



QUALIANCE

SA01

**EMA, Health Canada, FDA and PMDA:
Four agencies tackle Data Sharing.
Synergies and Differences**

US Connect 2019, Baltimore

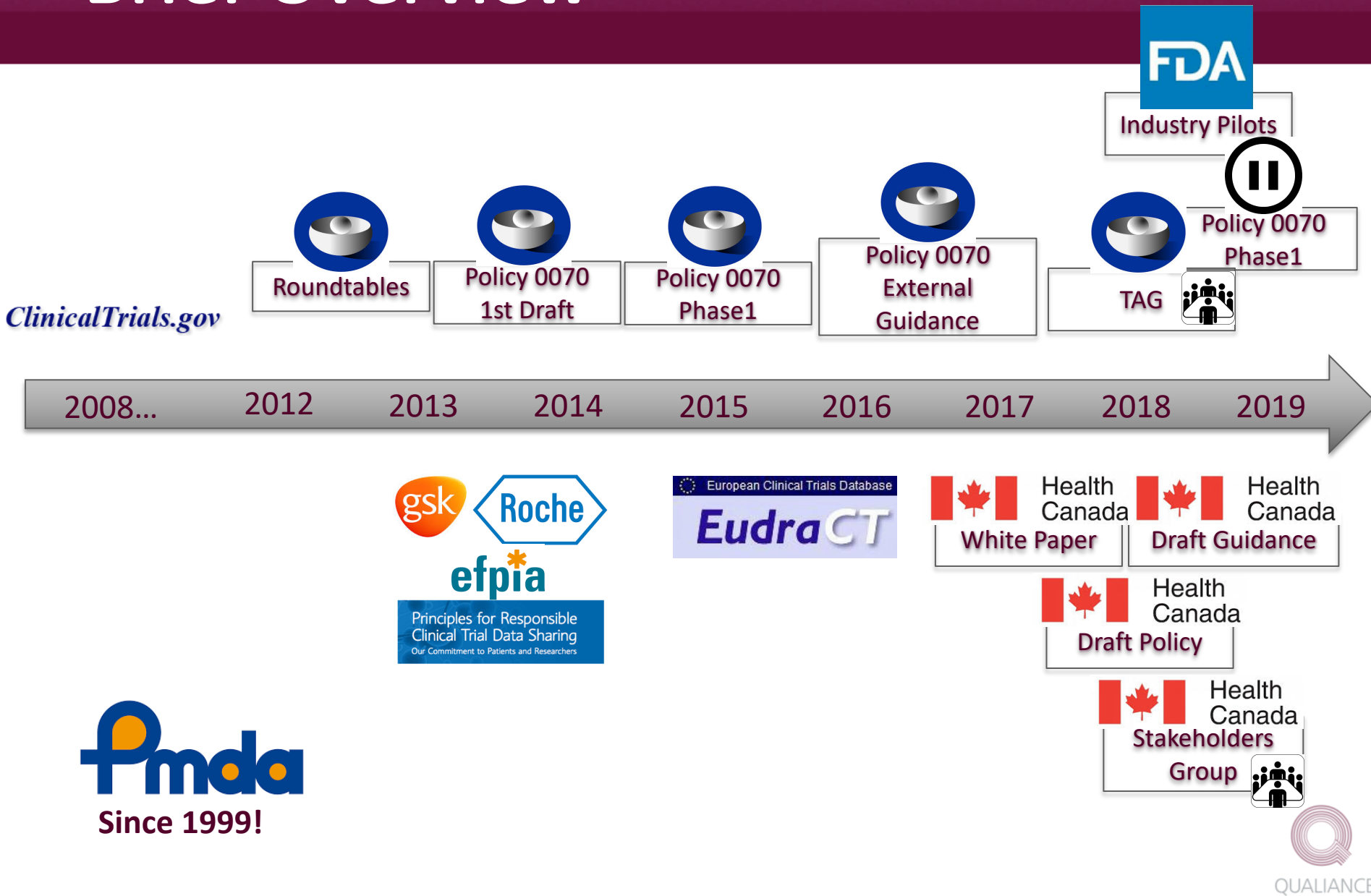
26. February 2019

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Agenda

- **Brief Overview**
- **Comparisons of the 4 Initiatives**
 - Processes
 - De-Identification Requirements
- **In Practice**
 - EMA Policy, 2 years on
 - Health Canada Draft Process
 - Focus on FDA approach
 - Insight into PMDA's published documents
 - Recognition Process?
- **Conclusions**

Brief Overview



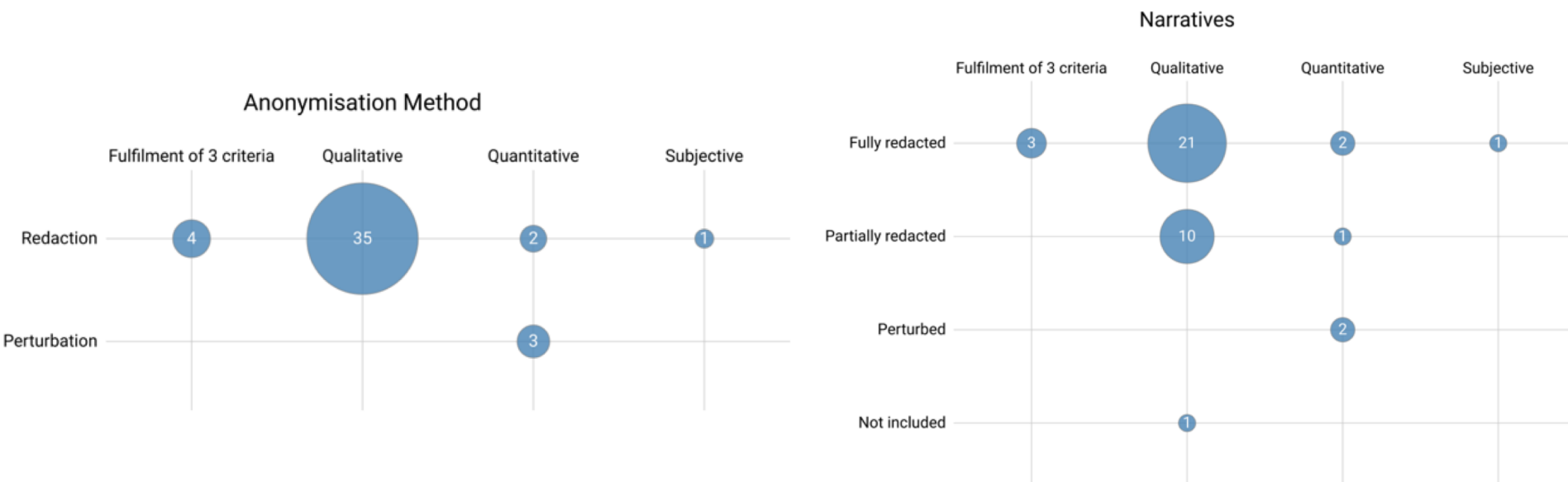
Processes

Item	EMA Policy 0070	Health Canada (Draft)	FDA (Pilot)	PMDA Disclosure of Information
Effective Date	1. January 2015	Not effective yet	Not effective yet	11. November 1999
Retrospective access to past CSR	Not in scope Possibility through Policy 0043. Sponsors conduct the redactions. Documents are sent to requester.	In scope, based on prioritization system <i>Sponsors conduct anonymization unless a certified EMA Policy 0070 document is available.</i> <i>Documents are made public.</i>	Not in scope Possibility through FOIA request FDA conduct the redactions Documents are sent to requester.	Not in scope
Studies in Scope	All studies part of a Central Application regardless of submission outcome	Step-wise approach over 4 years including Medical Devices studies from year 3 regardless of submission outcome	Only Phase III pivotal studies CSRs following approval of an NDA	CSR synopses included in Module 2 are in scope, but full CSRs in Module 5 are out of scope
Recognition Process with other Agencies	None has been communicated so far	Yes with EMA through a certification application	Not discussed	None
Review Process (De-Identification of PPD)	Using Annotated Documents and Anonymisation Report. Comments and recommendation are provided.	Same as EMA but HC validates de-identification of patient information and keeps decisions on what is publicly released.	None but Sponsor can notify FDA of special-attention item in CSRs	Sponsor states and substantiates rationale for redaction PMDA reviews and has final decision

De-Identification Requirements

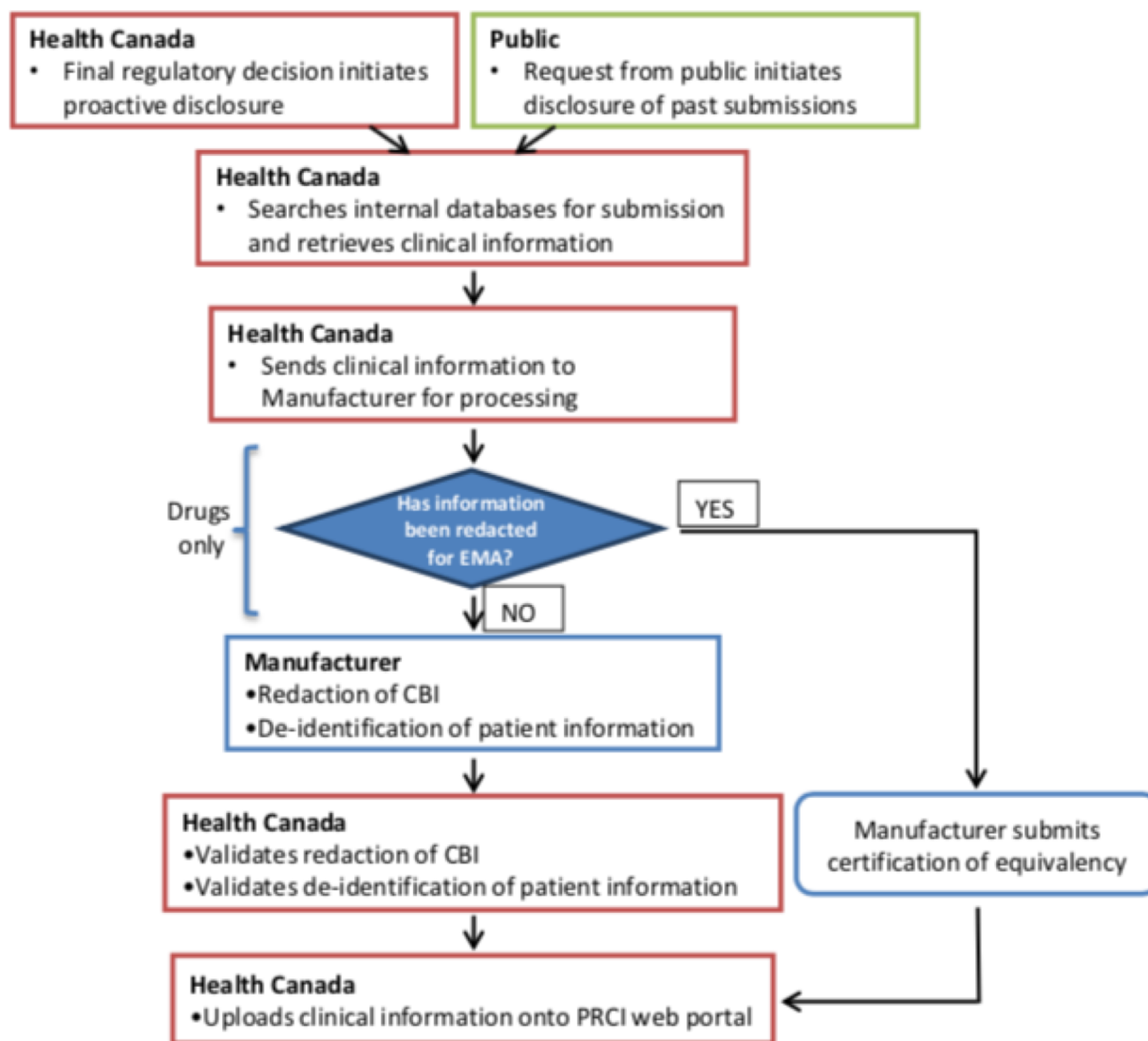
Item	EMA Policy 0070	Health Canada (Draft)	FDA (Pilot)	PMDA Disclosure of Information
Narratives in scope	Yes	Yes	No	Mini-narratives for all SAEs in CSR synopses
Risk analysis	WP29 Opinion 3-Criteria Qualitative Quantitative	Quantitative only	“Qualitative” based on FDA’s approach for FOIA request	Qualitative – sponsor to justify all proposed redactions
De-Identification Technique	Anonymization & Redaction	Anonymization	Redaction only based on FDA’s approach for FOIA request. In particular, “Demographic information, such as sex, age, and race, will generally not be redacted, except in very unusual circumstances”	Largely redaction with some transformations. PPD redaction is limited.
Guidance on Identification of Direct/Quasi Identifiers	Refer to PhUSE Standard and discuss in particular quasi identifiers such as: Dates Geographic Location Other Quasi-Identifiers (e.g. Demographics)	Indirectly-identifying variables are other identifying variables that fall within the definition of ‘personal information’ within Canada’s Privacy Act. And refer to Demographics and medical history and SAE. Country should remain unmodified.	Different type of identifiers discussed in Q&A page: Unique Patient Identifiers Dates Clinical Trial Site Geographic Location Demographics Relative dates (study days) are retained	The 2013 notification (No. 0325) provides some guidance
Guidance on Reference Population	No direct guidance but examples of plausible attacks to consider for risk modeling are listed.	4 populations are provided for consideration: - Study Population - Similar Sponsor Trials Population - Similar Trials Population - General Geographic Population	NA	NA

EMA Policy 0070, 2 years on...



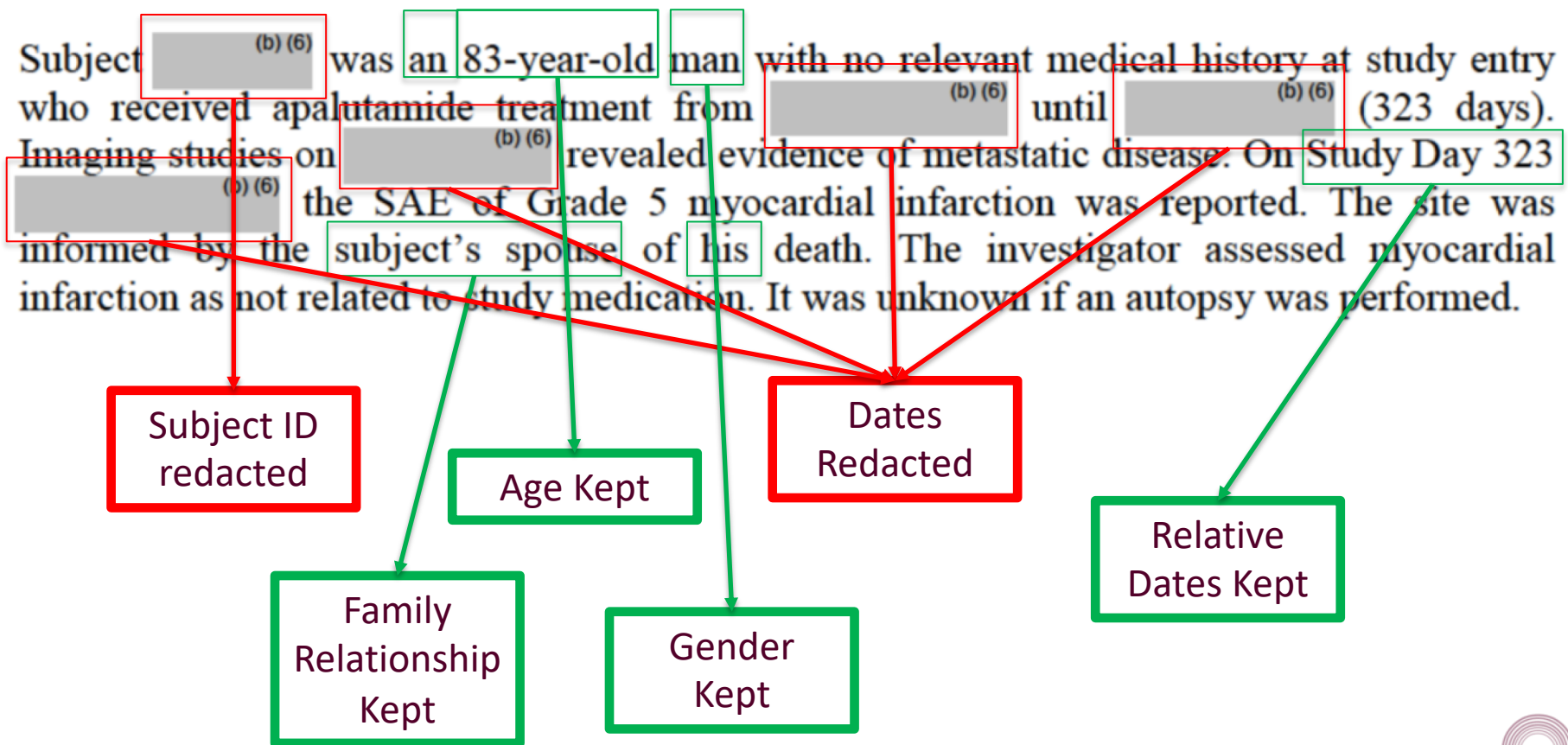
- 100+ Submission Packages published
- Sponsors still using in majoring qualitative approach coupled with redaction
- External Guidance updated 3 times, mainly for scope clarifications
- Due to Business Continuity Plan in connection with Brexit, Policy 0070 is posed since August 2018

Health Canada Draft Process



Focus on FDA Approach

- 1 Pilot Published so far, Janssen Pharmaceutica / ERLEADA
- Narratives out of scope, redaction only according to FOIA approach



Insight into PMDA's published documents

FTC/RPV/TAF FDC
2.5 Clinical Overview Addendum

Final

2. UPDATED EFFICACY AND SAFETY DATA

The original m2.5 Clinical Overview, dated [REDACTED], is based on a pivotal bioequivalence study (GS-US-366-1159) comparing FTC/RPV/TAF to Edurant® (marketed RPV 25-mg tablet) and Gilead's FDC tablet containing the HIV-1 integrase strand-transfer inhibitor (INSTI) elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), FTC, and TAF (E/C/F/TAF 150/150/200/10 mg). E/C/F/TAF was selected as the reference because the pivotal clinical data establishing the safety and efficacy of TAF in combination with FTC were generated using the E/C/F/TAF FDC in Phase 3 studies. Edurant was selected as a reference because the safety and efficacy of RPV have been established from the Edurant Phase 3 registrational studies.

Results provided in this Addendum demonstrate the continued potent and durable efficacy and continued safety profile of FTC/RPV/TAF. Interpretation of safety data after the longer duration of exposure remains unchanged relative to the data provided in the original m2.5 Clinical Overview dated [REDACTED].

2.1. Efficacy data

2.1.1. Updated Extension 96 week Results from Studies GS-US-292-0104 and GS-US-292-0111

The clinical efficacy and safety data for ART-naïve adults for studies GS-US-292-0104 and GS-US-292-0111 through 96 weeks treatment (vs 48 weeks in the original application) are presented in m2.5 Clinical Overview (Genvoya type II variation EMA/H/C/004042/II/0001, see [Attachment 1](#)). The clinical overview provides an updated evaluation of the benefits risks of E/C/F/TAF for use in the treatment of HIV-1 infection. These updated data also support the proposed FTC/RPV/TAF labeling.

The integrated Week 96 virology analyses for the GEN Phase 3 studies (Studies GS-US-292-0104 and GS-US-292-0111) in treatment-naïve, HIV-1 infected subjects are described in m5.3.5.4, PC-120-2027.

2.1.2. Full Week 48 Results from Study GS-US-292-0109

The primary analyses reported efficacy results for all virologically suppressed, HIV-1 infected adult subjects who switched from TDF-containing ART regimen and were randomized in Phase 3 Study GS-US-292-0109 through 31 October 2013. Subjects included in efficacy analyses had been followed through the lower limit of the Week 48 analysis window (ie, Week 42) or had discontinued study treatment before the data cutoff on [REDACTED]. As a consequence, at the time of the primary analyses, the Week 48 Full Analysis Set (FAS) did not include all subjects. Of the 1436 subjects who received at least 1 dose of study drug in the study, 1196 subjects were included in the primary analyses Week 48 FAS, and 1122 subjects were included in the Week 48 PP Analysis Set.

- Dates such as Clinical Overview or Submission dates and study cut-off dates are considered CCI and can be redacted.

Added New ARV	2 (0.2%)	1 (0.1%)		
No Virologic Data in Week 96 Window	77 (8.9%)	93 (10.7%)		
Discontinued Study Drug Due to AE/Death	11 (1.3%)	21 (2.4%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL ^b	52 (6.0%)	64 (7.4%)		
Missing Data During Window but on Study Drug	14 (1.6%)	8 (0.9%)		

Week 96 window is between Day 630 and 713 (inclusive).

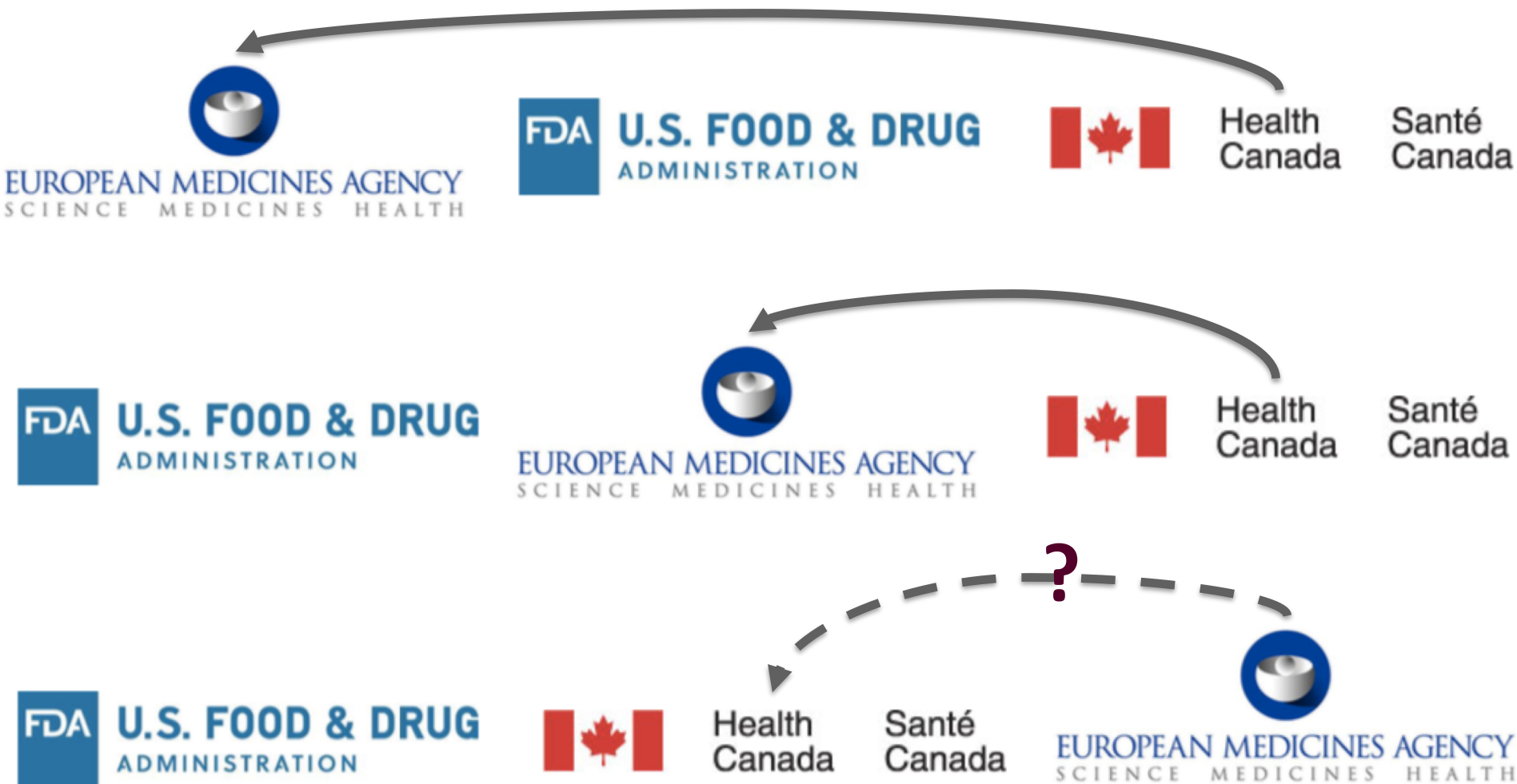
- a Difference in percentages of virologic success between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel (MH) proportions adjusted by baseline HIV-1 RNA, region, and study stratum. P-value for the superiority test comparing the percentages of virologic success was from the Cochran-Mantel-Haenszel test stratified by baseline HIV-1 RNA, region and study stratum, baseline HIV-1 RNA stratum: ≤ 100,000 or > 100,000 copies/mL; region stratum: United States (US) or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.
- b Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Programming Details: .../version1/prog/t-snapshot-pooled.sas v9.2 Output file: t-snapshot-50-wk96-pooled.out [REDACTED]
Source: m5.3.5.3, E/C/F/TAF Week 96 ISE, Table 2.1

- Program Execution Dates can also be redacted!

Ref: Gilead's FTC/RPV/TAF FDC New Marketing Application
Clinical Overviews published on PMDA website

Recognition Process?



Who is the Data Controller? Sponsor or Agency?

- EMA provides recommendation and comments...
- Health Canada plans to validate de-identification of PPD...
- PMDA reviews and has final decision...
- FDA conducts the redactions and Sponsors can notify FDA of special-attention items in CSRs...

Conclusions

- **EMA and Health Canada initiatives are very similar** while FDA's differ significantly in anonymization requirements and processes
 - Will FDA consider anonymized CSRs already published in other jurisdictions when conducting redaction on same documents? And vice-versa?
- **Use of Study Days in the CSRs** could minimize the anonymization effort and seems accepted by all 4 agencies as anonymized dates
- The question of **Joint Controllershship** should be clarified by all agencies as they review, validate or conduct anonymisation or redaction of documents
- **Four sources of same clinical documents** could be available in public domain. Which one will suit better the need of researchers?
- **Recognition processes** is only viable if there is an alignment of anonymization requirements

Thanks!

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Engaging Stakeholders

Item	EMA	Health Canada	FDA	PMDA
Consultation on:	Policy & Guidance through Stakeholders Review	Policy & Guidance through Public Review	Planned “ <i>public feedback through a Federal Register notice and docket for public comments</i> ” following the conduct of the pilots	None
Pilot	None	None	9 pilots to be planned with sponsors	None
Working Groups	EMA TAG	Stakeholders Group	Not planned so far	NA
Working Groups Application	Public call for applications CV & DoI required	Individual call for applications Application Letter & DoI required	NA	NA
Working Group Mandate	Maximum 2 years renewable	6 months between October 2018 and April 2019	NA	NA
Working Groups Deliverables	Q&A, Additional Guidance, Critical Review (TBA) developed by TAG members under EMA officers’ supervisions	Participation in 5 Meetings to comment on 5 key topics that led to the development of the guidance by Health Canada officers.	NA	NA