Regulator Perspectives and Updates on Sharing Clinical trial Documents and Data

14th June 2018

- 11:00 to 11:05
  - Introduction by Khaled El Emam
- 11:05 to 11:35
  - An overview of the EMA clinical data publication and technical anonymisation group, Anne-Sophie Henry-Eude and Monica Dias
- 11:35 to 12:05
  - Health Canada's Guidance on the Public Release of Clinical Information, Andre Molgat
- 12:12:05 to 12:35
  - FDA's Clinical Summary Report (CSR) Disclosure Pilot, Ann Witt
- 12:35 to 13:00
  - Virtual panel

uOttawa

PRIVACY ANALYTICS
an IQVIA company

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SCIENCE MEDICINES HEALTH

EMA Clinical Data Publication (CDP) & Technical Anonymisation Group (TAG)

Webinar – University of Ottawa

Presented by Anne-Sophie Henry-Eude and Monica Dias on 14 June 2018
European Medicines Agency

Disclaimer

Policy 0070 purpose

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Policy 0070:

- 2 October 2014, Clinical Data Publication (human medicinal products)

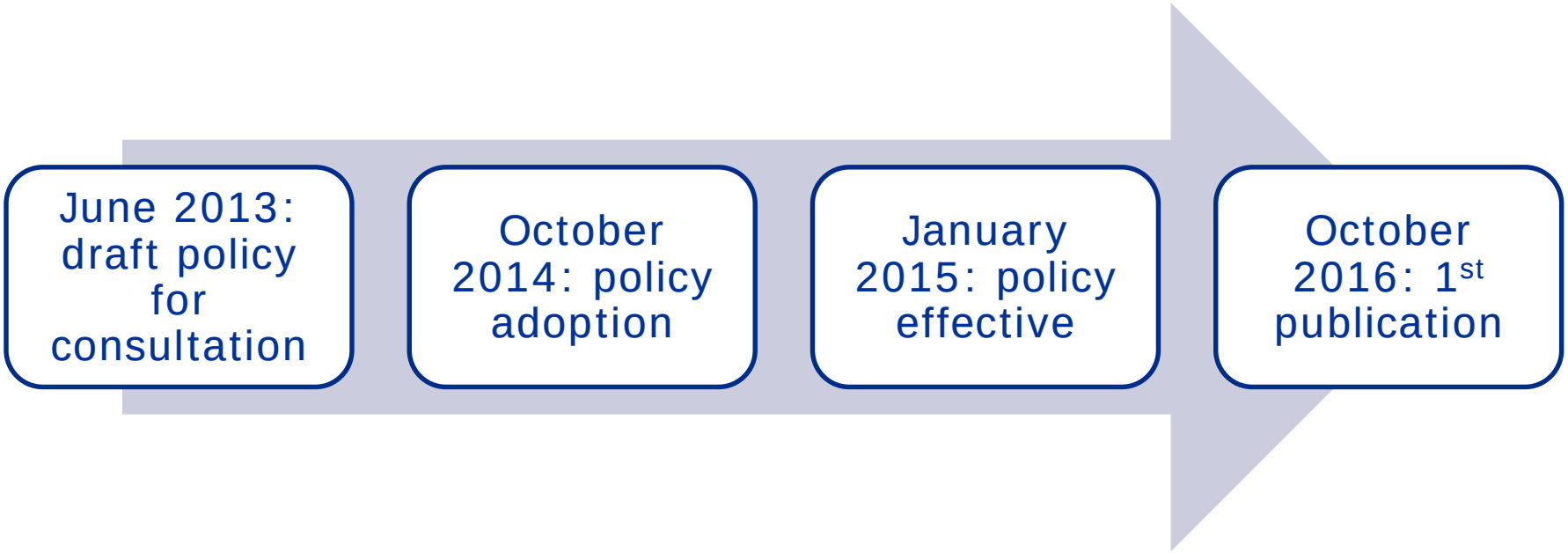
What is it:

- Publication of clinical data supporting CHMP Assessments

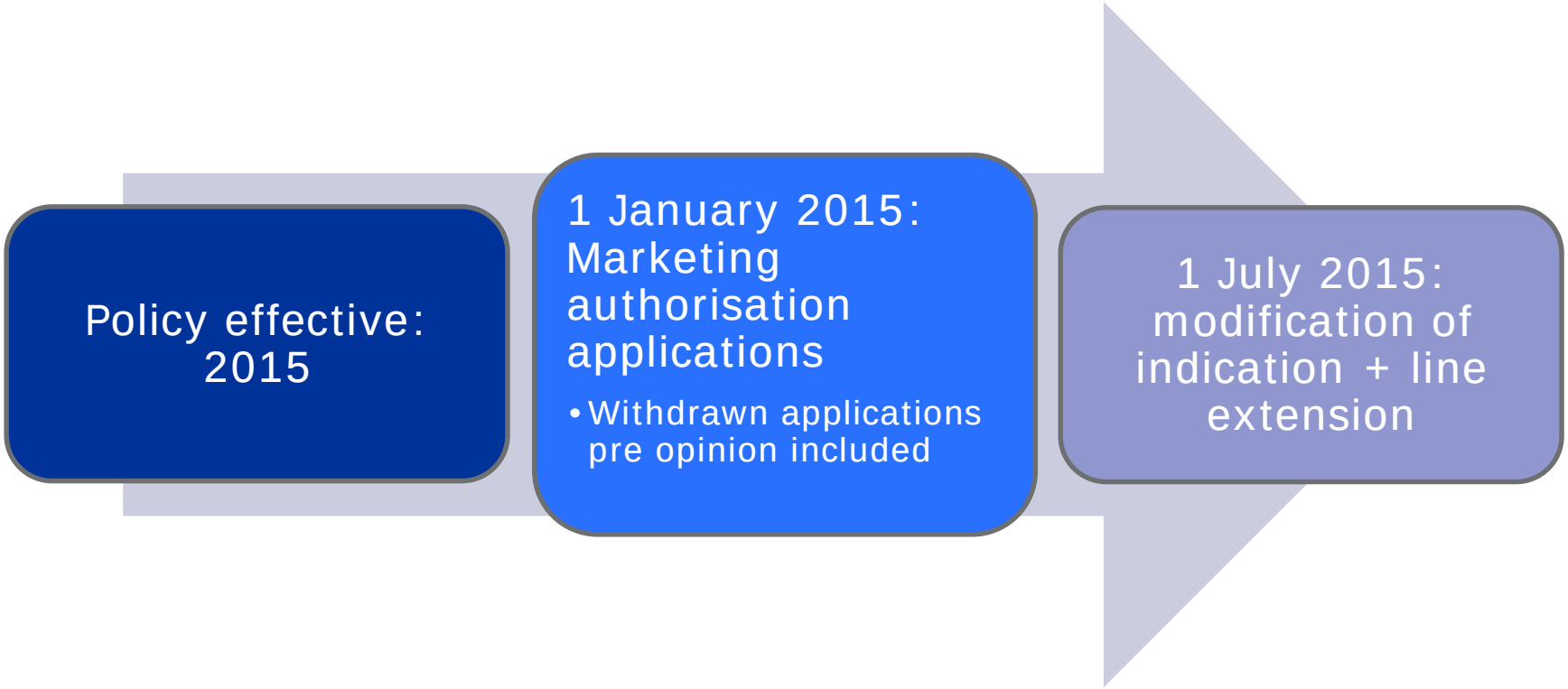
Benefits

- **Transparency**, continued EMA commitment
- Enables **public scrutiny**: establishes trust, confidence
- Avoids clinical trials **duplication**
- Enhanced **scientific knowledge**: value of secondary analysis

From Policy 0070 to CDP



Policy 0070 scope

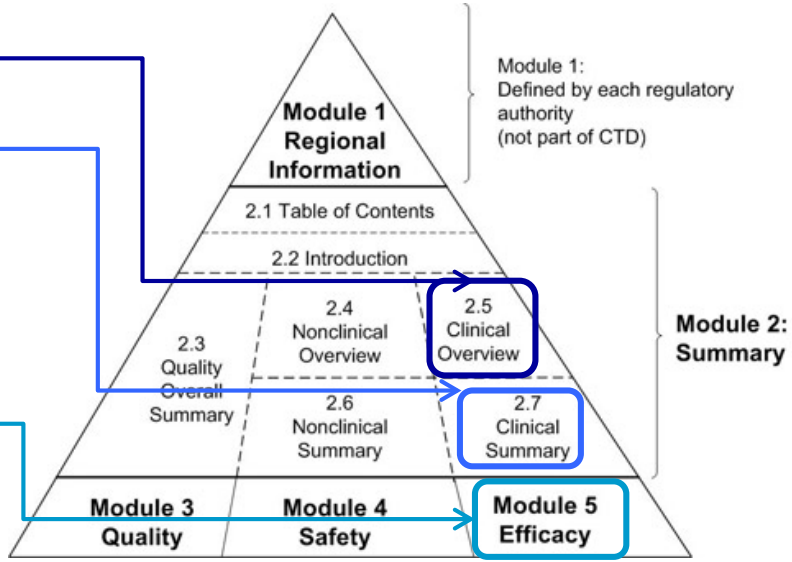


Type of published documents

- ***Module 2.5 - Clinical Overview***
- ***Module 2.7.1 to 2.7.4 - Clinical Summary***
- ***Module 5.3 Clinical Study Reports (CSR) - Body of the reports***
- ***Module 5.3 Clinical Study Reports – 3 appendices per CSR***
  - *16.1.1 (protocol and protocol amendments)*
  - *16.1.2 (sample case report form)*
  - *16.1.9 (documentation of statistical methods)*

+

- ***Anonymisation report***



- *For all applications falling within the scope of Policy 0070 whether studies were conducted in or outside the EU*
- *No Individual Patients Data (IPD) listings*

Policy implementation

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Phase I

- Clinical reports = clinical overview, clinical summary, clinical study reports, protocol & amendments, sample case report form, documentation of statistical methods
- **EMA is working on Phase I implementation**

Phase II

- Individual patient data (IPD)
- **Later stage**

CDP web access

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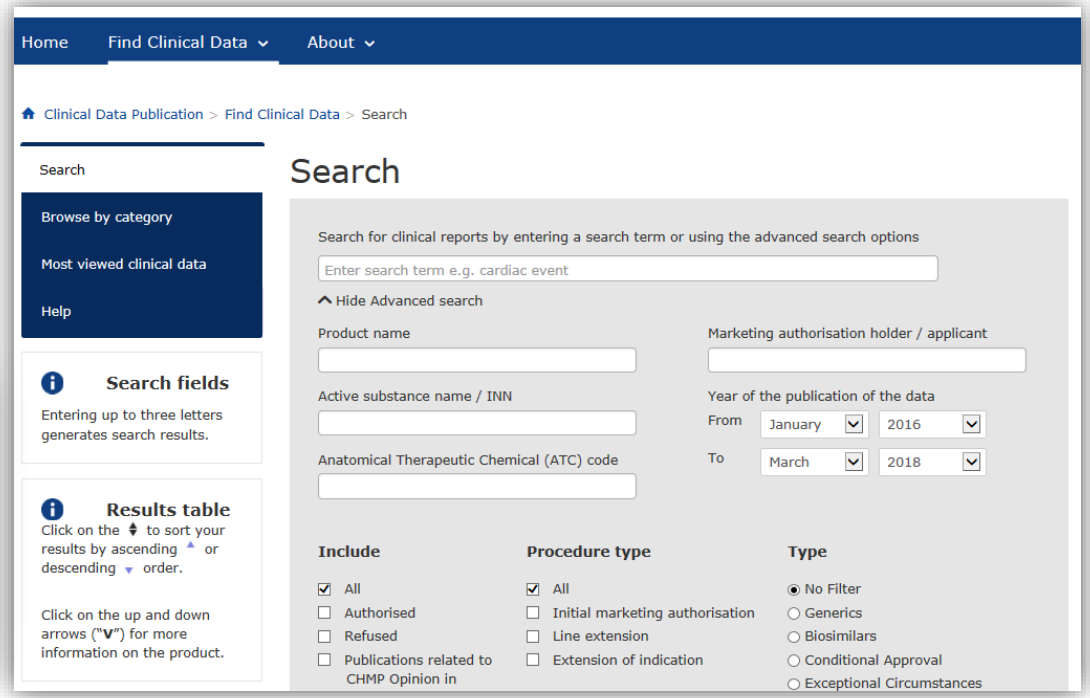
Press release

20/10/2016

Opening up clinical data on new medicines

EMA provides public access to clinical reports

As of today, the European Medicines Agency (EMA) gives open access to clinical reports for new medicines for human use authorised in the European Union (EU).



https://clinicaldata.ema.europa.eu

CDP web portal usage

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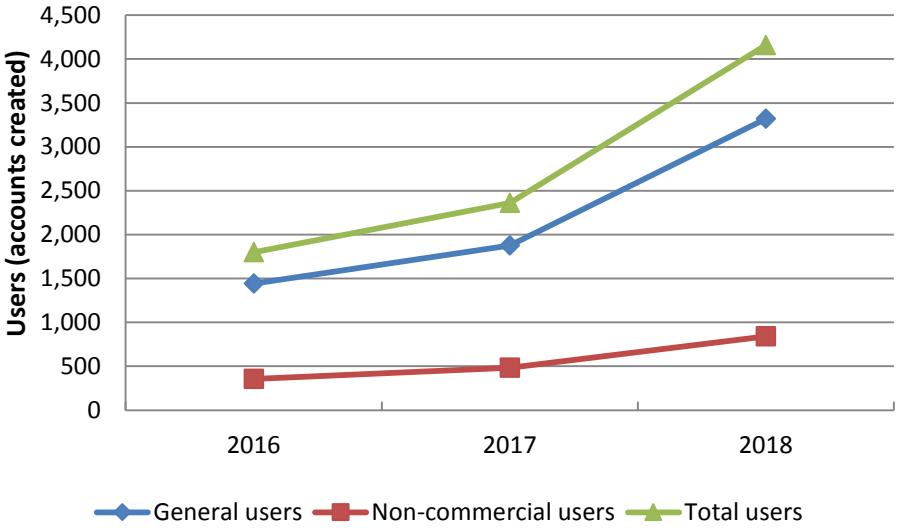
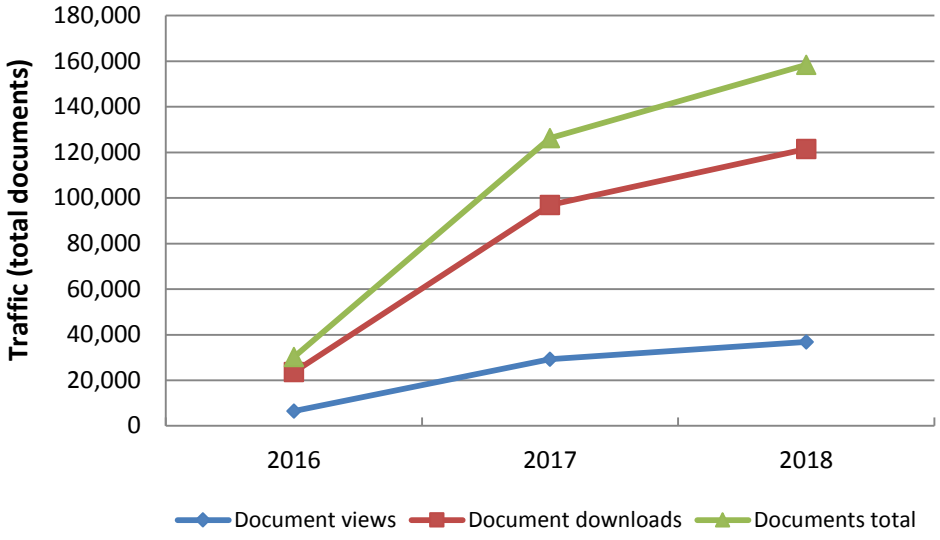
Registered accounts and documents views/downloads*





Average of:

- 11 documents viewed per **general user**
- 144 documents downloaded per **non-commercial user**

*Yearly cumulative data (Oct 2016- Q1 2018)

CDP process

More info on:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac05809f363e

- Support for industry on clinical data publication
- Technical Anonymisation Group
- Background to clinical data publication policy
- Documents from advisory groups on clinical-trial data

Data for the first 100 procedures published

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Type of published procedure	
Initial marketing authorisation	64
Extension of indication	33
Line extension	3
Total number of published procedures	**100**

Published documents	
Anonymisation Report	99
Module 2.5	127
Module 2.7.1-2.7.4	289
Module 5.3 (CSR)	4,656
Total number of documents	5,171
Total number of pages	2,231,330

Commercially Confidential Information (CCI)

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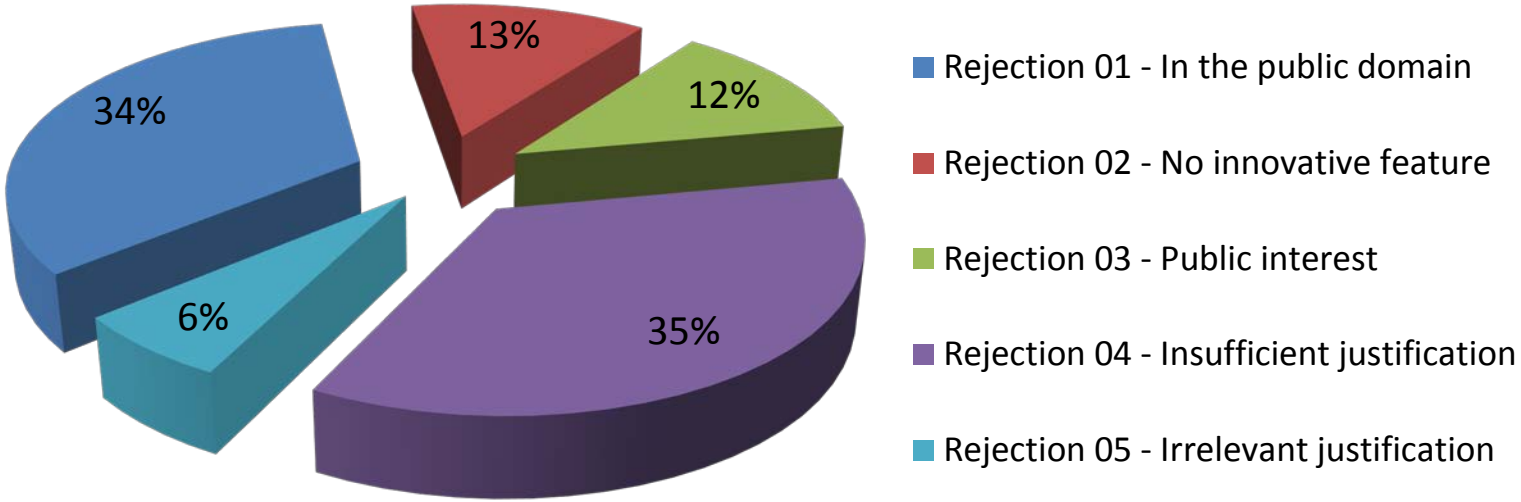
	Procedures		Documents		Pages	
Total published	**100**		**5,171**		**2,231,330**	
CCI proposed by the MAH/Applicant	56	56%	315	6.1%		
CCI accepted by EMA	41	41%	150*	**2.9%**	1,062	**0.0476%**

** documents with one or more proposed CCI redactions*

Rejection of CCI on 100 procedures

Of **943** instances (where CCI was proposed) in **315** individual documents, **35%** were accepted and **65%** rejected.



*An **instance** is defined as a single CCI proposal **per individual document** regardless of how many times it appears in that individual document.*

Anonymisation techniques (100 procedures)

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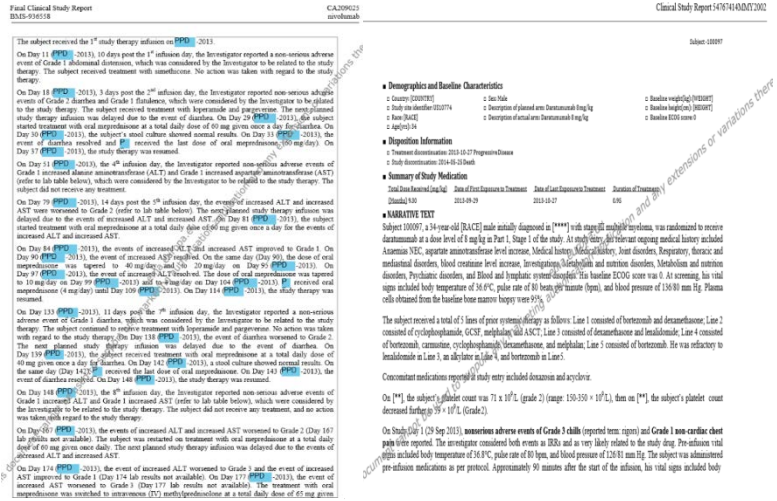

Final Clinical Study Report
BMS-936558

CA209025
nivolumab

Clinical Study Report 14767414DMY2002

The subject received the 1st study therapy infusion on PPD -2013.

On Day 11 (PPD -2013), 10 days post the 1st infusion day, the Investigator reported a non-serious adverse event of Grade 1 abdominal distension, which was considered by the Investigator to be related to the study therapy. The subject received treatment with simethicone. No action was taken with regard to the study therapy.

On Day 18 (PPD -2013), 3 days post the 2nd infusion day, the Investigator reported non-serious adverse events of Grade 2 diarrhea and Grade 1 flatulence, which were considered by the Investigator to be related to the study therapy. The subject received treatment with loperamide and pargeverine. The next planned study therapy infusion was delayed due to the event of diarrhea. On Day 29 (PPD -2013), the subject started treatment with oral mepredinisone at a total daily dose of 60 mg given once a day for diarrhea. On Day 30 (PPD -2013), the subject's stool culture showed normal results. On Day 31 (PPD -2013), the event of diarrhea resolved and P. received the last dose of oral mepredinisone (60 mg/day). On Day 37 (PPD -2013), the study therapy was resumed.

On Day 51 (PPD -2013), the 4th infusion day, the Investigator reported non-serious adverse events of Grade 1 increased alanine aminotransferase (ALT) and Grade 1 increased aspartate aminotransferase (AST) (refer to lab table below), which were considered by the Investigator to be related to the study therapy. The subject did not receive any treatment.

On Day 79 (PPD -2013), 14 days post the 5th infusion day, the events of increased ALT and increased AST were worsened to Grade 2 (refer to lab table below). The next planned study therapy infusion was delayed due to the events of increased ALT and increased AST. On Day 81 (PPD -2013), the subject started treatment with oral mepredinisone at a total daily dose of 60 mg given once a day for the events of increased ALT and increased AST.

On Day 84 (PPD -2013), the events of increased ALT and increased AST improved to Grade 1. On Day 90 (PPD -2013), the event of increased AST resolved. On the same day (Day 90), the dose of oral mepredinisone was tapered to 40 mg/day, and to 20 mg/day on Day 95 (PPD -2013). On Day 97 (PPD -2013), the event of increased ALT resolved. The dose of oral mepredinisone was tapered to 10 mg/day on Day 99 (PPD -2013) and to 4 mg/day on Day 104 (PPD -2013). P. received oral mepredinisone (4 mg/day) until Day 109 (PPD -2013). On Day 114 (PPD -2013), the study therapy was resumed.

On Day 133 (PPD -2013), 11 days post the 7th infusion day, the Investigator reported a non-serious adverse event of Grade 1 diarrhea, which was considered by the Investigator to be related to the study therapy. The subject continued to receive treatment with loperamide and pargeverine. No action was taken with regard to the study therapy. On Day 138 (PPD -2013), the event of diarrhea worsened to Grade 2. The next planned study therapy infusion was delayed due to the event of diarrhea. On Day 139 (PPD -2013), the subject received treatment with oral mepredinisone at a total daily dose of 60 mg given once a day for diarrhea. On Day 142 (PPD -2013), a stool culture showed normal results. On the same day (Day 142), P. received the last dose of oral mepredinisone. On Day 143 (PPD -2013), the event of diarrhea resolved. On Day 148 (PPD -2013), the study therapy was resumed.

On Day 148 (PPD -2013), the 8th infusion day, the Investigator reported non-serious adverse events of Grade 1 increased ALT and Grade 1 increased AST (refer to lab table below), which were considered by the Investigator to be related to the study therapy. The subject did not receive any treatment, and no action was taken with regard to the study therapy.

On Day 167 (PPD -2013), the events of increased ALT and increased AST worsened to Grade 2 (Day 167 lab results not available). The subject was restarted on treatment with oral mepredinisone at a total daily dose of 60 mg given once daily. The next planned study therapy infusion was delayed due to the events of increased ALT and increased AST.

On Day 174 (PPD -2013), the event of increased ALT worsened to Grade 3 and the event of increased AST improved to Grade 1 (Day 174 lab results not available). On Day 177 (PPD -2013), the event of increased AST worsened to Grade 3 (Day 177 lab results not available). The treatment with oral mepredinisone was switched to intravenous (IV) methylprednisolone at a total daily dose of 65 mg given

Subject-100097

- Demographics and Baseline Characteristics
  - Country [CODETRT]
  - Study site identifier [SITEID]
  - Race [RACE]
  - Age[yrs]:34
  - Sex: Male
  - Description of planned arm: Daratumumab 8 mg/kg
  - Description of actual arm: Daratumumab 8 mg/kg
  - Baseline weight[kg] [WEIGHT]
  - Baseline height[cm] [HEIGHT]
  - Baseline ECOG score:0
- Disposition Information
  - Treatment discontinuation: 2013-10-27 Progressive Disease
  - Study discontinuation: 2014-01-20 Death
- Summary of Study Medication

Total Dose Received [mg/kg]	Date of First Exposure to Treatment	Date of Last Exposure to Treatment	Duration of Treatment
[blanks] 9.00	2013-09-29	2013-10-27	0.95

- NARRATIVE TEXT

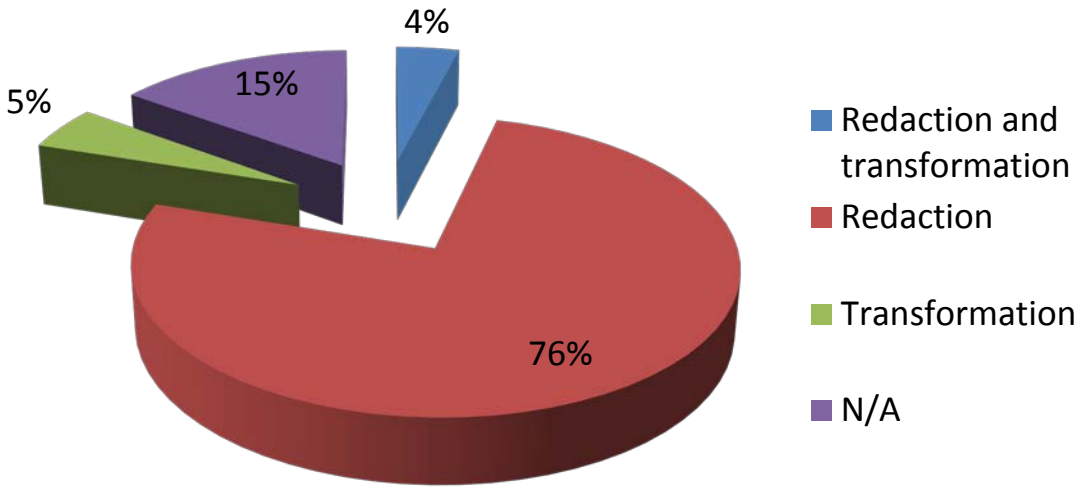
Subject 100097, a 34-year-old [RACE] male initially diagnosed in [****] with stage III multiple myeloma, was randomized to receive daratumumab at a dose level of 8 mg/kg in Part 1, Stage 1 of the study. At study entry, his relevant ongoing medical history included Anaemia NEC, aspartate aminotransferase level increase, Medical history, Medical history, Joint disorders, Respiratory, thoracic and mediastinal disorders, blood creatinine level increase, Investigations, Osteoporosis and nutrition disorders, Metabolism and nutrition disorders, Psychiatric disorders, and Blood and lymphatic system disorders. His baseline ECOG score was 0. At screening, his vital signs included body temperature of 36.6°C, pulse rate of 80 beats per minute (bpm), and blood pressure of 136/80 mm Hg. Plasma cells obtained from the baseline bone marrow biopsy were 95%.

The subject received a total of 5 lines of prior systemic therapy as follows: Line 1 consisted of bortezomib and dexamethasone; Line 2 consisted of cyclophosphamide, GCSF, melphalan, and ASCT; Line 3 consisted of dexamethasone and lenalidomide; Line 4 consisted of bortezomib, carmustine, cyclophosphamide, dexamethasone, and melphalan; Line 5 consisted of bortezomib. He was refractory to lenalidomide in Line 3, an alkylator in Line 4, and bortezomib in Line5.

Concomitant medications reported at study entry included donazonn and acyclovir.

On [**], the subject's platelet count was 71 x 10^9/L (grade 2) (range: 150-350 × 10^9/L), then on [**], the subject's platelet count decreased further to 39 × 10^9/L (Grade2).

On Study Day 1 (29 Sep 2013), **nonserious adverse events of Grade 3 chills** (reported term: rigors) and **Grade 1 non-cardiac chest pain** were reported. The investigator considered both events as IRRs and as very likely related to the study drug. Pre-infusion vital signs included body temperature of 36.9°C, pulse rate of 80 bpm, and blood pressure of 126/81 mm Hg. The subject was administered pre-infusion medications as per protocol. Approximately 90 minutes after the start of the infusion, his vital signs included body



Redaction vs. Transformation

2018 so far

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- Continue **collaboration** with industry towards:
  - Improving preparation of **CCI proposals** and rationales
  - Improving clarity and **quality** of **AnR** with implementation of a feedback step in the process

- Ensure **guidance**, **templates** and **tool kit** are used and up-to-date (update planned after summer)
- As of **13 June 2018**:
  - 102 procedures published
  - 24 procedures ongoing
  - 49 procedures for which applicants/MAHs have been contacted
  - 217 procedures in the pipeline

International Collaboration

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- Following respective transparency initiatives
- Sharing experience with Health Canada, FDA, Japan
- Organising staff visits to share knowledge and practice
- Examining opportunities for harmonisation and international alignment when legal frameworks permit

TAG Anonymisation – Background

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- The Agency published in March 2016 the External guidance on the anonymisation of clinical reports which provides information to the pharmaceutical industry on the anonymisation of clinical reports;
- The field of anonymisation, and in particular the techniques used by controllers of personal data to anonymise data, is a field of active research and rapidly evolving;
- Therefore, anonymisation poses a challenge for all parties involved in the anonymisation of clinical reports (pharmaceutical industry, CROs and EMA) as well as those wanting to access the data (patients and healthcare professionals);
- EMA has identified the need to continue the work undertaken during the development of the guidance and will seek input from experts in the field by setting up a **Technical Anonymisation Group** (TAG);
- In March 2017, EMA launched a public call for applications.

TAG Anonymisation – Composition

The TAG is composed of 20 members with a broad range of expertise, ensuring a diverse representation of the various stakeholders as follows:

- Data protection lawyers/experts from Data Protection Authorities
- Industry professionals with direct experience in the anonymisation of clinical reports
- Professionals involved in development of de-identification standards and/or guidance
- Patients organisations representative
- EMA staff members

TAG Anonymisation – Objectives (1/2)

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The overall objective of the TAG is to further develop best practices for the anonymisation of clinical reports, by monitoring and addressing any issues arising in the context of the implementation of phase I of policy 0070.

The following tasks will be undertaken:

- To learn from the **experience gained** with the publication of the first clinical reports and to assess best practices in the field of anonymisation, assess patient re-identification and any privacy risk, taking into account EU law on data protection;
- To understand the **challenges** encountered by **pharmaceutical industry** while anonymising the reports for publication.

TAG Anonymisation – Objectives (2/2)

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- To **investigate** if **data transformation** resulting from the anonymisation techniques used can lead to a different interpretation of the study results;
- To investigate the **scientific utility** of the clinical data published as a function of the methodology used by the Applicant/MAH in the anonymisation of the reports, and establish whether **secondary analysis** of clinical data can be successfully undertaken using the data published by the Agency;
- To follow **new technological developments** that might impact on the anonymisation of clinical reports and establish adequate measures to keep the risk of re-identification to an adequate level.

TAG Anonymisation – Deliverables

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The Agency, based on the outcome of the work of the TAG, will:

- make any necessary amendments to the external guidance on anonymisation of clinical reports.
- develop additional guidance (e.g. Q&A) to further clarify certain aspects of the methodology described in the external guidance on the anonymisation of clinical reports, if necessary.
- draft a critical review of the impact of new technological developments on the anonymisation of clinical reports, in particular on the methodology used to adequately anonymise clinical reports and the potential impact on the recommended threshold for public release.

TAG Anonymisation – Transparency

- The list of members of the TAG is published in the EMA website together with their declaration of interest (DoIs) and curriculum vitae (CV).
- The progress of the work undertaken by the TAG will be made public through the drafting of periodic reports which will subsequently be published in the Agency's website.
- Minutes and agendas of the meetings will also be published by the Agency.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001880.jsp&mid=WC0b01ac0580c77e78

TAG Anonymisation - First meeting

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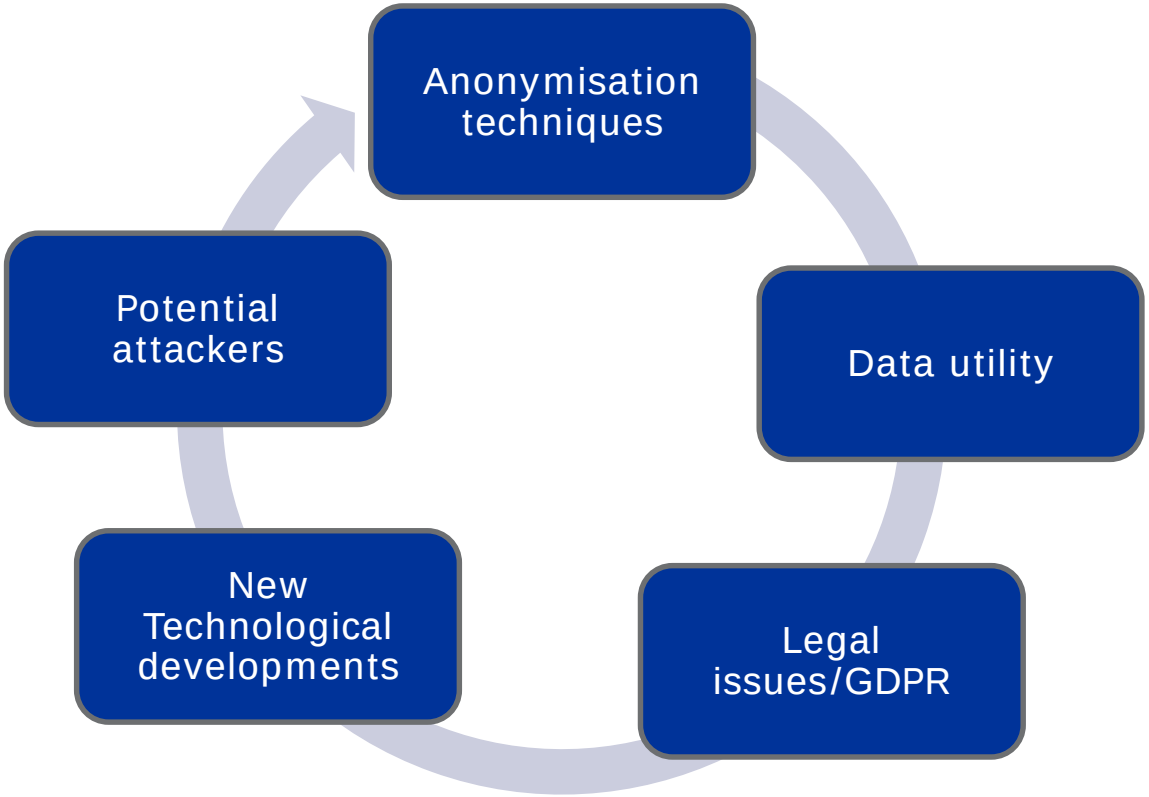
- The first TAG meeting took place on **29-30 November 2017**;
- Topics discussed during the meeting:
  - Review of clinical reports published from October 2016 to October 2017 performed by EMA and by PhUSE;
  - Experience from Pharmaceutical Industry with the anonymisation of clinical reports;
  - EMA experience with the review of Anonymisation Reports;
  - Review of quantitative methods to measure the risk of re-identification;
  - Data utility in anonymised clinical reports;
  - Adversary knowledge
  - Legal issues with the anonymisation of clinical reports and the impact of the GDPR.

TAG Anonymisation subgroups



TAG - Next Steps

- Next face-to-face meeting of the TAG to take place in 23-24 October 2018;
- Tele/video conferences of each subgroup are taking place ~ every 2 to 3 months and additional *ad hoc* TCs may also be organised;
- Based on the outcome of the discussions the Agency will develop additional guidance (e.g. Q&As).

Thank you for your attention

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Health Canada's Guidance on the Public Release of Clinical Information

uOttawa

14 June 2018

Context

- As part of Vanessa's Law (VL), the *Food and Drugs Act* was amended to increase the disclosure of information on therapeutic products (i.e. drugs and medical devices).
- VL introduced Governor-in-Council regulation making authorities to specify when information regarding therapeutic products ceases to be confidential business information, and to authorize the disclosure of the information.
- On December 9, 2017 regulations were proposed and published in Canada Gazette I.
- From October, 2017 to April, 2018 Health Canada met with an Expert Stakeholder Reference Group (with a balanced representation of stakeholders) to gather feedback on the implementation of the regulations.
  - Feedback focused on the criteria and redaction of commercially sensitive information, the de-identification of patient information, terms of use and the end-user experience.
- On April 10, 2018 Health Canada published a draft guidance document on the implementation of the Public Release of Clinical Information for a 75-day public consultation – deadline to submit comments is June 25th, 2018.

Policy Objective

- Make de-identified clinical information in drug submissions and medical device applications publicly available for non-commercial purposes following the completion of Health Canada's regulatory review process.

- Enable independent analyses of clinical data leading to a more comprehensive understanding of the drug or medical device.

Scope of proposed regulations

- **Drugs:** Clinical trial information (i.e. safety and efficacy information) related to completed clinical trials and studies, used to support the proposed conditions of use and purpose for which the new drug is recommended.
  - Information ceases to be CBI following final regulatory decision (negative or positive, e.g. NOC, NON-W, NOD-W)
  - Applies to information in past submissions and new submissions

- **Devices:** Clinical trial information (i.e. safety and effectiveness information) related to completed clinical trials and studies, which support its use for the medical conditions, purposes and uses for which it is manufactured, sold or represented.
  - Information ceases to be CBI following final regulatory decision (negative or positive, e.g. Device Licence or Refusal Letter)
  - Applies to information in past applications and new applications

What will be released?

Drugs:

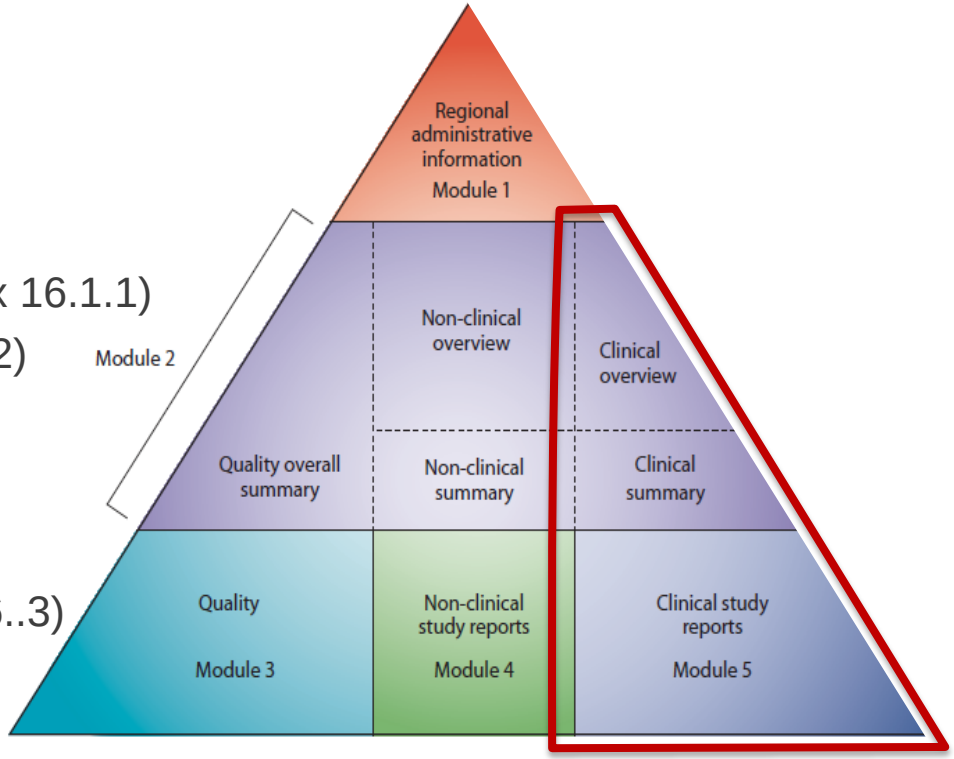
- Clinical summaries (module 2.5)
- Clinical overviews (module 2.7)
- Clinical study reports (module 5.3)

Including:

- Study protocol and amendments (appendix 16.1.1)
- Sample case report forms (appendix 16.1.2)
- Statistical analysis plan (appendix 16.1.9)

Excluding:

- Individual patient listings (appendix 16.2)
- Completed case report forms (appendix 16..3)



Medical devices:

Implementation delayed until the adoption of IMDRF-ToC

When will the release process be initiated?

Positive decisions

Drugs & Medical devices:

– HC will initiate publication on the date of the notice/licence.

Negative decisions

Drugs:

– HC will initiate publication 31 days after the date of the notice

– If a Letter of Intent for Reconsideration is received, upon completion of the reconsideration process (70-140 days) in accordance with the timelines set out in the Guidance “Reconsideration of Final Decisions Issued for Human Drug Submissions”.

Medical devices:

– HC will initiate publication 31 days after the date of the Refusal Letter

– If first level appeal, 21 days after receipt of Letter of Intent to Appeal, or if second level appeal, upon notification of decision in accordance with the timelines set out in the Guidance “Management of Applications for Medical Device Licenses and Investigational Testing Authorizations”.

Past submissions

- Upon receipt of a complete request, subject to prioritization.

Implementation steps for the proactive public release of clinical information

Proposed Phase-in	Scope of application types
Year 1	NDS-NAS, SNDS-c & Rx-switch
Year 2	All NDS + SNDS-c & Rx-switch
Year 3	All NDS, all SNDS & Class IV devices
Year 4	All NDS, SNDS, ANDS, SANDS, Class III & IV devices

See Appendix D of the Draft Guidance for publication timelines.

On request publication process for clinical information within past submissions and applications

- Request form
  - Members of the public complete an electronic request form, which includes:
    - product name and information requested (e.g. clinical study report, clinical overview, clinical summary).

    And, where possible:
    - submission/application number
    - study name
    - name of the manufacturer
    - date of the regulatory decision (e.g. notice of compliance).
- Prioritization
  - Health Canada will prioritize requests should the demand for past clinical information exceed the Department's administrative capacity.
  - Prioritization will focus on disclosing information with the highest health system impact, e.g. considerations will be given to requests from health system organizations, products that are abundantly used, and products that have demonstrated to be of high public interest.

Redactions of commercially valuable information

- Given adequate justification, Health Canada will not release three categories of information:
  A. Clinical information falling within scope of the two exceptions to the regulations and subject to the FDA definition of CBI
  B. Non-clinical information subject to the FDA definition of CBI
  C. Confidential information from foreign regulators

- Proposed redactions are to be submitted to Health Canada using the Redaction Control Sheet (template provided in Appendix F of the Draft Guidance)

Redactions of commercially valuable information

Category A: Clinical information falling within scope of the two exceptions to the regulations and subject to the FDA definition of CBI

1. Clinical information that was not used by the manufacturer in the submission, application or supplement to support the proposed conditions of use for the new drug or the purpose for which the new drug is recommended.
   - E.g. secondary outcome measure data presented in a CSR being used to support additional trials to gain approval for a new indication of use. Release of this information could provide a competitor with insight about the drug's future uses.

2. Clinical information that describes tests, methods or assays used exclusively by the manufacturer.
   - E.g. Confidential novel modifications to a bioassay used exclusively by the manufacturer to collect clinical data. Such modifications may rely on considerable effort and investment by the manufacturer and may be used for other ongoing studies or routine use.

Redactions of commercially valuable information

Category B: Non-clinical information subject to the FDA definition of CBI

- Information that does not fall within the two exceptions to the regulations, but is not in scope of the public release of clinical information (i.e. not clinical information) may be protected when it meets the FDA definition of CBI
- This may include:
  - Chemistry information that meets the definition of CBI
  - Manufacturing information that meets the definition of CBI
  - Contract information that meets the definition of CBI
  - Confidential information from a foreign regulator

Review of proposed redactions

- Proposed redactions may be rejected for the following reasons:
  I. When the manufacturer fails to adequately demonstrate how the information was not used to support the conditions of use or purpose for the drug or device, as set out in the submission or application;
  II. When the manufacturer fails to adequately justify how the proposed information describes a test, method, or assay that is used exclusively by the manufacturer;
  III. When the manufacturer fails to demonstrate the specified information is out of scope;
  IV. When the proposed redaction pertains to information already in the public domain.
- Health Canada will inform the manufacturer of any proposed redactions that the Department rejects. Manufacturers will be given one additional opportunity to further justify a redaction following Health Canada's review.

Anonymization of clinical data

Guiding principles:

1 - All transformation of data should be conducted for the sole purpose of preventing the disclosure of personal information;

2 - All data transformations should be accompanied by robust justification, and be applied to limited variables that risk re-identification, not to broad sections of clinical information;

3 - Data transformation should favour methods that retain analytical value, e.g. generalization, randomization and offsetting, as opposed to redaction.

Process:

- Step 1: Classify the variables
- Step 2: Measure the data risk
- Step 3: De-identify the data

Anonymization report

Anonymization of clinical data
Step 1: Classify the variables

- Directly-identifying variables:
  - Generally directly-identifying variables are not used for analysis
  - Can include subject identification numbers
  - Risk to re-identification may be high

- Indirectly-identifying variables:
  - Other identifying variables that fall within the definition of ‘personal information’ within Canada’s *Privacy Act*.
  - Indirectly-identifying variables may be used for analysis
  - Risk to re-identification must be measured in order to require anonymization
  - Anonymization is required when the variable poses a serious risk of re-identifying an individual, when combined with other available information
  - Anonymization must be carefully justified, in line with the guiding anonymization principle number 2.
  - Variables which do not present a serious risk of re-identifying an individual are not considered personal information and should not be transformed.

Anonymization of clinical data
Step 2: Measure the data risk

- Risk measurement must be documented to justify any subsequent data transformation
- The overall risk of re-identification is the product of the risk inherent to the data and the risk associated with the context of the release.
- The context risk for the PRCI is unreducible
- Health Canada recommends an overall risk threshold of 9%
- A risk threshold of 9% equates to a cell size of 11 patients
- Indirectly-identifying variables that are associated with a patient belonging to a cell of less than 11 should be anonymized
- Directly-identifying variables should be assumed to carry a 100% risk of re-identification

Anonymization of clinical data
Step 3: Anonymization of the data

- Directly-identifying variables may be anonymized through the process of redaction, pseudonymization, or randomization.
- Health Canada encourages the generalization of indirectly identifying variables.
- Resynthesis of the variable following generalization may avoid the appearance of anonymization and achieve further risk reduction due to inability to identify leaked identifiers.

Anonymization report

- Health Canada requests that the manufacturer submit a single anonymization report for each clinical submission
- The anonymization report aims to describe:
  - The methodological approach taken,
  - The classification of the data variables (directly vs indirectly identifying) with justification
  - The risk measurement of the original clinical information
  - The anonymization techniques employed
  - The risk measurement following the process of anonymization
  - The efforts and considerations taken to maximize the utility of the data

Relying on previously-redacted information

- The manufacturer may submit to Health Canada final redacted documents that were previously accepted by the EMA.
- Upon receipt of Health Canada's initiation of the clinical data publication process, a manufacturer may submit the certification letter when the identical information in scope of PRCI was previously released by the EMA under policy 0070.
- A template certification letter, to certify equivalency of the information submitted to the EMA and Health Canada, is provided in Appendix H of the Draft Guidance
- For partial certification, manufacturers may resubmit the same information with certification, and only redact the outstanding components for Health Canada.
- All submissions should be transmitted through the CESG.

Thank you

The draft guidance will be open for public comments for a 75-day period (closing June 25, 2018).

When preparing your comments, please indicate the relevant section(s) and line numbers (in PDF version) to which your comments relate.

Comments can be sent by email to: hc.rmod.stakeholders-intervenants.dgro.sc@canada.ca.

Guidance Appendix D: Publication timelines

PRCI Process step(s):	1 – Commence PRCI process:	2 – Product sponsor provides data package for PRCI:	3 – Health Canada internal review	4 – Sponsor review of PRCI package (if required):	5 – Publication of records in scope of PRCI:
Positive regulatory decision: **FDR:** **C.08.004,** **C.08.004.01** **MDR:** **36(1)(a) or (b)**	Process starts on day of decision	i. Sponsor notified, PRCI data package requested; ii. *If required, Health Canada provides digitised records; iii. Sponsor prepares proposed redactions & anonymizations, as per guidance; iv. Sponsor provides Health Canada with PRCI data package.	i. Health Canada receives redaction & anonymization package from sponsor; ii. Health Canada conducts quality assurance for data completeness; iii. Health Canada vets proposed redactions & anonymization report; iv. (If required, Health Canada returns package to sponsor for corrections (triggering step-4 otherwise Health Canada proceeds to step-5).	i. Sponsor makes corrections to PRCI data package; ii. Sponsor provides corrected database package to Health Canada; iii. Health Canada will consider revised and valid redaction justifications.	i. Health Canada publishes data in accordance with applicable regulations; ii. Requestor(s) and sponsors of data notified, if applicable.
Negative regulatory decision: **FDR:** **C.08.004(3)** **C.08.004.01(3)** **MDR:** **38**	Process delayed for 30 days for sponsor reconsideration(s) or appeal. Trigger of reconsideration or appeal process would delay process an additional 70-120 days.				
Negative Decision	Day 0 + 30	Day 31-50	Day 51-65	Day 66-80	Up to 90 days total
Time forecasts:	(pos) = 0 days (neg) = +30 days	+20 days	+15 days	+15 days (if required)	+10 days

FDA's Clinical Summary Pilot

Regulatory Background

- Requirement for disclosure of "Summary Basis of Approval" at the time of drug approval
  - 21 CFR 314.430(e)(2); sec 505(l) of the Federal Food, Drug, and Cosmetic Act
  - SBA may be prepared by applicant or FDA
- Current practice: release of "action package"
  - FDA reviews for all relevant disciplines, e.g., medical and toxicology, and other decision documents
  - Labeling
  - Certain documents submitted by the sponsor, e.g., Risk Evaluation and Mitigation Strategies (REMS)
  - All action packages are redacted for confidential information such as trade secret (TS) and confidential commercial information (CCI) and personal privacy information (PPI)

Reasons for pilot

- Action packages are a sometimes cumbersome way to share information about approval decisions
- Medical reviews often recapitulate Clinical Study Reports (CSRs)
- FDA's views and assessments may be hard to discern
- Calls for more transparency and more accessible information about the basis for approval decisions
- Current international trend toward greater clinical data disclosure

Goals of Pilot

- To test whether releasing portions of CSRs is a better way to provide a summary basis of each approval to:
  - Increase transparency of approvals
  - Increase usefulness to the healthcare community of the information we release
  - Ultimately, improve clarity of FDA's communication about the basis for NDA approvals by allowing streamlined medical reviews

Design of pilot

- Select up to 9 volunteer sponsors to participate
  - Criteria for selection:
    - NMEs and efficacy supplements of scientific/public health interest
    - Variety of disease areas
    - Timing of approval
      - Approvals to be spaced out over 2018
  - BLAs excluded in initial pilot

Design of pilot II

- If sponsor agrees to participate:
  - FDA makes final decision whether to include in pilot
- After approval, FDA posts the following portions of CSRs:
  - Summary of studies
    - Minus adverse event report (AER) listings at end of summary section
  - Protocols and amendments
  - Statistical analysis plan
- Pivotal trials supporting approval only

Redactions

- FDA redacts for CCI, trade secrets, and PPI
- Same process/standards as for Action Packages and Freedom of Information Act (FOIA) requests
  - No sponsor pre-review of redactions
- FDA's redactions may differ from those in the European Medicines Agency (EMA) program
  - Different legal standards for CCI and PPI

Personal Privacy Information

- FDA regulations generally require deletion of "the names or other information which would identify patients or research subjects in any medical or similar report, test, study, or other research project," before FDA records are made publicly available. 21 CFR 20.63

- FDA also protects personal privacy information (PPI) under exemption (b)(6) of the Freedom of Information Act (FOIA), if disclosure "would constitute a clearly unwarranted invasion of personal privacy."

- FOIA does not provide absolute protection of PPI.

- Instead, it creates a balancing test: does the privacy interest outweigh the public interest in disclosure?
  - Presumption in favor of disclosure

Patient Data

- FDA will not be disclosing line level patient data.
  - FDA's goal in the pilot is to disclose only "summary" data, not full data sets.
  - FDA will not disclose full narratives of adverse events.
  - If individual AERs or other patient level information are summarized in body of CSR, FDA will redact:
    - Patient identifiers and associated site identifiers
    - Other information that could identify a patient, e.g., death date, SSN.
  - Demographic information generally will not be redacted.

Other Individual Information

- FDA generally will not redact:
  - Names of sponsor employees, clinical investigators, and data monitoring committee members, 21 CFR 20.63(d)
  - Names of contractor employees if the contract relationship is public
  - Signatures, including wet signatures, and business contact information when the individual's name (e.g., name of a sponsor's employee) is otherwise disclosable

Next steps

- FDA will conduct an internal assessment of the pilot.
- FDA plans to solicit feedback through a Federal Register notice.
- FDA will evaluate in context of initiatives to modernize new drug review.
- FDA will continue interactions with EMA/Health Canada.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Biographies of Presenters

Anne-Sophie Henry-Eude *graduated as Doctor in Pharmacy in 1999 at the University of Lille in France. She also has a post graduate in Pharmacovigilance & Pharmacoepidemiology as well as in Regulatory Affairs. After two years in the pharmaceutical industry where she worked in Regulatory Affairs and in the field of medical devices, Dr. Anne-Sophie Henry-Eude joined the anti-infectives and immunology team at EMA in 2001 where she worked on in particular referral procedures, pandemic influenza and infectious diseases. In 2011 she transferred to the EMA paediatric team to work especially on paediatric investigation plans to prevent and treat HIV in children. In 2013 Dr. Henry-Eude became the Head of the new Access to Documents Service at EMA and later on, with the implementation of Policy 0070 (Clinical Data Publication), the Head of Documents Access and Publication Service within the Office of the Deputy Executive Director. Dr Henry-Eude is also a member of the EMA Technical Anonymisation Group (TAG).*

Dr. Monica Dias *studied pharmacy in Lisbon, Portugal and graduated with a Pharmacy graduate degree from the University of Lisbon in 1996. She proceeded to postgraduate studies and obtained her PhD from the University of Cardiff, UK. Her research focused on the permeation of drugs through the skin. Her postgraduate studies were funded by the Portuguese Ministry of Science and technology. She has several publications in Peer review journals. Dr. Dias joined Disperse Technologies Limited in Guildford, UK in 2000. She was involved in the research and development of a range of topical dosage forms. She joined the European Medicines Agency in London, UK in 2004. She worked in the Quality Office, Specialised Scientific Disciplines Department, for 10 years managing marketing authorisation applications and providing technical and scientific input to scientific advice procedures, paediatric investigation plans and referral procedures. In March 2013 she joined the Office of the Deputy Executive Director at EMA where she is now a Policy and Crisis Coordinating Officer. She was involved in the development and finalisation of Policy 0070 and continued with the implementation of this policy focusing on the data privacy aspects of the publication of clinical data. She led the development of the External guidance on the anonymisation of clinical reports for publication. Dr Dias is also the Chair of the EMA Technical Anonymisation Group (TAG).*

Andre Molgat *is a Senior Regulatory Policy Adviser in the Health Products and Food Branch of Health Canada with scientific review responsibilities. He is a core member of the team responsible for Health Canada's initiative on the Public Release of Clinical Information.*

Ann Witt *received her BA from Bryn Mawr College, and JD from Stanford Law School. After 1-year clerkship in the 9th Circuit Court of Appeals, she came to work at FDA in 1980 in the Office of Chief Counsel. Ann worked on new drug and device issues until 1991, and then spent a year heading the office responsible for overseeing prescription drug promotion. For the next 10 years, she worked in the Office of the Commissioner on issues including the tobacco investigation and the development pediatric testing requirements. Beginning in 2002, she worked in the House of Representatives for Congressman Henry Waxman and the Energy and Commerce Committee, and returned to the FDA in 2009 and worked in the Office of the Commissioner on issues including transparency, drug safety, and modernization of FDA's authority over cosmetics and OTC drugs. Ann recently began work in CDER's Office of New Drugs, where she is working on the CSR Disclosure pilot among other projects.*