure sensor 3%
Coronary Drug-Eluting Stent 16%
Other, Implantable Monitor 3%
Other, Cardiac lead 5%
Peripheral Drug-Eluting Stent 3%
Other, Cardiac ablation catheter 1 3%
Covered Stent 3%
Peripheral Atherectomy Device 3%
Other, PICC 5%
Mitral Valve 3%
Aortic Valve 22%
Thrombectomy Device 3%

DESCRIPTION OF REAL-WORLD DATA

Regulatory Process Used

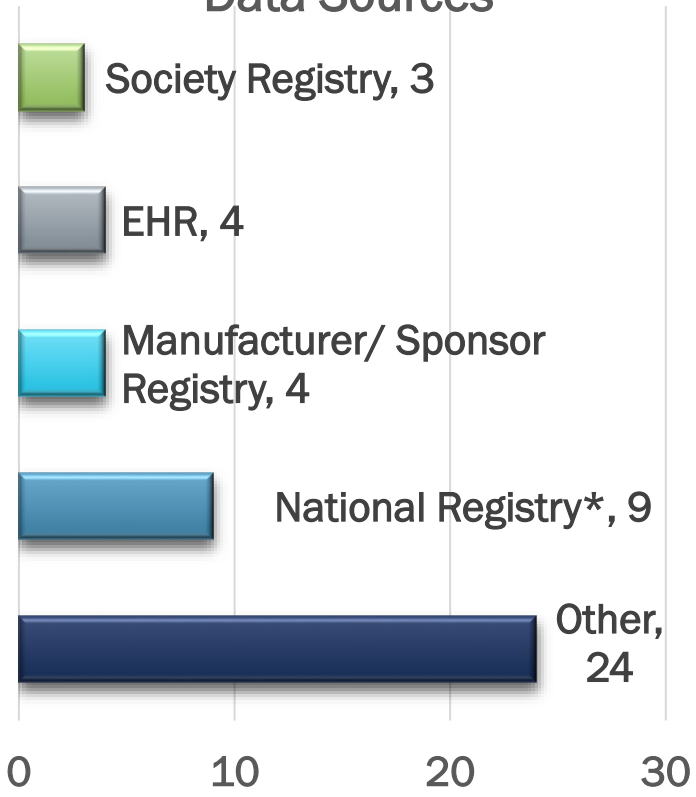


Type of Data



Note: One RWE Experience used both Primary and Supplemental Data

Data Sources



** National Registry may be country of origin (2) or external to country of origin (7)*

"Other" included:
Literature Reviews
Retrospective Studies
Hospital/EHR/ Claims Data
Healthcare database
Physician sponsored Studies
Etc.

REGULATORY DECISION MAKING

Official Discussions with Regulators

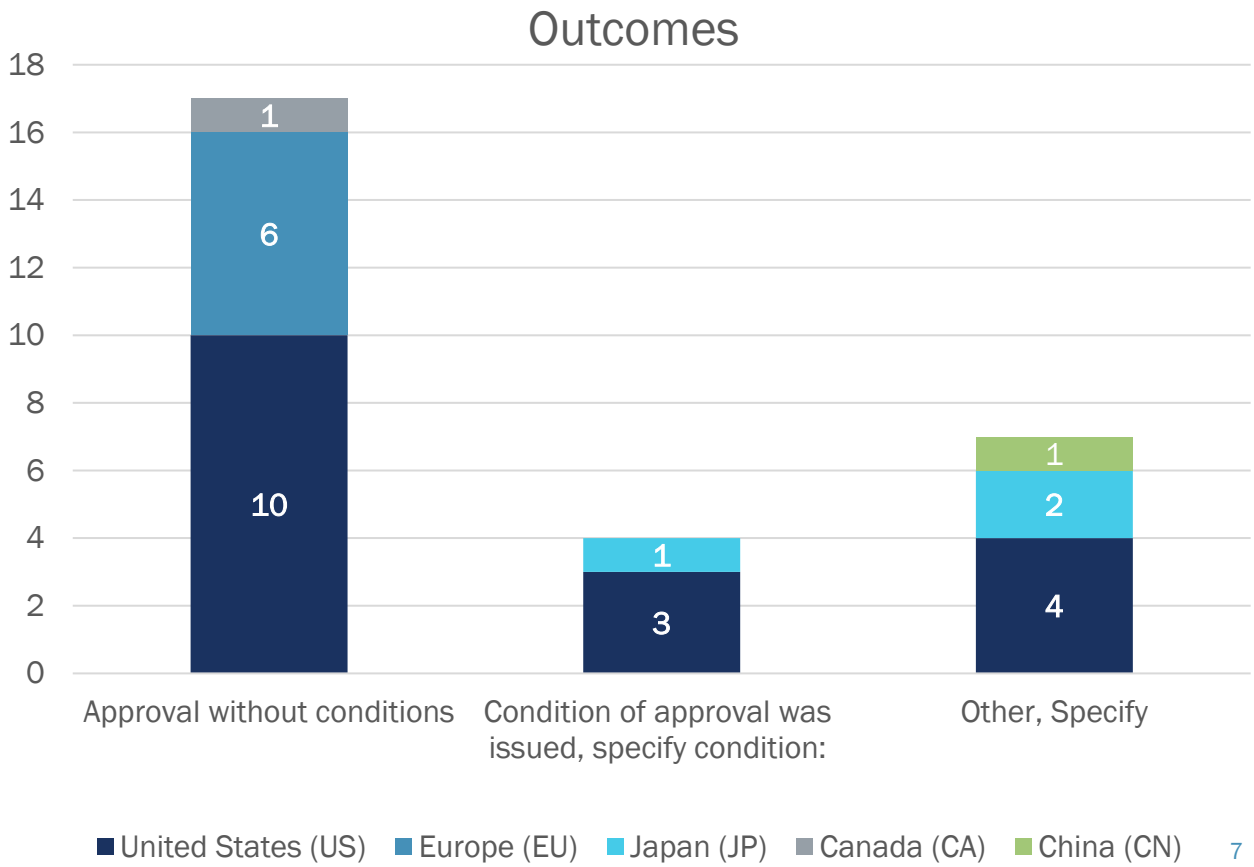
5/6 Unsuccessful
24/31 Successful

Note: Responses indicating "No Official Discussions" resulted in 1 Unsuccessful submission (US) and 7 Successful submissions (US – 3, EU – 3, CA - 1)

Feedback during Regulatory Review

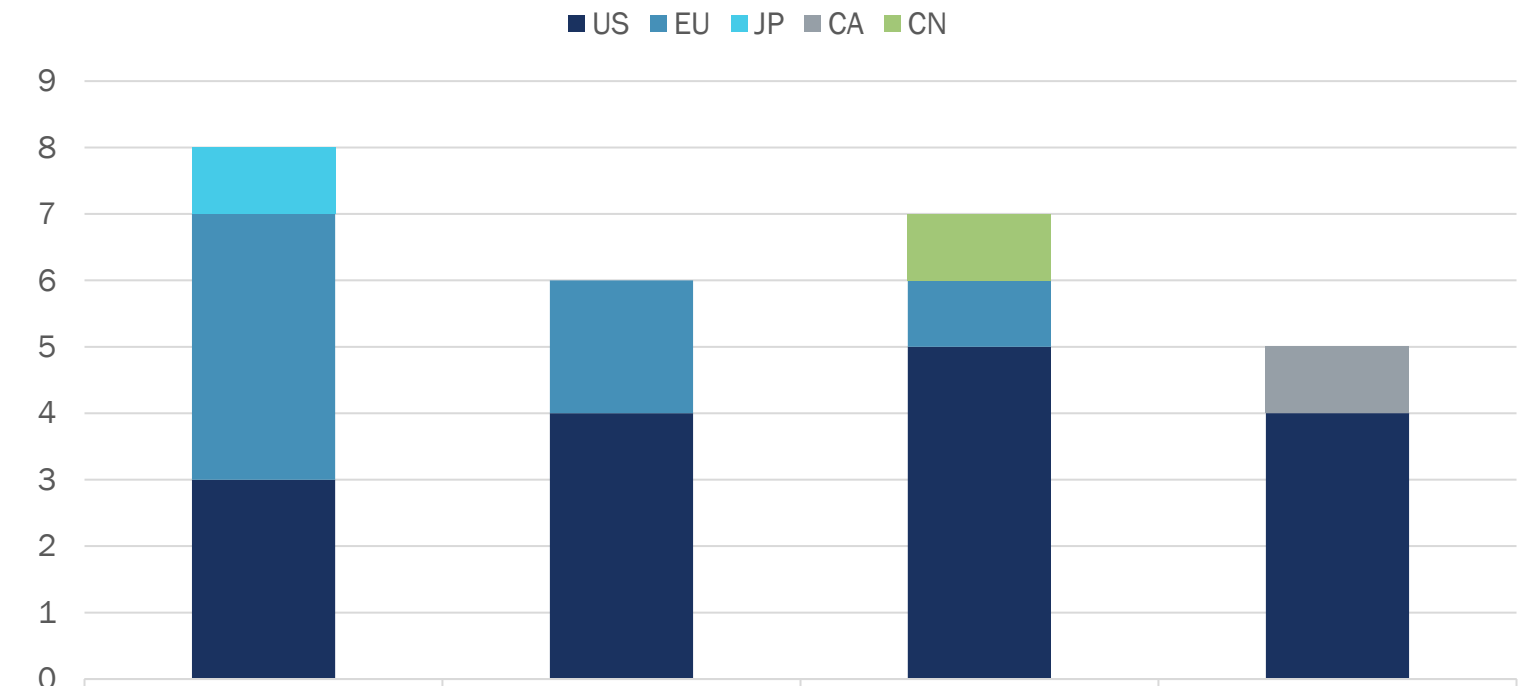
Issue	#
Additional analysis required	6
Additional clinical data needed	4
Other, specify	11

Note: One RWE Experience indicated both analysis and clinical data needed



Note: This was an optional question, and 5 Responses were not answered

INDICATE HOW MANY MONTHS YOU HAVE SAVED FOR THE RWE EXPERIENCE COMPARED TO TRADITIONAL INDEPENDENT INDUSTRY STUDIES FOR THE REGULATORY PROCESS



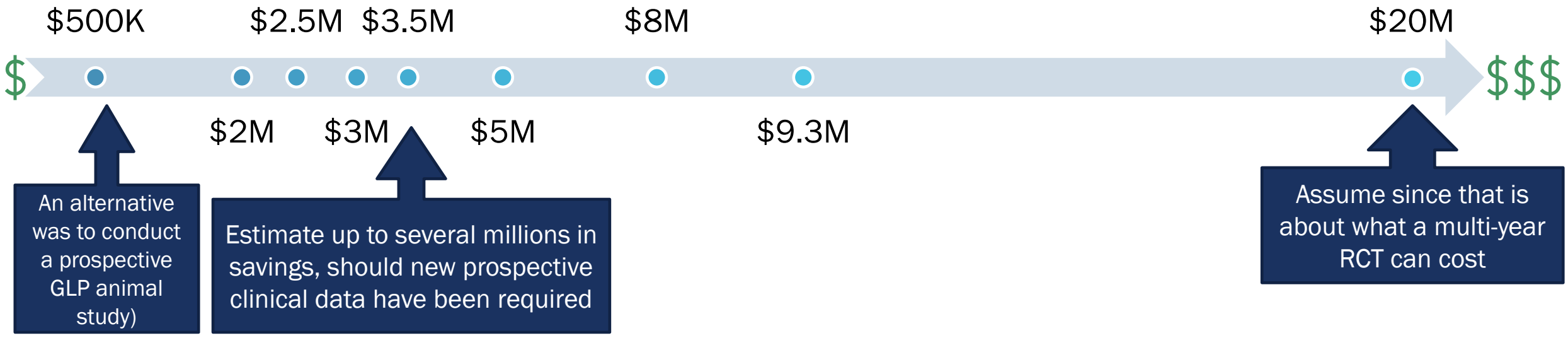
	0-6 months	6-12 months	12-24 months	2-5 years
CN			1	
CA				1
JP	1			
EU	4	2	1	
US	3	4	5	4

Totals

0-6 Months = 8
6-12 Months = 7
12-24 Months = 7
2-5 Years = 5

Unanswered = 5

INDICATE ANY COST SAVINGS FOR THE RWE EXPERIENCE COMPARED TO TRADITIONAL INDEPENDENT INDUSTRY STUDIES FOR THE REGULATORY PROCESS (INCLUDE VALUE AND CURRENCY)



Other Benefits

- Accelerated Timelines
- Resource and Time Savings
- Savings on patient fee costs
- Earlier Revenue Generation

RELUCTANCE TO SUBMITTING RWE SUMMARIZED

Inability to use the same data across regions

- Rigid Data Requirements
- Insufficient data to support regulatory decisions
- Long-term follow-up not available in all [registry] data sources and are required in some regions

Not enough Guidance from Regulators (Japan)

Data Confidentiality not guaranteed (EU/France)

LESSONS LEARNED SUMMARIZED

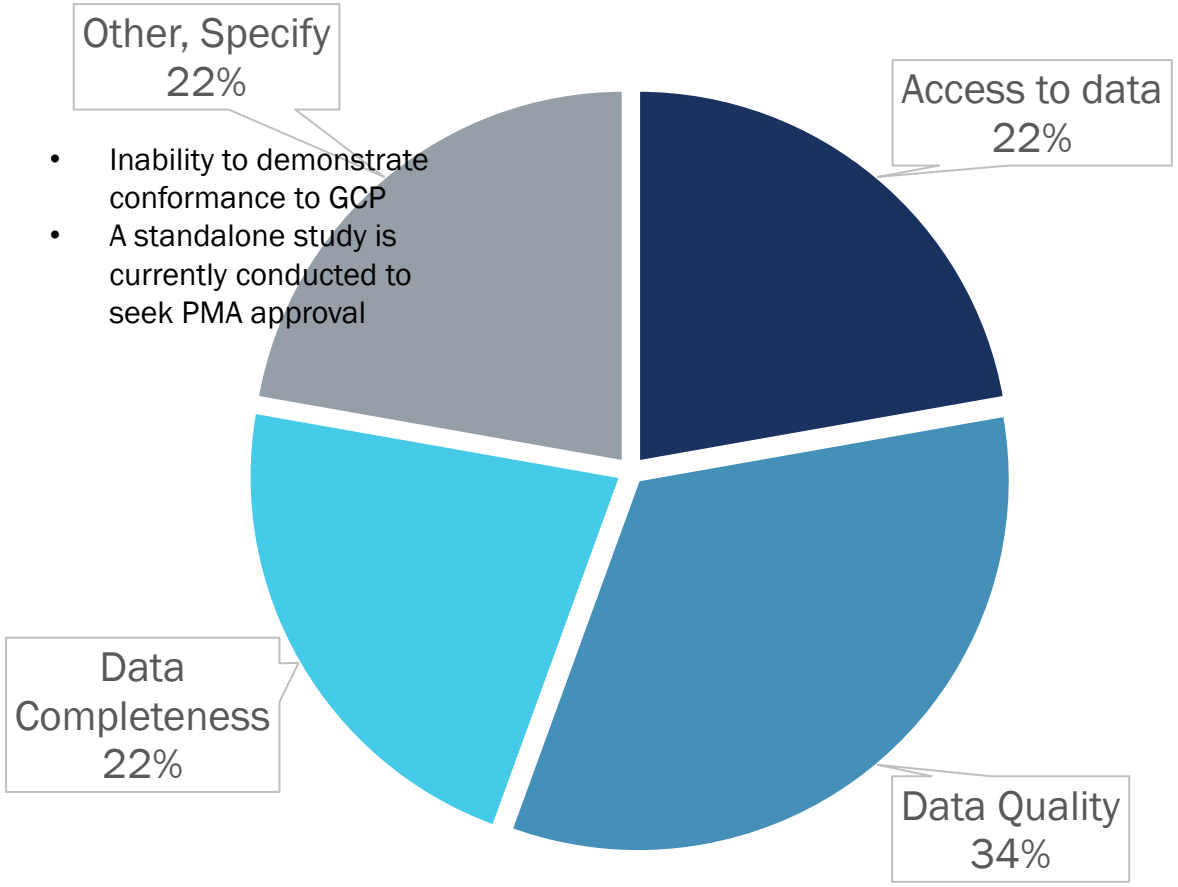
Interaction with Regulators is important for successful experiences

New Guidance or Support for RWE is becoming available in some Jurisdictions (China, Japan)

Ongoing discussion (with Health Canada) about Sharing Real-world Data Publicly, which may be challenging to do

Reusable infrastructure can be created for answering multiple research questions about real-world medical device safety and effectiveness

WHAT ISSUES WERE RAISED BY THE REGULATOR WITH YOUR RWE EXPERIENCE THAT WAS UNSUCCESSFUL?

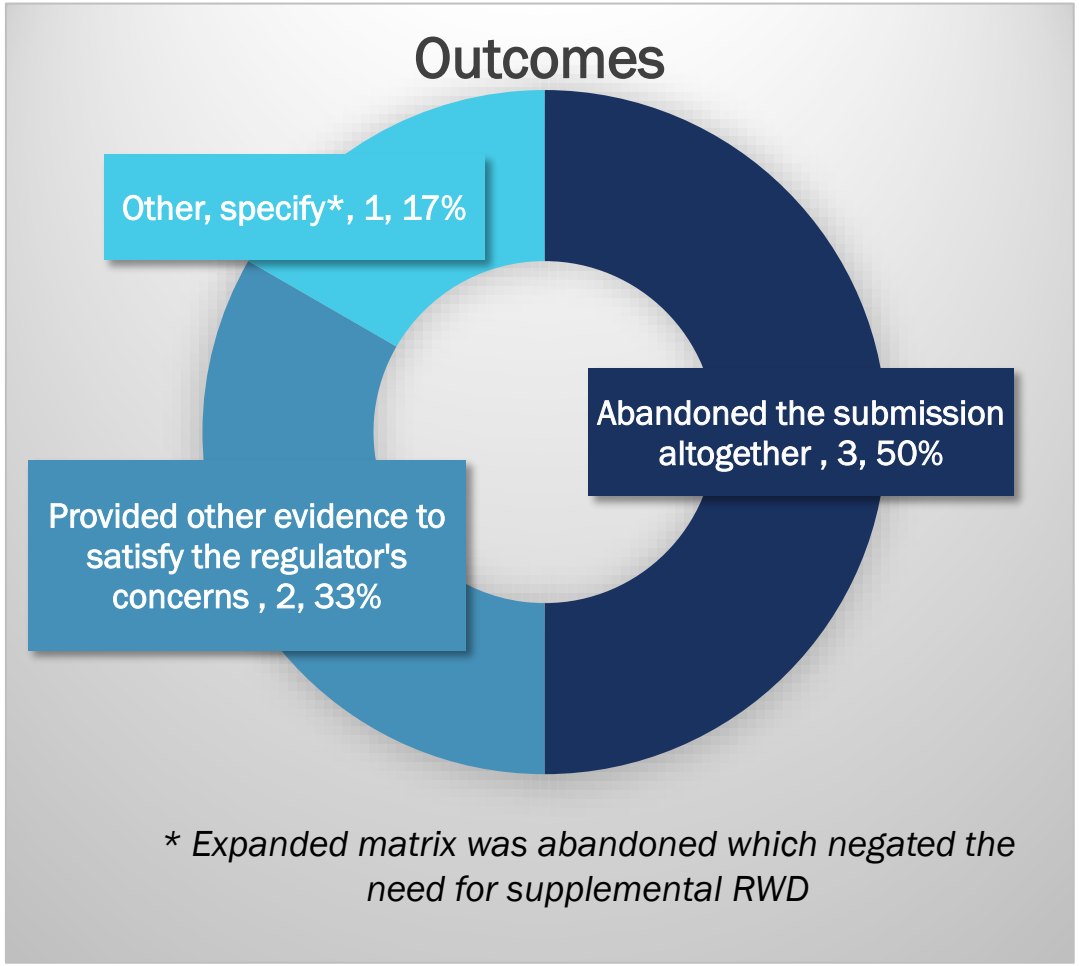


- Inability to demonstrate conformance to GCP
- A standalone study is currently conducted to seek PMA approval

WHAT REASON WAS GIVEN FOR WHY THE RWE WAS UNSUCCESSFUL?

Country	Comment
United States (5)	• Data reliability • Actual clinical data was required (not just generalized lit search for device type) • Data were not of high enough quality • Investigator Sponsored Research (ISRs) did not meet their endpoint (using an earlier generation of the device). The approval strategy was discussed with FDA and plan was changed.
Japan (1)	• Region has no guidance document/pathway to support RWE to support regulatory submission like the US does.

INDICATE THE OUTCOME OF THE UNSUCCESSFUL RWE SUBMISSION



** Expanded matrix was abandoned which negated the need for supplemental RWD*

WHAT WOULD ENCOURAGE YOU TO ATTEMPT TO SUBMIT RWE AGAIN

- Maintain consultation mechanisms
- Ability to consult about whether the available data would be sufficient
- Region develops pathways/guidance documents for how RWE (in Japan)
- Transparency of data availability by RWD holders
- Suggestions from Regulator when the development of a RWE plan may be considered

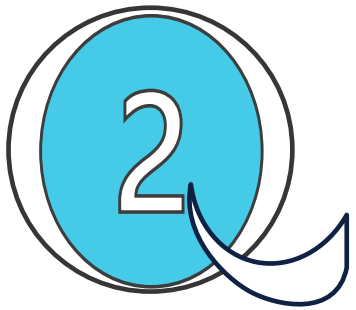
Want to share your RWE Experiences with the Working Group?

- Survey is open
- If you were not able to respond prior to October 14, 2022, please submit each RWE Experience (Note: one response per experience)
- Survey will take 4-6 mins if you have the data available
- Survey Link: https://duke.qualtrics.com/jfe/form/SV_2bnQLKgQKawrRZQ
- Please submit by November 30, 2022

Global Regulatory Acceptance WG Goals
ACTIVITIES BY 2023 QUARTER

Explore opportunity with CRT – US/Japan to discuss RWE

Explore opportunities IMDRF within this forum to discuss RWE



Explore opportunities to collaborate with CORE–MD – the European Union Horizon 2020 project, that will run from April 2021 until March 2024. EC-led/EU Society for Cardiology

Deliver a Playbook for success – to include considerations for submitting RWE successfully (based on survey results)

Report Global Regulatory Acceptance Working Group Achievements

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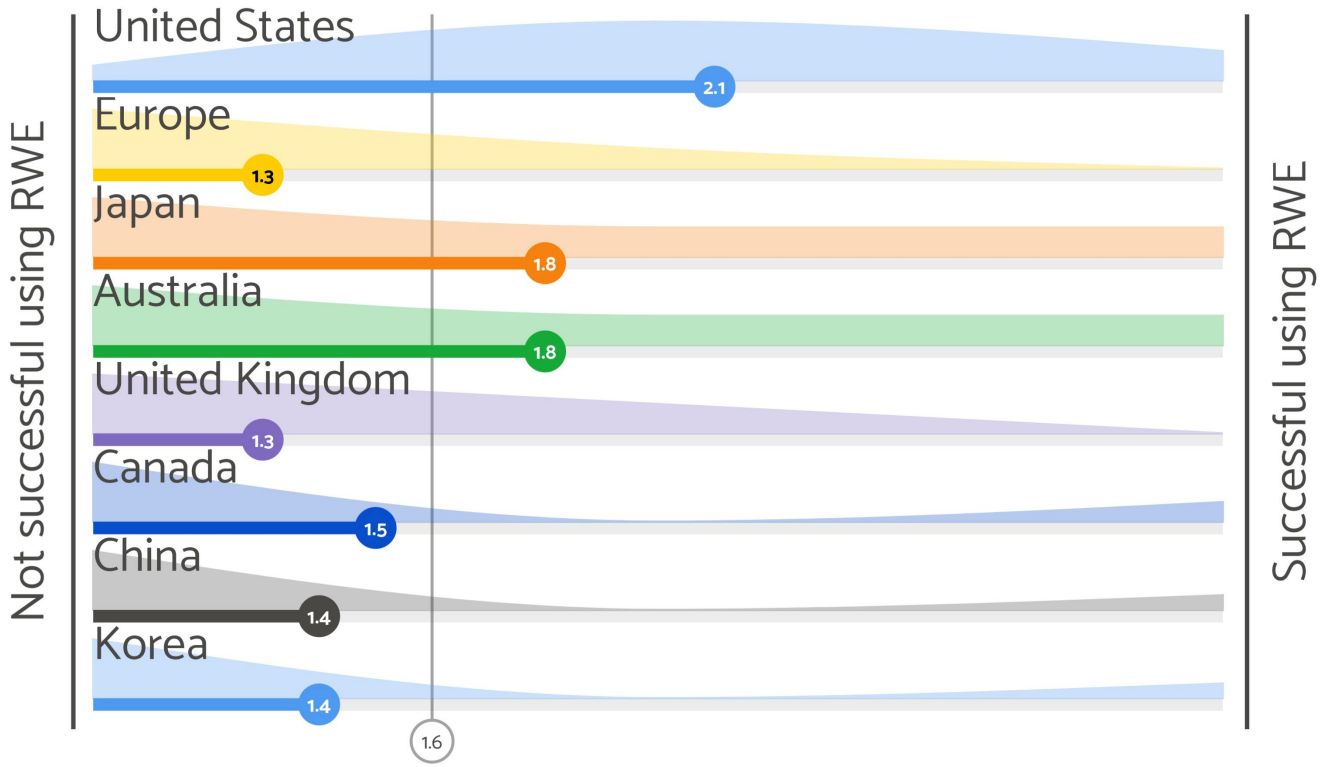
POLL RESULTS

Rate your experience submitting RWE to Regulatory Authorities



If you were successful, what advice would you share with others?

be sure the data is fit for purpose

Consult with regulator ahead of submission

comparable 1) patient population; 2) data quality; 3) clinical practice

If you were unsuccessful using RWE, what do you think would help you be successful?

Not successful

Additional up front guidance from FDA. Very difficult to retrofit registry data after it has been collected to meet the need.

Greater transparency in RWD sources before investing in generating RWE

Future Directions and Final Thoughts

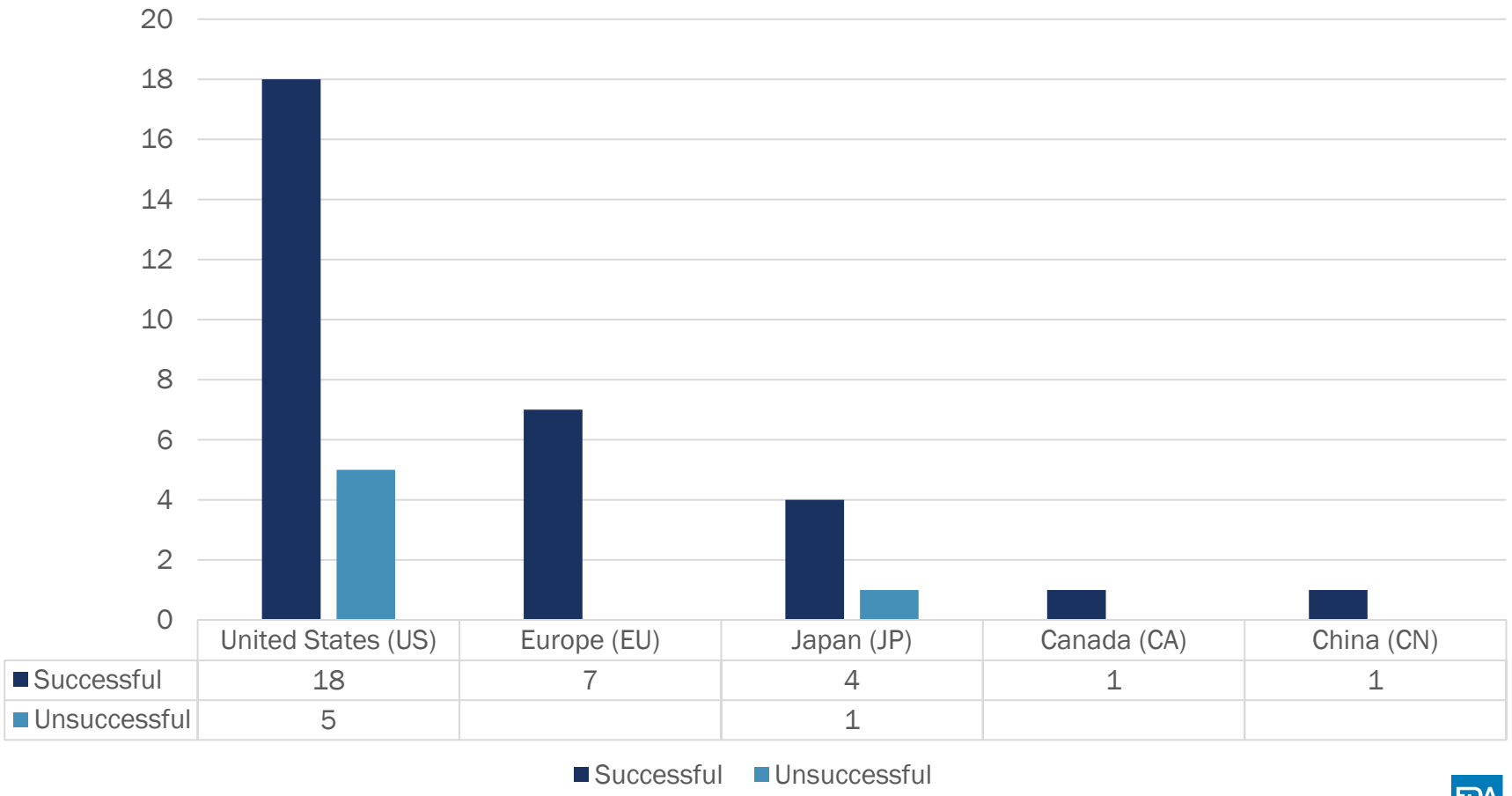
From the Global Regulatory Acceptance WG Co-Chairs

Questions

Appendix

- Includes Back-up slides
- Supporting information
- Full report will include more information

RWE EXPERIENCES STATUS BY REGION



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KR - 0/0 (0)
Other - 0/0 (0)

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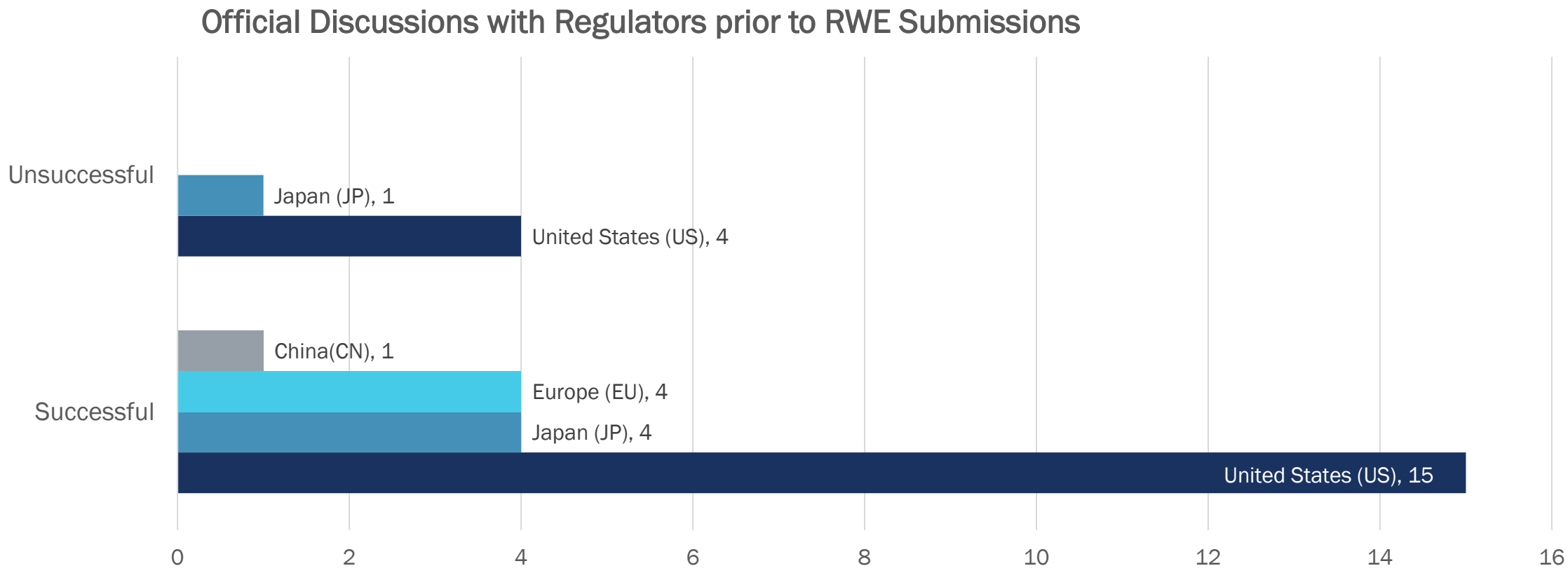
DEVICE TYPE COUNT

Device Type	Totals
Aortic Valve	8
Coronary Drug-Eluting Stent	6
Angioplasty Balloon	2
Coronary Drug-Coated Balloon	1
Peripheral Drug-Coated Balloon	1
Peripheral Bare Metal Stent	1
Peripheral Drug-Eluting Stent	1
Covered Stent	1
Peripheral Atherectomy Device	1
Thrombectomy Device	1
Mitral Valve	1

Device Type	Totals
Other, EU Class III, single-use, non-implantable, ancillary device	4
Other, PICC	2
Other, Cardiac lead	2
Other, Cardiac ablation catheter	1
Other, Implantable Monitor	1
Other, PA pressure sensor	1
Other, Spinal cord stimulator	1
Other, Left atrial appendage occluder	1

REGULATORY PROCESSES



Note: Responses indicating "No Official Discussions" resulted in 1 Unsuccessful submission (US) and 7 Successful submissions (US – 3, EU – 3, CA - 1)

DATA SOURCES

** National Registry may be country of origin (2) or external to country of origin (7)*

Raw Data for "other"

Other (unique values only)
Clinical literature/Literature review
Compared to literature for comparison/performance goal
Hospital data
Interim analysis of a subset of randomized patient from an ongoing IDE study
Interim analysis of prospective data from ongoing IDE trial
Investigator-sponsored study
Medical Claims data (e.g., CMS/Medicare)
Multi-national registry
One pre-market study combined with one post market study both conducted outside of China
Physician Sponsored Study
Post market clinical follow-up mandated after CE Mark approval
Post-market EU Investigator Sponsored Research converted to a collaborative research study; plan was to pool the data of two studies with a smaller US IDE trial
Premier Healthcare Database
Retrospective database review
Retrospective study using EHR
Retrospective study

INDICATE THE CONCERNS/ISSUES RAISED OR ADDITIONAL INFORMATION REQUESTS MADE BY THE REGULATOR DURING THEIR REVIEW OF YOUR RWE EXPERIENCE

Issue	#
Additional analysis required	6
Additional clinical data needed	4
Other, specify (in table)	11

Note: One RWE Experience indicated both analysis and clinical data needed

Additional preclinical data
None, other than request for clarification of acceptability of data in the context of the full CER
No clinical investigations has been carried out on this Class III device as the device is equivalent to a marketed device of the same manufacturer for which conformity with the safety and performance requirements is demonstrated. However the available PMCF plan does not contain PMCF studies for the device (only a literature and database review). Per MDR 2017/745 Article appropriate and includes post market studies to demonstrate the safety and performance of the device. This requirement could not be verified.
None other than request for clarification of acceptability of data in the context of the full CER
questions about the PMCF plan
(c) in order to reduce the data collected in an IDE study, the sponsor proposed to use the PMCF study conducted in EU. It was agreed with FDA to use the same core labs to reduce variability of data analysis
Required very robust NDA and "firewall" process to get FDA to allow sponsor to proceed with plan for using interim data from an ongoing IDE
Note this is an attempt to pull in the timelines it is anticipated additional data may be needed
Clarification requested regarding required sample size for subgroup analyses
Still waiting to hear back from them
Reporting schedule has to be adjusted compared to traditional studies because of data availability timing.

DID YOU EXPERIENCE ANY REGULATOR-SPECIFIC BARRIERS TO SUBMITTING THE RWE EXPERIENCE

Successful

- No regulator-specific barriers encountered (US –3) (JP – 1)
- No recommendations about how to successfully provide RWE (US –1)
- Lack of clear guidance in the Guidance documents (JP – 2)
- Unanswered (US – 1)

Unsuccessful

- No regulator-specific barriers encountered (US – 2)
- Regulator did not accept the RWE provided (US – 2)
- Unanswered (US – 1, JP – 1)

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WERE THERE ANY ISSUES WITH THE METHODOLOGY USED FOR YOUR RWE SUBMISSION? IF SO, PLEASE INDICATE THE METHODOLOGY, ISSUES AND ANYTHING YOU DID TO RESOLVE THEM?

Specific attributes of the data are not available, therefore some extrapolation was performed

Specific attributes of the data are not available, therefore some extrapolation was performed

Clarification was needed regarding reporting schedules Linked Registry data to Medicare claims data for post-approval study

Note: Pre-EU MDR

Many issues, outlined in recent publications

Proof of concept was required to demonstrate that the method was accurate.

"Lack of understanding and misalignment between the sponsor and FDA on prospectively data analysis vs retrospective (post-hoc) data analysis to meet the regulatory requested scientific level of evidence.

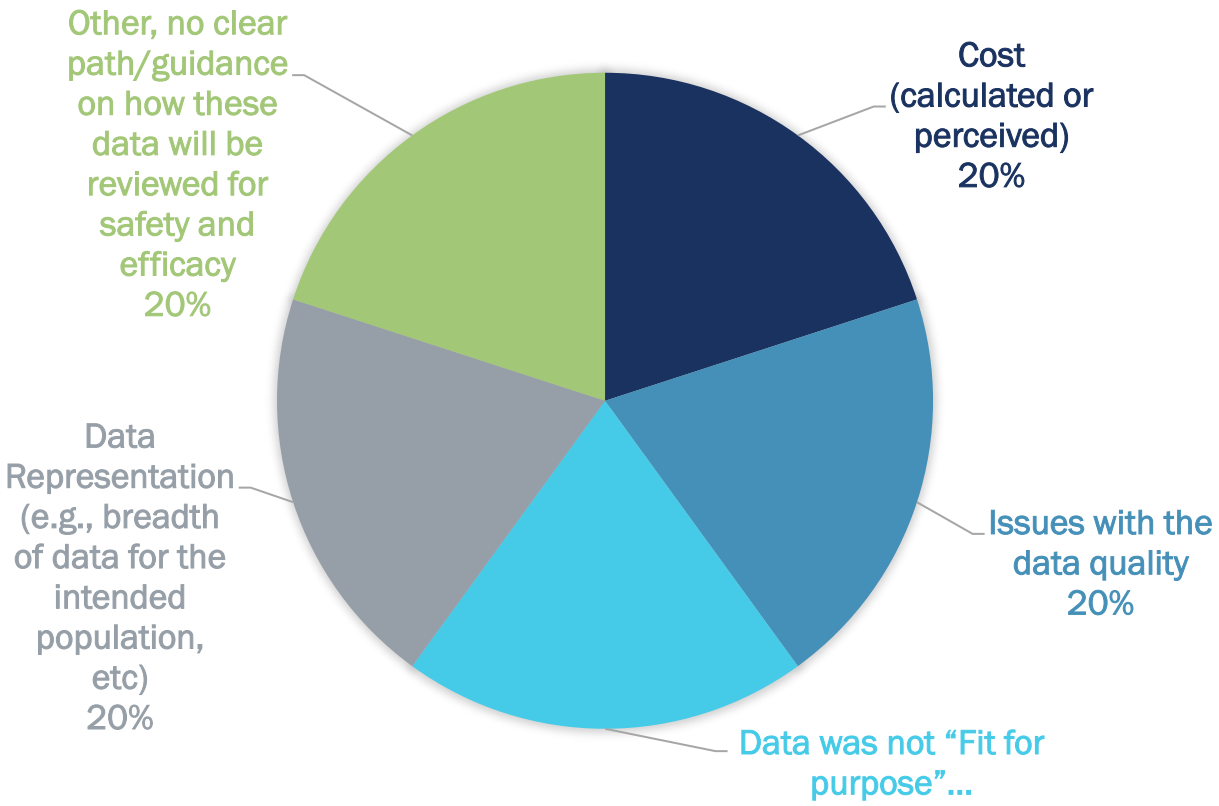
Initially led with trying to use less data. After multiple rounds of discussion, the additional studies were required to support the indication expansion

Following the MHLW/PMDA guidance on the use of outside Japan clinical registry data to support an approval of a product line extension. Required Japan GCP conformity assessment by PMDA. Collected available documentation for assessment (just allowed for review of electronic trial records).

Applicability/generalizability to Japanese patient population; applicability to Japan clinical practice"

NO RWE EXPERIENCES – 3 RESPONSES (1)

In general, why haven't you used RWE for a regulatory submission?



Which regions are you reluctant to use RWE and why?

United States (US)

- biases data captured in claims/EHR
- no clear regulatory guidance

NO RWE EXPERIENCES – 3 RESPONSES (2)

Were there any regulator-specific barriers to submitting RWE?	Regions
Lack of clear guidance in the Guidance documents as to what RWE can be used	US (1) EU (1)
No recommendations about how to successfully provide RWE when inquiry to regulator was submitted	US (1)

What would persuade you to submit RWE?	Regions
Increased Industry experience	US (2), EU (2), JP (1), CN (1)
Better Access to data	US (2), EU (2), JP (1), CN (1)
Regulator training	US (2), EU (2), JP (1), CN (1)

Please share any additional concerns about using RWE in regulatory submissions:	Pathway to success is very dependent on the disease state and our understanding of natural course of disease and documentation patterns