Transparency of Regulatory Data across the European Medicines Agency, Health Canada, and US Food and Drug Administration

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Abstract: Based on an analysis of relevant laws and policies, regulator data portals, and information requests, we find that clinical data, including clinical study reports, submitted to the European Medicines Agency and Health Canada to support approval of medicines are routinely made publicly available.

Historically, sponsors and regulatory agencies have kept confidential much of the clinical data generated to support the approval and continued monitoring of small molecule and biologic drugs (i.e., regulatory data). Notable cases, such as rofecoxib (Vioxx) and gabapentin (Neurontin), revealed how treating data as confidential can conceal important information about drug safety and efficacy, as well as improper research practices, including the selective publication and reporting of trial results.[1] Providing access to these data may not only help prevent unscrupulous research practices, but also advance our understanding of the safety and effectiveness of medical products.[2]

Over the past two decades numerous initiatives have been launched to make regulatory data, including clinical study reports (CSRs) and individual patient-level data (IPD), publicly available.[3] For instance, there are data sharing initiatives organized by industry (e.g. ClinicalStudyDataRequest.com [CSDR]) and independent organizations (e.g. Yale University Open Data Access [YODA] Project).[4] While these efforts have advanced transparency for many medical products,[5] they have not gained traction industry-wide and remain constrained by their lack of authority to require companies to make data publicly available.[6] In contrast, regulatory agencies, as gatekeepers of market authorization, are best positioned to disclose data, particularly clinical data submitted for regulatory review.

Several laws and policies — some recent — authorize the European Medicines Agency (EMA) in Europe, Health Canada (HC) in Canada, and the Food and Drug Administration (FDA) in the United States

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to make clinical data of drugs publicly available, either proactively or reactively in response to information requests. These data (**Box 1**), such as clinical summaries, CSRs, individual case safety reports, and other information sponsors must submit to regulators, contain substantially more information than published articles and can be used to more comprehensively ascertain the risks and benefits of drugs, assess regulatory decisions, and inform clinical decision making.[7]

While regulatory data have been relied on for many studies, including systematic reviews and meta-analyses,[8] there is substantial opportunity to increase use of regulatory data for secondary research.[9] For example, one survey found that only 3% of authors of Cochrane Reviews obtained data from regulatory agencies.[10] Raising awareness of the scope of clinical data made available across the EMA, HC, and FDA, and the most efficient ways to obtain it, may increase the use and utility of clinical research data for patients, clinicians, and researchers.

In this analysis, we provide an overview of the key laws and policies governing disclosure of data at the EMA, HC, and FDA, including how each regulator defines certain data as "confidential commercial information" (CCI) that may be kept secret. Based on a review of agency data sharing portals, published research on information requests, and our own parallel information requests, we then compare the accessibility and comprehensiveness of data proactively disclosed and made available upon request by the EMA, HC, and FDA. Lastly, we propose ways for these regulatory bodies to enhance transparency.

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Transparency Laws and Policies

European Medicines Agency

Policy 0043 and Policy 0070 govern the EMA's approach to providing access to regulatory data for drugs and biologics (**Table 1**). Policy 0043, adopted in 2010, authorizes the EMA to release data reactively.[11] Policy 0070, adopted in 2014, authorizes the EMA to proactively publish data on an online data sharing portal.[12] The scope of policy 0043 is expansive, providing access to any document originated, received, or held by the EMA. The scope of Policy 0070 is narrower, applying only to data submitted under the central marketing authorization procedure after January 1, 2015. EMA plans to implement Policy 0070 in two phases. Phase 1 publishes clinical reports, which include clinical overviews, clinical summaries, CSRs, along with several appendices to the CSRs, including protocol and protocol amendments, sample case report forms (CRFs), and statistical analysis plans (SAPs). Phase 2 will publish IPD. However, in 2018 EMA temporarily suspended its proactive publication of data, citing the disruption and resource constraints caused by the United Kingdom's withdrawal from the European Union.[13]

EMA's proactive and reactive disclosure policies take a similar position on CCI, generally considering information contained in clinical reports not as CCI, unless disclosure undermines the competitive position of the information's owner. This position faced several challenges in court but was recently validated by the European Court of Justice. The Court found that clinical reports were not covered by a general presumption of confidentiality and that market authorization holders must meet a high standard to qualify any data included in the reports as CCI, by establishing that disclosure poses the risk of concrete harm to their commercial interests.[14] Additional details regarding data accessibility and the timeline for data publication are available in Table 1.

Health Canada

In March 2019, HC launched its Public Release of Clinical Information (PRCI) initiative, which goes beyond

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Box 1

Categories of regulatory data

Type of document	Information provided[a]	Potential uses
Clinical overview and clinical summary	Provide a factual summary and critical analysis of the clinical data submitted in the dossier. These documents present the strengths and limitations of the development program, analyze the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.	• Provide insight into the quality and limitations of studies, issues encountered during product development and testing, and unusual prescribing information
Clinical study report	Comprehensively describes the methodology and results of a clinical trial. It contains more detail regarding trial design, conduct, and results than is contained in published versions of the same trial. It has several appendices, which include protocol and protocol amendments, sample case report forms, and statistical analysis plans.	• Appraise a trial and synthesize evidence, including evaluation of product safety and effectiveness • Inform systematic reviews, meta-analyses, and risk of bias evaluations • Provide greater detail than journal publications, which are often subject to word-count restrictions, particularly on secondary effectiveness endpoints and safety • Determine improper research practices, such as data-dredging, outcome switching, and selective reporting
Protocol and protocol amendments	Describe the original objectives, design, methods, statistical considerations and organization of a clinical trial, and include any subsequent protocol modifications. Both the protocol and later modifications are reviewed by an ethics committee.	• Assess study design and facilitate replication • Identify unscrupulous research practices, such as outcome switching and P-hacking
Case report forms	Questionnaires used by the sponsor of the clinical trial to record information about each trial participant.	• Ensure the accuracy of individual patient-level data
Statistical analysis plan	Provides a complete description of the planned methods for collection, analysis, interpretation, presentation, and organization of the data.	• Assess statistical methodology, including clinical trial power calculations, endpoint definitions, and proposed and conducted analyses • Appraise and replicate statistical methods
Individual case safety report	Provides detailed information related to a suspected adverse reaction to a medicinal product that occurs in a single patient at a specific point of time.	• Identify an increase in the reporting of a known adverse event, a new serious adverse event not listed in a medicines label, or a new drug-drug interaction
Individual patient-level data	Individual data recorded for each participant in a clinical study, such as age, gender, race, efficacy and safety outcomes, laboratory results, etc.	• Appraise a trial and synthesize evidence, including for evaluation of product safety and effectiveness and for use in systematic reviews and meta-analyses • Classify all adverse events when performing a meta-analysis focused on safety • Perform relevant subgroup analyses • Allow for longer follow-up compared to publications • Perform time-to-event analyses • Inform risk of bias evaluations • Check the validity of previously reported findings • Derive effects from data • Standardize units of analyses • Conduct more complex analyses • Account for a wider range of covariates • Answer secondary clinical questions • Explore prognostic factors and surrogate outcomes

IPD=individual patient-level data.

[a]Definitions were adapted from EMA's definitions of regulatory data.[37]

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EMA Policy 0070 by proactively releasing data for not only approved, unapproved, and withdrawn drug and biologic submissions but also Class III and IV medical device applications (**Table 1**).[15] The clinical data made available is similar in scope to EMA Policy 0070, with HC publishing clinical reports. HC also intends to make clinical reports available upon request for medical products that had a final regulatory decision prior to March 2019, similar to Policy 0043. However, HC will not release IPD under the PRCI initiative. HC plans to phase in the proactive release of clinical reports over four years, beginning in 2019.

HC construes CCI (known as "confidential business information" in Canada) narrowly, protecting only clinical information not used by the applicant to support the proposed conditions of use or clinical information that describes tests, methods, or assays used exclusively by the manufacturer, and then only with adequate justification.[16] Going forward, HC aims to publish data within 120 days after issuance of a final regulatory decision or after an information request is lodged. Unlike the EMA, data posted in response to information requests are made available on HC's online portal, requests are not limited to the citizens of the nation's regulator (i.e. Canadians), and registration is not required to access data.

US Food and Drug Administration

In January 2018, FDA launched a new pilot program to proactively publish CSRs of pivotal studies for nine recently-approved novel drugs, including trial protocols, protocol amendments, and SAPs (**Table 1**).[17] However, FDA announced in March 2020 that it was ending the pilot, with only a single CSR having been made available.[18]

The Freedom of Information Act (FOIA), enacted in 1966, requires federal agencies, including the FDA, to disclose records upon request by the public, unless records fall under one of nine specific exemptions protecting interests such as CCI and personal privacy.[19] FOIA is the only mechanism to access certain types of regulatory data, such as CSRs, for medical products approved by the FDA.[20] The FDA has defined CCI as "valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs."[21] However, even if information meets the definition of CCI, FDA may have discretion to release it if there is a compelling public interest in disclosure.[22]

Assessing Proactive Disclosure of Regulatory Data

To assess the EMA and HC's proactive publication of clinical data under Policy 0070 and the PRCI initiative, respectively, we systematically searched each agency's online data sharing portal,[23] documenting for each data release through April 2021: the type of medical product (drug, biologic, medical device, or vaccine); regulatory procedure (initial marketing authorization application (MAA) or post-authorization application); regulatory decision (approved, unapproved, or withdrawn); regulatory decision date; public release date; and time from regulatory decision to release. EMA and HC generally release the same categories of data across medical product types and regulatory procedures. Thus, to compare the data released across agencies, we randomly selected a single product for which both EMA and HC had made clinical data available, and then characterized the category of data released, number of pages, presence of redactions, reason for redactions provided (protected personal data (PPD) or CCI), and described the information redacted.

Assessing Reactive Disclosure of Regulatory Data

To assess EMA, HC, and FDA's reactive data disclosure processes, we first reviewed the literature to identify studies on information requests submitted to EMA, HC, or FDA. To better understand the scope of data made available by EMA, HC, and FDA in response to information requests, we submitted a FOIA request to FDA in 2014 for a wide range of clinical data and regulatory records for Gilead's Hepatitis C drugs sofosbuvir (Sovaldi) and ledipasvir/sofosbuvir (Harvoni) (**Appendix Box 1**), as well as a parallel request to EMA in 2016 under Policy 0043 and to HC in 2020 under the PRCI initiative. Sovaldi and Harvoni were selected as illustrative test cases because of their novelty, the safety issues that were being evaluated at the time we initiated this work, their use in the treatment of Hepatitis C, a major global health problem, and high cost.[24] We documented the date of each request milestone (e.g. initial request filed, appeal filed) and the date of each document production. For each production, we then characterized the category of data and the number of pages made available. We then described the information that had been redacted and compared the number of pages and redactions in CSRs of phase 2 and 3 trials produced by EMA, HC, and FDA.

Since HC releases information in response to requests on the same online data sharing portal as the information it proactively discloses, we followed the

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Table 1

Characteristics of transparency laws or policies across the European Medicines Agency, Health Canada, and US Food and Drug Administration

Law or Policy	EMA Policy 0043	EMA Policy 0070	HC's Public Release of Clinical Information Initiative	Freedom of Information Act	FDA Clinical Data Summary Pilot Program
Effective date (Current status)	December 1, 2010 (Active)	Phase 1: January 1, 2015 Phase 2: Unspecified future date (Temporarily suspended)	March 20, 2019 4 year phase-in schedule for proactive disclosure (Active)	July 5, 1967 (Active)	January 16, 2018 (Concluded)
Type of disclosure	Reactive	Proactive	Proactive (new submissions/ applications) Reactive (Past submissions/ applications)	Reactive	Proactive
Medical products covered	• Drugs and biologics • Approved, unapproved, or withdrawn • Any year	• Drugs and biologics • Approved, unapproved, or withdrawn • After January 1, 2015 (MAA or Article 58 procedure) and July 1, 2015 (line extension or new indication)	• Drugs, biologics, and medical devices • Approved, unapproved, or withdrawn • 2019: NDS-NAS, SNDS-c, and Rx–switch • 2020: All NDS, SNDS-c, and Rx-switch • 2021: All NDS, all SNDS, and Class IV medical devices • 2022: All NDS, SNDS, ANDS, SANDS, and Class III and IV medical devices • Upon request: NDS, SNDS, ANDS, SANDS, EUNDS, SEUNDS, Class III and Class IV medical device applications or application amendments (all must have a final regulatory decision prior to March 20, 2019)	• Drugs, biologics, and medical devices • Approved • Any year	• Drugs • Approved • Recently approved
Documents published	Any document originated, received, or held by the EMA.	Phase 1: • clinical overviews • clinical summaries • CSR (body) • Protocols and protocol amendments • Sample CRFs • SAPs Phase 2: IPD	• clinical overviews • clinical summaries • CSR (body) • Protocols and protocol amendments • Sample CRFs • SAPs	Records held by the FDA unless records fall under nine specific exemptions protecting interests, such as trade secrets and other confidential commercial information, personal privacy, and national security.	• CSR (body) • Protocols and protocol amendments • Sample CRFs • SAPs
Publication channel	Documents released only to the requesters	EMA clinical data sharing portal	HC clinical data sharing portal	Documents released only to the requesters	FDA website with drug approval package

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Accessibility	Since October 2018, only European Union citizens or legal residents may make requests.	Anyone, but must create an EMA account to access the clinical data.	Anyone can access and request data, does not require registration.	Anyone may submit a FOIA request, not limited to US citizens or residents. A requester must provide a name, address, phone number, a description of the records being sought, and agree to pay fees, if necessary.	Anyone can access the data, does not require registration.
Timeline for publication	Within 15 working days. In exceptional cases, such as requests for a large number of documents, the time-limit may be extended.	• 60 days after the European Commission decision and following publication of the EPAR (MAA and line extension or new indication) • Within 150 days after the CHMP opinion (Article 58 procedure) • Within 150 days after receipt of a withdrawn application	• Within 120 calendar days after issuance of the final regulatory decision or a request is received.	Agencies are required to respond to FOIA requests within 20 days unless there are unusual circumstances, such as a need to review a voluminous number of records. In practice, agencies routinely take much longer to process and fulfill FOIA requests.[38]	Not specified
Definition of CCI	Any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information.[39]	Any information contained in the clinical reports submitted to the Agency by the applicant/MAH that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the applicant/MAH.[40]	Confidential business information, in respect of a person to whose business or affairs the information relates, means – subject to the regulations – business information: a. That is not publicly available b. In respect of which the person has taken measures that are reasonable in the circumstances to ensure that it remains not publicly available, and c. That has actual or potential economic value to the person or their competitors because it is not publicly available and its disclosure would result in a material financial loss to the person or a material financial gain to their competitors.[41]	Valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs.[42]	Not specified

ANDS=abbreviated new drug submission; CCI=confidential commercial Information; CHMP=Committee for Medicinal Products for Human Use
CRF=clinical report form; CSR=clinical study report; EMA=European Medicines Agency; EPAR=European public assessment report; EUNDS=extraordinary use new drug submissions; FDA=United States Food and Drug Administration; HC=Health Canada; IPD=individual patient-level data; MAA=market authorization application; MAH=market authorization holder; NAS=new active substance; NDS=new drug submission; Rx-switch=submissions to switch an authorized medicinal ingredient to non-prescription status; SANDS=supplemental abbreviated new drug submissions; SAP=statistical analysis plan; SEUNDS=supplemental extraordinary use new drug submissions; SNDS-c=supplemental new drug submission containing confirmatory trials; SNDS=supplemental new drug submission.

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same methodology (described above) for extracting information on HC's reactive disclosure as we did for the agency's proactive disclosure.

Findings: Proactive Disclosure of Regulatory Data

Between 2016 and April 2021, EMA proactively released data for 123 unique medical products (**Appendix Table 1**), including 81 drugs, 38 biologics, and 4 vaccines (**Table 2**). Data supporting 147 regulatory procedures reviewed by the EMA between 2015 and 2021 were made publicly available, including 95 initial MAAs and 52 post-authorization applications; of which 135 were approved and 12 were withdrawn. Between 2019 and April 2021, HC proactively released data for 73 unique medical products, including 45 drugs, 23 biologics, 3 vaccines, and 2 medical devices. HC disclosed data supporting 62 initial MAAs and 13 post-authorization applications; all 75 were approved between 2016 and 2021. In 2018, FDA proactively disclosed data supporting the initial MAA of 1 drug that was approved in 2018. EMA, HC, and FDA took a median of 511 (interquartile range 416-574), 150 (interquartile range 122-204), and 33 days, respectively, after each agency's regulatory decision to release data.

At the time of initial data collection (April 30, 2020), no data supporting the same MAA were proactively released by both EMA and HC. However, data supporting the same initial MAA for 4 medicines were made available proactively by EMA and reactively by HC. After reviewing HC's data releases and confirming the agency typically makes available equivalent categories of information proactively and reactively, we randomly selected daratumumab (Darzalex) among those 4 medicines to compare the information shared across EMA and HC. EMA and HC released 28 and 29 documents, respectively, for Darzalex, including all of the same categories of data: a clinical overview; summaries of biopharmaceutical and pharmacological studies, summaries of safety and efficacy, a biomarker technical report, and a population pharmacokinetic report; for each of its 5 clinical trials: a CSR (4 full, 1 synoptic), protocol and protocol amendments, sample CRFs, and SAPs for 3 of the trials (**Table 3**). There were no substantive discrepancies in the released data. However, EMA disclosed a more updated clinical overview, while HC posted an additional clinical overview addendum describing Canadian treatment approaches for multiple myeloma. The full CSRs, protocols, including those with amendments, CRFs, and SAPs had a median length of 1612, 108, 115, and 76 pages, respectively, for both EMA and HC. Redactions were comparable and minimal across EMA and HC: PPD and CCI were provided as the reasons for redactions in 3 and 15 documents, respectively. Names of report investigators or subject ID numbers were the most common redactions.

Findings: Reactive Disclosure of Regulatory Data

We identified two studies on information requests to EMA under Policy 0043, no studies on information requests to HC under the PRCI initiative, one study on FOIA requests to FDA, and one study examining CSRs released in response to information requests to EMA and FDA, among other sources. One study determined that of the 457 information requests EMA received between 2010 and 2012, 66% were granted, 27% were denied, and 7% were pending.[25] Requests were processed in a median of 26 days. In a case series of 12 information requests filed between 2011 and 2015, the EMA released a wide variety of regulatory data, including CSRs, regulatory comments, meeting and decision records, periodic safety update reports, correspondence, and postmarket data and took a median of 301 days to process the requests.[26] A study examining 78 CSRs, including 11 obtained from information requests to EMA and FDA, found that key appendices of CSRs, such as protocols and case report forms were frequently omitted.[27] Based on a study of FOIA requests to FDA between 2008 and 2017, FDA fully or partially granted 72% of requests.[28] FDA processed one-fifth of requests in 20 days but took more than 61 days to process two-thirds of requests.

HC released data for 55 unique medical products in response to 70 processed requests between February 2019 and April 2021, including for 23 drugs, 6 biologics, 6 vaccines, and 20 medical devices. HC took a median of 132 (interquartile range 103-167) days to process requests and published the same categories of regulatory data reactively as it had proactively.

In response to our parallel requests for information supporting approval of Sovaldi and Harvoni, FDA and HC released substantially more regulatory data than EMA, including clinical overviews, summaries and integrated summaries of safety and efficacy, clinical study protocols and amendments, and narratives of deaths and serious adverse events. Information only made available by FDA include individual safety case reports; records and correspondence related to product labeling, safety concerns, pediatric studies, expedited approval pathway designations, and postmarket study requirements and commitments; safety update reports; site initiation visit reports; and IPD, albeit heavily redacted (**Appendix Table 2**). Information only produced by HC include sample case report forms and statistical analysis plans (**Appendix Table 3**).

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Table 2

Characteristics of the medical products in which the European Medicines Agency, Health Canada, and US Food and Drug Administration have proactively made data available through April 2021

Regulatory Agency	EMA	HC	FDA
Medical product type[a]			
Pharmacologic	81	45	1
Biologic	38	23	0
Medical device	0	2	0
Vaccine	4	3	0
Regulatory procedure			
Initial marketing authorization[b]	95	62	1
Post-authorization[c]	52	13	0
Regulatory decision			
Approved	135	75	1
Unapproved	0	0	0
Withdrawn	12	0	0
Regulatory decision year[d]			
2015	3	0	0
2016	113	2	0
2017	24	0	0
2018	0	1	1
2019	0	28	0
2020	3	42	0
2021	2	2	0
Data release year			
2016	6	0	0
2017	58	0	0
2018	78	0	1
2019	0	10	0
2020	1[e]	51	0
2021	4[e]	14	0
Median time from regulatory decision to release	511 days[d] (IQR 416-574)	150 days[f] (IQR 122-204)	33 days

EMA=European Medicines Agency; FDA=United States Food and Drug Administration; HC=Health Canada; IQR=interquartile range.

[a]Alternative formulations were combined, along with generics or biosimilars with original products.

[b]For HC, initial marketing authorization includes new drug submission-new active substances (n=42), new drug submissions (n=15), Class III medical devices (n=1), Class IV medical devices (n=1), and 2 vaccines and 1 biologic authorized under Interim Order (n=3). For FDA, initial marketing authorization includes 1 new drug application.

[c]For EMA, post-authorization includes extension of indications (n=45), line extensions (n=5), and workshare (n=2) procedure types. For HC, post-authorization includes supplemental new drug submissions (n=2) and supplemental new drug submissions containing confirmatory trials (n=11).

[d]For EMA, dates of two post-authorization procedures were unavailable, and were excluded from processing time calculations.

[e]EMA's temporary suspension of Policy 0070 remains in place, however, clinical data for these 5 medical products were published in line with EMA's exceptional measures to maximize the transparency of its regulatory activities on treatments and vaccines for Coronavirus Disease 2019 that are approved or are under evaluation.

[f]One biologic and one medical device package proactively released by HC were identified as part of the agency's pilot program and thus were excluded from processing time calculations.

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Table 3

Comparison of the data made available by the European Medicines Agency and Health Canada. A case study of daratumumab (Darzalex)

Type of document	NCT No.	EMA	HC	Pages	Contains Redactions	Reasons for redactions provided	Redaction description	Discrepancies
Anonymization report		☑	☑	45 (EMA) 46 (HC)	No	NA	NA	HC version contains an anonymization report attestation
Biomarker technical report	NCT01985126	☑	☑	49	Yes	PPD	Names of report authors and reviewers	No
Clinical overview		☑	☑	70 (EMA) 62 (HC)	Yes	PPD	Patient subject numbers in Figure 6: Response and duration of response; responders in all treated analysis set (studies MMY2002 and GEN501 Part 2)	EMA's version has more updated results of trials (dated ~2 months after HC's version); EMA's version also contains a section on real world data
Clinical overview addendum		✗	☑	7	No	NA	NA	No
Clinical study protocol and amendments	NCT02116569	☑	☑	95	No	NA	NA	No
Clinical study protocol and amendments	NCT01615029	☑	☑	111	Yes	PPD	Name of responsible medical officer	No
Clinical study protocol and amendments	NCT01998971	☑	☑	129	Yes	PPD	Name of responsible medical officer	No
Clinical study protocol and amendments	NCT01985126	☑	☑	94	Yes	CCI	Single nucleotide polymorphisms that may be measured	No
Clinical study protocol and amendments	NCT00574288	☑	☑	108	Yes	PPD	Subject IDs on a figure of relative change in paraprotein from baseline	No
Clinical study report addendum	NCT01985126	☑	☑	13	Yes	PPD	Names of report contributors	No
Clinical study report addendum	NCT00574288	☑	☑	13	Yes	PPD	Names of report contributors	No
Clinical study report body	NCT02116569	☑	☑	400	Yes	PPD	Names of report contributors and information on lymphocyte, neutrophil, hemoglobin, and platelet line plots by subject	No
Clinical study report body	NCT01615029	☑	☑	1297	Yes	PPD	Names of report contributors and subject IDs on two swim lane plots of responders	No

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Clinical study report body	NCT01985126	☑	☑	1926	No	NA	NA	No
Clinical study report body	NCT00574288	☑	☑	2082	Yes	PPD	Subject IDs on one figure and two plots and names of report contributors	No
Population pharmacokinetic report		☑	☑	266	Yes	PPD	Subject IDs on a PK observation plot showing individual fits for a sample of 25 subjects	No
Sample case report forms	NCT02116569	☑	☑	98	No	NA	NA	No
Sample case report forms	NCT01615029	☑	☑	75	No	NA	NA	No
Sample case report forms	NCT01998971	☑	☑	168	No	NA	NA	No
Sample case report forms	NCT01985126	☑	☑	115	No	NA	NA	No
Sample case report forms	NCT00574288	☑	☑	954	No	NA	NA	No
Statistical analysis plan	NCT01615029	☑	☑	47	No	NA	NA	No
Statistical analysis plan	NCT01985126	☑	☑	124	Yes	PPD	Names of those on the independent review committee charter	No
Statistical analysis plan	NCT00574288	☑	☑	76	Yes	PPD	Names and contact info of IMDC members	No
Summary of biopharmaceutical studies		☑	☑	21	Yes	CCI	The major N-linked glycans and the range of the molecular masses of the major daratumumab glycoforms	No
Summary of clinical efficacy		☑	☑	70	Yes	PPD	Patient subject numbers in Figure 3: Response and duration of response and responders in all treated analysis set (studies MMY2002 and GEN501 Part 2)	No
Summary of clinical pharmacology studies		☑	☑	86	Yes	CCI	The major N-linked glycans and the range of the molecular masses of the major daratumumab glycoforms	No
Summary of clinical safety		☑	☑	529	No	NA	NA	No
Synoptic clinical study report body	NCT01998971	☑	☑	94	Yes	PPD	Names of report contributors	No

CCI=confidential commercial information; EMA=European Medicines Agency; HC=Health Canada; NCT=national clinical trial; PK=pharmacokinetic; PPD=protected personal data.

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Information only made available by EMA include periodic safety update reports and pharmacovigilance risk assessment committee reports (**Appendix Table 4**).

All three agencies made available CSRs for phase 1, 2, and 3 trials. Comparing the productions of CSRs of phase 2 and 3 clinical trials, EMA released CSRs corresponding to more phase 2 and 3 trials than FDA and HC (25 vs. 18 vs. 24); however, of the 16 CSRs produced for the same clinical trials by all three regulators, 11 released by FDA and HC were longer, 4 were the same, and 1 released by EMA was longer (**Appendix Table 5**). Among the 16 CSRs, those produced by FDA had an average of 473 pages compared to 464 and 179 pages for those produced by HC and EMA, respectively. EMA, HC, and FDA redactions of the CSRs were minimal, most commonly redacting names and contact information of study investigators and administrators and subject ID numbers. EMA and FDA also commonly redacted information about the drug manufacturer and supplier, citing CCI, while HC redacted narratives of deaths and serious adverse events, citing PPD. Time from initial request to final data production was 918 and 968 days for FDA and EMA, respectively (**Appendix Table 6**). While HC processed the information request much faster, publicly posting the data packages for Harvoni and Sovaldi 155 and 351 days, respectively, after the initial request. The request to FDA required considerably more resources, including multiple appeals and court filings. Additionally, FDA waived processing fees; however, the agency normally charges fees unless it is shown disclosure of the requested information is in the public interest.[29] Last, HC organizes its data productions into categories, making the information much easier to navigate and process.

Enhancing Regulatory Data Transparency in the 2020s

Over the past decade, EMA and HC have greatly expanded the public availability of regulatory data, while FDA has lagged behind by not proactively publishing clinical reports. EMA and HC's routine publication of clinical reports, including clinical overviews and summaries, CSRs, protocols, sample CRFs, and SAPs, which just a decade ago had largely been treated by regulators as CCI, represents a paradigm shift in clinical trial transparency. HC's more recent PRCI initiative goes beyond EMA Policy 0070 in proactively posting clinical reports supporting medical device applications, not just drug and biologic MAAs. HC also offers the most efficient source of regulatory data, typically posting clinical reports about 5 months after a regulatory decision, nearly a year quicker than EMA, and processing most information requests in less than 5 months, about 150 days quicker than EMA takes to release requested regulatory data that are complex or voluminous.[30] EMA and FDA required nearly three years to process our request for comprehensive regulatory data supporting the approvals of Sovaldi and Harvoni, substantially longer than EMA had previously taken to process requests for CSRs.[31]

While EMA and FDA processing times vary widely,[32] our findings suggest there may be an opportunity for EMA and FDA to increase their processing speed to align with HC. The CSRs released upon request by FDA and HC were more than double the length of those produced by EMA, suggesting FDA and HC may source more comprehensive CSRs. A similar request to FDA may require greater resources than to EMA and HC. Nonetheless, use of EMA or FDA's information request processes may be necessary to gain access to other types of regulatory data, such as sponsor-regulator correspondence. Consistent with findings from other recent studies, redactions across the agencies were mostly minor (e.g., primarily researcher and participant identifying information) and generally did not impede interpretation of the evidence.[33] Two notable exceptions are FDA and HC's complete redaction of IPD and narratives of serious adverse events and deaths, respectively.

Our study has several limitations. First, HC's start date, the date when HC initiates the process to prepare information for public release, was used to calculate HC's processing time for information requests, not the actual date information requests were submitted, which is not publicly available. HC may take several weeks, and in some cases months, to begin processing requests, particularly when a request requires clarification or where paper records need to be digitized. Therefore, HC may take moderately longer than a median of 132 days to process requests. However, it is unlikely to impact the study's finding that HC is the most efficient source of clinical reports, given EMA required a median of 301 days to process a series of comparable information requests and HC also completed our requests for information on Sovaldi and Harvoni in about one-third the time that EMA and FDA required.[34] Second, parts of the study were based on analyses of case studies, including Sovaldi, Harvoni, and Darzalex, which represent just a few of the many medical products for which data has been made publicly available. Third, the length of CSRs was used to compare the scope of data made available reactively by each agency; specific differences in the content of CSRs were not examined. Last, the study was limited to transparency of regulatory data, which comprises just a portion of data generated in clinical trials. Given the progress government agencies have made toward

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transparency of regulatory data, non-governmental led data sharing initiatives, such as the YODA Project, might consider shifting their focus and resources toward advancing data transparency of trials not submitted to regulators (e.g., academic trials).

While clinical reports and other categories of regulatory data supporting MAAs of drugs, biologics, and medical devices have been made accessible, there are several ways regulators could enhance transparency over the next decade. First, EMA and FDA should mitigate or remove barriers to accessing clinical reports, including citizenship requirements and processing costs associated with information requests, particularly for those requesting information in the public interest. Second, to improve access to information, EMA and FDA should post requested clinical data on a public online portal and increase their processing speed to more closely align with HC. To reduce delays, regulators should consider hiring more personnel and devoting greater resources to responding to requests. Third, EMA and FDA should extend access to data supporting medical devices. Last, while EMA remains committed to make available IPD in Phase 2 of Policy 0070, FDA and HC also should implement policies to share IPD, which would provide the raw data necessary to conduct secondary analyses. While sharing IPD poses increased risks of patient reidentification, data sharing initiatives, such as the YODA Project and CSDR, have demonstrated that through use of a "trusted intermediary," regulatory agencies could share IPD with researchers to maximize the use and utility of the data while still protecting patient privacy.[35]

The administrative and redaction costs incurred by industry and regulatory authorities represent a substantial obstacle to the future of clinical data sharing programs, exemplified by the ongoing, albeit temporary, suspension of Policy 0070 and the restriction of information requests to EMA to EU citizens and legal residents in 2018. To address this challenge, governments and institutions, such as the European Union, should give greater priority and funding to regulatory data sharing programs. Concurrently, efforts to improve the efficiency of data sharing initiatives should be considered. For instance, multiregional disclosure requirements with varying anonymization standards for CCI and PPD increase costs. Regional regulators may consider a harmonized approach for clinical report disclosure to help reduce inefficiencies. In fact, HC has already begun accepting clinical information previously published under Policy 0070 for its PRCI initiative. Also, FDA recently announced that sharing of CSRs in harmony with international regulators is a long-term goal.[36] However, an important benefit of a multiregional approach is that it encourages greater transparency by incentivizing sponsors to anonymize data in accordance with the standards least amenable to CCI claims. For example, we found that names of drug manufacturers and suppliers were often redacted by EMA and FDA, but HC did not consider this information as CCI, and thus pharmaceutical sponsors may be encouraged to not devote resources to redact such information in a multiregional approach, recognizing the data will become public under the PRCI initiative. Therefore, it is important that measures, such as enforcement of HC's narrower definition of CCI, are taken to prevent harmonization of disclosure standards toward less transparency.

In summary, regulatory data pertinent to public health and clinical medicine that were used to support the approval of medicines and medical devices are now available proactively or in response to information requests. Over the next decade, regulatory agencies should make IPD available, and additional resources might be needed to ensure the long-term viability of regulatory data sharing programs and to encourage researchers to take advantage of the data that is — for now — more available than ever before.

In summary, regulatory data pertinent to public health and clinical medicine that were used to support the approval of medicines and medical devices are now available proactively or in response to information requests. Over the next decade, regulatory agencies should make IPD available, and additional resources might be needed to ensure the long-term viability of regulatory data sharing programs and to encourage researchers to take advantage of the data that is — for now — more available than ever before.

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Note

Author Contributions: Mr. Egilman and Dr. Ross had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ACE and JSR contributed to study concept and design; ACE, MEM, and ATL abstracted the data; all authors contributed to the analysis and interpretation of the data; ACE drafted the manuscript; all authors contributed to the critical revision of the manuscript; and JSR provided study supervision.

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Data availability: Requests for the dataset can be made to the corresponding author at joseph.ross@yale.edu.

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Supplementary Appendix

Appendix Table 1

The medical products in which the European Medicines Agency, Health Canada, and US Food and Drug Administration have made data available through April 2021

Generic Name (Brand)	EMA	HC	FDA
5-Aminolevulinic Acid (Ameluz)	☑	✕	✕
840 PB Ventilator	✕	☑ (R)	✕
Abatacept (Orencia)	☑	✕	✕
Abemaciclib (Verzenio)	✕	☑ (P)	✕
Abiraterone Acetate (Zytiga)	☑	✕	✕
Acalabrutinib (Calquence)	✕	☑ (P)	✕
Accu-Chek Inform II	✕	☑ (R)	✕
Accu-Chek Inform II Test Strips	✕	☑ (R)	✕
Accu-Chek Mobile Monitor	✕	☑ (R)	✕
Aceneuramic Acid (Kepnetic)	☑	✕	✕
Adalimumab (Humira)	☑	✕	✕
Afatinib (Giotrif)	☑	✕	✕
Albutrepenonacog Alfa (Idelvion)	☑	✕	✕
Alectinib (Alecensa)	☑	✕	✕
Alendronic Acid; Colecalciferol	☑	✕	✕
Alpelisib (Piqray)	✕	☑ (P)	✕
Amifampridine (Firdapse)	✕	☑ (P)	✕
Amifampridine (Ruzurgi)	✕	☑ (P)	✕
Amlodipine;Valsartan	☑	✕	✕
Antihemophilic Factor Viii (Esperoct)	✕	☑ (P)	✕
Apalutamide (Erleada)	✕	✕	☑
Aripiprazole	☑	✕	✕
Aripiprazole (Abilify Maintena)	✕	☑ (R)	✕
Arsenic Trioxide (Trisenox)	☑	✕	✕
Asfotase Alfa (Strensiq)	✕	☑ (P)	✕
AT LISA tri	✕	☑ (R)	✕
Atezolizumab (Tecentriq)	✕	☑ (P)	✕
Atorvastatin (Lipitor)	✕	☑ (R)	✕
Autologous CD34+ cells transfected with retroviral vector containing adenosine deaminase gene (Strimvelis)	☑	✕	✕
Avelumab (Bavencio)	✕	☑ (P)	✕
Axicabtagene Ciloleucel (Yescarta)	✕	☑ (R)	✕
Baloxavir Marboxil (Xofluza)	✕	☑ (P)	✕
Bamlanivimab	✕	☑ (P)	✕
Baricitinib (Olumiant)	☑	✕	✕

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Generic Name (Brand)	EMA	HC	FDA
Baylis V4C-560 Ventilator	✗	☑ (R)	✗
Begelomab (Begedina)	☑	✗	✗
Bevacizumab (Avastin)	☑	✗	✗
Bezlotoxumab (Zinplava)	☑	✗	✗
Bortezomib	☑	✗	✗
Brentuximab Vedotin (Adcetris)	✗	☑ (P)	✗
Brilliant Blue G (Tissueblue)	✗	☑ (P)	✗
Brolucizumab (Beovu)	✗	☑ (P)	✗
Buprenorphine Hydrochloride; Naloxone Hydrochloride Dihydrate (Suboxone)	✗	☑ (R)	✗
C1 Esterase Inhibitor (Cinryze)	☑	✗	✗
Cabozantinib (Cabometyx)	☑	✗	✗
Canakinumab (Ilaris)	☑	✗	✗
Cannabidiol (Sativex)	✗	☑ (R&P)	✗
Caplacizumab (Cablivi)	✗	☑ (P)	✗
Carfilzomib (Kyprolis)	☑	✗	✗
Caspofungin Acetate	☑	✗	✗
Cedazuridine; Decitabine (Inqovi)	✗	☑ (P)	✗
Cediranib (Zemfirza)	☑	✗	✗
Ceftazidime; Avibactam (Zavicefta)	☑	✗	✗
Cemiplimab (Libtayo)	✗	☑ (P)	✗
Chenodeoxycholic Acid	☑	✗	✗
Chlorhexidine (Umbipro)	☑	✗	✗
Chlormethine (Ledaga)	☑	✗	✗
Clomiphene Citrate (Serophene)	✗	☑ (R)	✗
Conestat Alfa (Ruconest)	☑	✗	✗
Crizotinib (Xalkori)	☑	✗	✗
Cysteamine Bitartrate (Procysbi)	✗	☑ (R)	✗
Daclatasvir (Daklinza)	☑	✗	✗
Daclizumab (Zinbryta)	☑	✗	✗
Daptomycin (Cubicin)	☑	✗	✗
Daratumumab (Darzalex)	☑	☑ (R)	✗
Darolutamide (Nubeqa)	✗	☑ (P)	✗
Darunavir	☑	✗	✗
Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir (Cokiera)	☑	✗	✗
Dasatinib (Apo-Dasatinib)	✗	☑ (R)	✗
Deferiprone (Ferriprox)	☑	✗	✗
Deoxycholic Acid (Belkyra)	✗	☑ (R)	✗
Dexamethasone phosphate (Dexamethasone Taw)	☑	✗	✗

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Appendix Table 1 (continued)

The medical products in which the European Medicines Agency, Health Canada, and US Food and Drug Administration have made data available through April 2021

Generic Name (Brand)	EMA	HC	FDA
Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis, and Haemophilus Influenzae Type-B Conjugate Vaccine (Infanrix Hexa)	✗	☑ (R)	✗
Diphtheria, Tetanus, Pertussis, Poliomyelitis Vaccine (Adacel-Polio)	✗	☑ (R)	✗
Docetaxel	☑	✗	✗
Dolutegravir (Tivicay)	✗	☑ (R)	✗
Drisapersen (Kyndrisa)	☑	✗	✗
Durvalumab (Imfinzi)	✗	☑ (P)	✗
Edotreotide (SomaKit TOC)	☑	✗	✗
Eftrenonacog Alfa (Alprolix)	☑	✗	✗
Elbasvir; Grazoprevir (Zepatier)	☑	✗	✗
Elotuzumab (Empliciti)	☑	✗	✗
Eluxadoline (Truberzi)	☑	✗	✗
Empagliflozin (Jardiance)	☑	✗	✗
Empagliflozin; Linagliptin (Glyxambi)	☑	✗	✗
Emtricitabine; Rilpivirine; Tenofovir Alafenamide (Odefsey)	☑	☑ (R)	✗
Emtricitabine; Tenofovir Alafenamide (Descovy)	☑	✗	✗
Emtricitabine; Tenofovir Disoproxil (Truvada)	☑	✗	✗
Enoxaparin Sodium (Thorinane; Inhixa)	☑	✗	✗
Entrectinib (Rozlytrek)	✗	☑ (P)	✗
Epoetin Alfa (Eprex)	✗	☑ (R)	✗
Erdafitinb (Balversa)	✗	☑ (P)	✗
Eribulin (Halaven)	☑	✗	✗
Erlotinib (Tarceva)	☑	✗	✗
Ertapenem	☑	✗	✗
Etelcalcetide (Parsabiv)	☑	✗	✗
Etomidate (Tomvi)	✗	☑ (P)	✗
Everolimus (Afinitor)	☑	✗	✗
Evolocumab (Repatha)	☑	☑ (R)	✗
Exablate 2100	✗	☑ (R)	✗
Fedratinib Hydrochloride (Inrebic)	✗	☑ (P)	✗
Fluoxetine (Prozac)	✗	☑ (R)	✗
Fluvastatin (Lescol)	✗	☑ (R)	✗
Follitropin Delta (Rekovelle)	☑	✗	✗
Fostamatinib Disodium (Tavalisse)	✗	☑ (P)	✗
Fotona Dynamis Laser System	✗	☑ (R)	✗

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Generic Name (Brand)	EMA	HC	FDA
Freestyle Libre Flash GMS	✗	☑ (R)	✗
Fremanezumab (Ajovy)	✗	☑ (P)	✗
Galcanezumab (Emgality)	✗	☑ (P)	✗
Gallium Ga 68 Dotatate (Netspot)	✗	☑ (P)	✗
Gemtuzumab Ozogamicin (Mylotarg)	✗	☑ (P)	✗
Germanium Chloride; Gallium Chloride (Galliapharm)	✗	☑ (P)	✗
Gilteritinib Fumarate (Xospata)	✗	☑ (P)	✗
Givosiran (Givlaari)	✗	☑ (P)	✗
Glasdegib (Daurismo)	✗	☑ (P)	✗
Gynecare Gynemesh Ps	✗	☑ (R)	✗
Htlv-I/Ii	✗	☑ (P)	✗
Human Coagulation Factor X (Coagadex)	☑	✗	✗
Human Normal Immunoglobulin (HyQvia)	☑	✗	✗
Human Papillomavirus 9-valent Vaccine (Gardasil 9)	✗	☑ (R)	✗
Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (Gardasil)	✗	☑ (R)	✗
Ibrutinib (Imbruvica)	☑	✗	✗
Id Now Covid-19	✗	☑ (R)	✗
Idarucizumab (Praxbind)	☑	✗	✗
Idelalisib (Zydelig)	✗	☑ (P)	✗
Infliximab (Flixabi)	☑	✗	✗
Influenza Vaccine (Supemtek)	✗	☑ (P)	✗
Insulin Aspart (Fiasp)	☑	☑ (R)	✗
Insulin Aspart (Novorapid)	☑	✗	✗
Insulin Glargine (Lusduna)	☑	✗	✗
Insulin Human (Ryzodeg)	☑	✗	✗
Irinotecan Hydrochloride (Onivyde)	☑	✗	✗
Isatuximab (Sarclisa)	✗	☑ (P)	✗
Ivabradine	☑	✗	✗
Ixazomib (Ninlaro)	☑	✗	✗
Ixekizumab (Taltz)	☑	✗	✗
Juvederm - Volbella	✗	☑ (R)	✗
Lacosamide (Vimpat)	☑	✗	✗
Larotrectinib (Vitrakvi)	✗	☑ (P)	✗
Ledipasvir; Sofosbuvir (Harvoni)	✗	☑ (R)	✗
Lemborexant (Dayvigo)	✗	☑ (P)	✗
Lenvatinib (Kisplyx)	☑	✗	✗
Lesinurad (Zurampic)	☑	✗	✗
Linagliptin (Trajenta)	☑	✗	✗

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Appendix Table 1 (continued)

The medical products in which the European Medicines Agency, Health Canada, and US Food and Drug Administration have made data available through April 2021

Generic Name (Brand)	EMA	HC	FDA
Linagliptin; Metformin (Jentadueto)	☑	✗	✗
Liraglutide (Victoza)	☑	✗	✗
Lonoctocog Alfa (Afstyla)	☑	☑ (Pilot)	✗
Lutetium Chloride (EndolucinBeta)	☑	✗	✗
Mammomat Revelation	✗	☑ (Pilot)	✗
Measles, Mumps and Rubella Vaccine (Priorix)	✗	☑ (R)	✗
Measles, Mumps, Rubella, and Varicella Virus Vaccine (Proquad)	✗	☑ (R)	✗
Meningococcal Group A, C, W135, and Y Conjugate Vaccine (Nimenrix)	☑	✗	✗
Methotrexate (Nordimet)	☑	✗	✗
Methylphenidate Hydrochloride (Foquest)	✗	☑ (R)	✗
Metronidazole (Flagyl)	✗	☑ (R)	✗
Migalastat (Galafold)	☑	✗	✗
Moderna COVID-19 Vaccine	☑	☑ (P)	✗
Mona Lisa 10 Intrauterine Device	✗	☑ (R)	✗
Nelarabine (Atriance)	✗	☑ (P)	✗
Nepafenac (Nevanac)	☑	✗	✗
Neratinib (Nerlynx)	✗	☑ (P)	✗
Niraparib (Zejula)	✗	☑ (P)	✗
Nivolumab (Opdivo)	☑	☑ (P)	✗
Obeticholic Acid (Ocaliva)	☑	✗	✗
Obinutuzumab (Gazyvaro)	☑	✗	✗
Ofatumumab (Arzerra)	☑	✗	✗
Olaratumab (Lartruvo)	☑	✗	✗
Osimertinib (Tagrisso)	☑	✗	✗
Oxycodone Hydrochloride (OxyContin and Oxyneo)	✗	☑ (R)	✗
Ozanimod (Zeposia)	✗	☑ (P)	✗
Palbociclib (Ibrance)	☑	✗	✗
Paliperidone (Trevicta)	☑	✗	✗
Palonosetron	☑	✗	✗
Pancreas Powder (Enzepi)	☑	✗	✗
Pandemic Influenza Vaccine H5N1	☑	✗	✗
Patisiran (Onpattro)	✗	☑ (P)	✗
Pembrolizumab (Keytruda)	☑	☑ (P)	✗
Pemetrexed	☑	✗	✗
Pemetrexed Diacid (Armisarte)	☑	✗	✗

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Generic Name (Brand)	EMA	HC	FDA
Pfizer-BioNTech COVID-19 Vaccine	☑	☑ (P)	✕
Pirfenidone (Esbriet)	✕	☑ (R)	✕
Plecanatide (Trulance)	✕	☑ (P)	✕
Polatuzumab Vedotin (Polivy)	✕	☑ (P)	✕
Prasterone (Intrarosa)	✕	☑ (P)	✕
Pravastatin (Pravachol)	✕	☑ (R)	✕
Pregabalin	☑	✕	✕
Ranibizumab (Lucentis)	☑	✕	✕
Ranolazine (Corzyna)	✕	☑ (P)	✕
Rasagiline	☑	✕	✕
Ravulizumab (Ultomiris)	✕	☑ (P)	✕
Redexis	✕	☑ (R)	✕
Remdesivir (Veklury)	☑	☑ (P)	✕
Reslizumab (Cinqaero)	☑	✕	✕
Rilpivirine; Cabotegravir (Cabenuva;Vocabria)	✕	☑ (P)	✕
Riociguat (Adempas)	☑	✕	✕
Ripretinib (Qinlock)	✕	☑ (P)	✕
Risankizumab (Skyrizi)	✕	☑ (P)	✕
Rituximab (Truxima)	☑	✕	✕
Rociletinib (Xegafri)	☑	✕	✕
Romosozymab (Evenity)	✕	☑ (P)	✕
Rosuvastatin Calcium (Crestor)	✕	☑ (R)	✕
Rufinamide (Inovelon)	☑	✕	✕
Salmeterol; Fluticasone Propionate (Aerivio Spiromax; Airexar Spiromax)	☑	✕	✕
Satralizumab (Enspryng)	✕	☑ (P)	✕
Saxagliptin; Dapagliflozin (Qtern)	☑	✕	✕
Sildenafil	☑	✕	✕
Simvastatin (Zocor)	✕	☑ (R)	✕
Siponimod (Mayzent)	✕	☑ (P)	✕
Sodium Zirconium Cyclosilicate (Lokelma)	✕	☑ (P)	✕
Sofia SARS Antigen Fluorescent Immunoassay	✕	☑ (R)	✕
Sofosbuvir (Sovaldi)	✕	☑ (R)	✕
Sofosbuvir;Velpatasvir (Epclusa)	☑	✕	✕
Sonidegib (Odomzo)	✕	☑ (P)	✕
Spartan Covid-19 System	✕	☑ (R)	✕
Spartan Covid-19 V2 System	✕	☑ (R)	✕
Tadalafil (Talmanco)	☑	✕	✕
Tafamidis Meglumine (Vyndaqel)	✕	☑ (P)	✕

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Appendix Table 1 (continued)

The medical products in which the European Medicines Agency, Health Canada, and US Food and Drug Administration have made data available through April 2021

Generic Name (Brand)	EMA	HC	FDA
Talazoparib (Talzenna)	✗	☑ (P)	✗
Tecnis Multifocal Intraocular Lens	✗	☑ (R)	✗
Teduglutide (Revestive)	☑	✗	✗
Tenapanor (Ibsrela)	✗	☑ (P)	✗
Tenofovir Alafenamide (Vemlidy)	☑	✗	✗
Tenofovir Disoproxil	☑	✗	✗
Teriparatide (Forteo; Movymio; Terrosa)	☑	☑ (R)	✗
Tisagenlecleucel (Kymriah)	✗	☑ (R)	✗
Tocilizumab (RoActemra)	☑	✗	✗
Trientine Hydrochloride (Mar-Trientine)	✗	☑ (P)	✗
Trifarotene (Aklief)	✗	☑ (P)	✗
Trifluridine; Tipiracil (Lonsurf)	☑	✗	✗
Tucatinib (Tukysa)	✗	☑ (P)	✗
Upadactinb (Rinvoq)	✗	☑ (P)	✗
Ustekinumab (Stelara)	☑	✗	✗
Venetoclax (Venclyxto)	☑	☑ (P)	✗
Vigileo Arterial Pressure Cardiac Output/Oximetry Monitor	✗	☑ (R)	✗
Vorapaxar (Zontivity)	☑	✗	✗
Voretigene Neparvovec (Luxturna)	✗	☑ (P)	✗
Xpert Xpress Sars-Cov-2	✗	☑ (R)	✗
Zonisamide	☑	✗	✗

EMA=European Medicines Agency; FDA=United States Food and Drug Administration; HC=Health Canada; P=proactive; R=reactive.

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Appendix Table 2

Summary of documents released by the US Food and Drug Administration in response to our Freedom of Information Act request

Production No.	Date of Production	Pages	Document types
1	9/19/16	10362	Individual case safety reports
2	10/11/16	503	Records related to fast track and breakthrough therapy designations; memos of review cycle meetings and teleconferences between FDA and Gilead; and FDA reviews
3	10/13/16	8945	Clinical overviews; clinical safety summaries; clinical efficacy summaries; integrated summaries of safety; integrated summaries of efficacy; interim synoptic CSRs; and interim CSRs
4	10/18/16	5894	Clinical study protocols
5	10/27/16	2372	Records and correspondence from new drug applications related to product labeling, adverse events and safety issues, postmarketing requirements and commitments, mid- and late-cycle communications, and proposed pediatric study requests; regulatory compliance audit reports; site initiation visit reports; and safety update reports
6	11/2/16	720	New drug application annual report, including annual status report of postmarketing requirements and commitments
7	11/14/16	9535	Interim CSRs; interim synoptic CSRs; and final CSRs
8	11/18/16	7979	Clinical study protocols
9	12/23/16	16840	Final reports of animal studies
10	1/6/17	10944	Records and correspondence from new drug applications, supplementary new drug applications, and investigational new drug applications related to product labeling, clinical investigator disclosures, sponsor requests for pediatric study deferrals, FDA postmarketing requirement proposals, fast track, breakthrough therapy, priority review designations, adverse events and safety issues; clinical study protocols and protocol amendments
11	1/31/17	electronic files	IPD datasets
12	2/14/17	6213	Individual case safety reports
13	3/24/17	1153	Final clinical study report and an abbreviated clinical study report
14	4/6/17	electronic files	IPD datasets
15	6/22/17	electronic files	IPD datasets
Total		**81460**	

CSR=clinical study report; FDA=United States Food and Drug Administration; IPD=individual patient-level data.

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Appendix Table 3

Summary of documents released by Health Canada in response to our information requests through the Public Release of Clinical Information initiative

Production No.	Date of Production	Pages	Document Types
1	7/31/20 (Harvoni)	54052	Clinical overview; summary of biopharmaceutical studies and associated analytical methods; summary of clinical pharmacology studies; summary of clinical efficacy; summary of clinical safety; comparative bioavailability and bioequivalence study reports; plasma protein binding study reports; reports of hepatic metabolism and drug interaction studies; reports of studies using other human biomaterials; healthy subject PK and initial tolerability study reports; patient PK and initial tolerability study reports; intrinsic factor PK study reports; extrinsic factor PK study reports; population PK study reports; healthy subject PD and PK/PD study reports; patient PD and PK/PD study reports; study reports of controlled clinical studies pertinent to the claimed indication; integrated summary of safety; integrated summary of efficacy, and other study reports. Most study reports include a synopsis, report body, protocol and protocol amendments, sample case report forms, and statistical analysis plans, and all study reports of Phase 2 and 3 trials also included narratives of SAEs (albeit completely redacted)
2	2/12/21 (Sovaldi)	31466	Clinical overview; summary of biopharmaceutical studies and associated analytical methods; summary of clinical pharmacology studies; summary of clinical efficacy; summary of clinical safety; comparative bioavailability and bioequivalence study reports; plasma protein binding study reports; reports of hepatic metabolism and drug interaction studies; reports of studies using other human biomaterials; healthy subject PK and initial tolerability study reports; patient PK and initial tolerability study reports; intrinsic factor PK study reports; extrinsic factor PK study reports; population PK study reports; healthy subject PD and PK/PD study reports; patient PD and PK/PD study reports; study reports of controlled clinical studies pertinent to the claimed indication; integrated summary of safety; integrated summary of efficacy, and other study reports. Most study reports include a synopsis, report body, protocol and protocol amendments, sample case report forms, and statistical analysis plans, and several study reports of Phase 2 and 3 trials also included narratives of SAEs (albeit completely redacted).
Total		**85518**	

PD=pharmacodynamic; PK=pharmacokinetic; SAE=serious adverse event.

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Appendix Table 4

Summary of documents released by the European Medicines Agency in response to our information request under Policy 0043

Production No.	Date of Production	Pages	Document Types
1	12/1/16	102	1 final CSR
2	12/14/16	322	2 PSURs, 2 PRAC reports
3	1/10/17	1471	3 final CSRs
4	1/31/17	476	2 final CSRs, 1 CSR amendment
5	2/21/17	872	1 synoptic CSR, 2 final CSRs
6	3/27/17	202	2 final CSRs, 2 CSR amendments
7	4/4/17	338	1 interim CSR
8	5/4/17	131	1 final CSR
9	5/30/17	136	2 final CSRs, 1 CSR amendment
10	6/21/17	204	2 final CSRs, 1 CSR amendment
11	7/12/17	165	2 final CSRs, 2 CSR amendments
12	8/7/17	254	1 final CSR, 1 interim CSR
13	9/13/17	283	2 final CSRs, 1 tabular listing of clinical studies
14	10/4/17	307	2 final CSRs
15	10/25/17	396	3 interim CSRs
16	11/20/17	492	3 interim CSRs
17	12/11/17	99	1 interim CSR, 1 2nd interim synoptic CSR
18	1/11/18	132	2 abbreviated CSRs
19	2/7/18	514	2 interim CSRs
20	3/7/18	245	1 interim CSR, 1 interim synoptic CSR
21	4/20/18	151	1 interim CSR, 1 interim synoptic CSR
22	5/28/18	194	3 abbreviated CSRs
23	7/3/18	578	2 final CSRs, 1 abbreviated CSR, 1 2nd interim CSR
24	7/25/18	50	1 PRAC
25	8/24/18	373	2 PSURs, 1 PRAC report
26	9/20/18	259	1 PSUR, 1 PRAC report
27	10/12/18	274	1 PSUR, 1 PRAC report
28	11/21/18	200	1 PSUR, 1 PRAC report
29	12/12/18	258	1 PSUR, 1 PRAC report
30	1/14/19	243	1 PSUR, 1 PRAC report
31	2/19/19	244	1 PSUR, 1 PRAC report
32	3/12/19	178	1 PSUR, 1 PRAC report
33	5/3/19	107	1 final CSR
34	5/21/19	242	1 2nd interim CSR
35	6/20/19	58	2 final synoptic CSRs
36	7/10/19	371	1 2nd interim CSR
Total		**10921**	

CSR=clinical study report; PRAC=pharmacovigilance risk assessment committee; PSUR=periodic safety update report.

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Appendix Table 5

Comparison of clinical study reports[a] of phase 2 and 3 clinical trials released by the European Medicines Agency, Health Canada, and the Food and Drug Administration in response to our information requests

Drug	Trial name (nickname)	Trial phase	FDA release (pages)	CSR type	Redaction description	EMA release (pages)	CSR type	Redaction description	HC release (pages)	CSR type	Redaction description
SOF	GS-US-334-0107 (POSITRON)	III	Yes (338)	Interim CSR	Contact information; Manufacturer/ Supplier information; Subject ID numbers	Yes (338)	Interim CSR	Contact information; Subject ID numbers; Dates related to SAEs	Yes (338)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Narratives of deaths and SAEs
SOF	GS-US-334-0108 (FUSION)	III	Yes (326)	Interim CSR	Contact information; Manufacturer/ Supplier information	Yes (131)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers	Yes (326)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers
SOF	GS-US-334-0110 (NEUTRINO)	III	Yes (321)	Interim CSR	Contact information; Manufacturer/ Supplier information; Subject ID numbers	Yes (121)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers	Yes (321)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers
SOF	GS-US-334-0123 (PHOTON-1)	III	Yes (73)	Interim synoptic CSR	Contact information	Yes (73)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers	Yes (73)	Interim synoptic CSR	Contact information; Investigator and study administrator names; Subject ID numbers
SOF	GS-US-334-0133 (VALENCE)	III	Yes (1,545)	Interim synoptic CSR	Contact information; Study ID numbers	Yes (24)	Interim synoptic CSR	Contact information; Subject ID numbers	No		
SOF	P7977-0422 (PROTON)	IIB	Yes (471)	Final CSR	Contact information; Manufacturer/ Supplier information	Yes (153)	Final CSR	Contact information; Investigator and study administrator names; Manufacturer/ Supplier information; Subject ID numbers	Yes (471)	Final CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Narratives of deaths and SAEs
SOF	P7977-0724 (ATOMIC)	IIB	Yes (540)	Final CSR	Contact information; Manufacturer/ Supplier information	Yes (164)	Final CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Dates related to SAEs	Yes (540)	Final CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Dates related to SAEs; Narratives of deaths and SAEs

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SOF	P7977-1231 (FISSION)	III	Yes (409)	Interim CSR	Contact information; Manufacturer/ Supplier information	Yes (144)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers	Yes (409)	Contact information; Investigator and study administrator names; Subject ID numbers
SOF	P7977-2025	II	Yes (104)	Interim synoptic CSR	Contact information	Yes (104)	Interim synoptic CSR	Contact information; Subject ID numbers; Dates related to SAEs	Yes (104)	Interim synoptic CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Narratives of deaths and SAEs.
SOF	P7977-0221	IIA	Yes (1100)	Final CSR	Contact information; Manufacturer/ Supplier information; Subject ID numbers	No			Yes (1179)	Final CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Individual patient listings of race and ethnicity; Narratives of deaths and SAEs
SOF	P7977-1910	I/II	No			Yes (156)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers	Yes (609)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Individual patient listings
SOF	11-I-0258	I/IIA	Yes (53)	Abbreviated CSR	Contact information; Investigator and study administrator names; Subject ID numbers	Yes (53)	Abbreviated CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Dates related to SAEs	Yes (53)	Abbreviated CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Narratives of deaths and SAEs.
SOF/ LDV	GS-US-337-0102 (ION-1)	III	Yes (756)	Interim CSR	Short portions of the methods and statistical methods and study design sections detailing an agreement between FDA and Gilead regarding the efficacy data required for the sponsor's initial NDA filing; contact information; manufacturer/ supplier information; Subject ID numbers	Yes (166)	Interim CSR	Investigator and study administrator names; Manufacturer/ Supplier information; Subject ID numbers	Yes (756)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers

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Appendix Table 5 (continued)

Comparison of clinical study reports[a] of phase 2 and 3 clinical trials released by the European Medicines Agency, Health Canada, and the Food and Drug Administration in response to our information requests

Drug	Trial name (nickname)	Trial phase	FDA release (pages)	CSR type	Redaction description	EMA release (pages)	CSR type	Redaction description	HC release (pages)	CSR type	Redaction description
SOF/ LDV	GS-US-337-0109 (ION-2)	III	Yes (673)	Interim CSR	Contact information; Manufacturer/ Supplier information; Subject ID numbers	Yes (175)	Interim CSR	Contact information; Investigator and study administrator names; Manufacturer/ Supplier information; Subject ID numbers	Yes (673)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers
SOF/ LDV	GS-US-337-0108 (ION-3)	III	Yes (417)	Interim CSR	Contact information; Manufacturer/ Supplier information; Subject ID numbers	Yes (151)	Interim CSR	Investigator and study administrator names; Manufacturer/ Supplier information; Subject ID numbers	Yes (417)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers
SOF/ LDV	GS-US-337-0118 (LONESTAR)	IIA	Yes (427)	Interim CSR	Contact information; inactive ingredients of drug; manufacturer/ supplier information	Yes (127)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers	Yes (427)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers
SOF and SOF/ LDV	P7977-0523 (ELECTRON)	IIA	Yes (1,944)	Interim and second interim CSRs	Contact information; Short portion of Conclusions section; drug ingredients; manufacturer/ supplier information	Yes (335)	Interim and second interim CSRs	Contact information; Investigator and study administrator names; Manufacturer/ Supplier information; Subject ID numbers	Yes (1944)	Interim and second interim CSRs	Contact information; Investigator and study administrator names; Subject ID numbers; Narratives of deaths and SAEs.
SOF/ LDV	GS-US-337-0122 (ELECTRON-2)	II	Yes (54)	Interim synoptic CSR	Contact information	Yes (371)	Second interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers	Yes (54)	Interim synoptic CSR	Contact information; Investigator and study administrator names
SOF/ LDV	GS-US-337-0123 (SOLAR-1)	II	No			Yes (32)	Final synoptic CSR	Contact information; Investigator and study administrator names; Subject ID numbers	No		
SOF and GS-0938	P2938-0721 (QUANTUM)	II	Yes (663)	Interim CSR	Contact information; Manufacturer/ Supplier information; Subject ID numbers	Yes (257)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers	Yes (514)	Interim CSR	Contact information; Investigator and study administrator names; Subject ID numbers; Narratives of deaths and SAEs.

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LDV/ VDV/ TGV/ RBV	GS-US-248-0120	II	No			Yes (152)	Final CSR	Contact information; Investigator and study administrator names; Manufacturer/ Supplier information; Subject ID numbers	Yes (783)	Final CSR	Contact information; Investigator and study administrator names
LDV/ VDV	GS-US-248-0121	II	No			Yes (80)	Abbre-viated CSR	Name and contact information of medi-cal monitor; Manu-facturer/Supplier information; Subject ID numbers	Yes (455)	Abbre-viated CSR	Contact information; Investigator and study administrator names
LDV/ VDV/ TGV	GS-US-248-0131	II	No			Yes (480)	Synoptic CSR	Subject ID numbers	Yes (480)	Synoptic CSR	Contact information; Investigator and study administrator names
LDV/ VDV/ TGV	GS-US-248-0132	II	No			Yes (56)	Abbre-viated CSR	Name and contact information of medi-cal monitor; Manu-facturer/Supplier information; Subject ID numbers	Yes (407)	Abbre-viated CSR	Contact information; Investigator and study administrator names
LDV/ VDV/ TGV	GS-US-256-0124	IIB	No			Yes (58)	Abbre-viated CSR	Name and contact information of medi-cal monitor; Manu-facturer/Supplier information; Subject ID numbers	Yes (357)	Abbre-viated CSR	Contact information; Investigator and study administrator names
LDV/ VDV	GS-US-256-0148	IIB	No			Yes (67)	Abbre-viated CSR	Contact information of medical monitor; Manufacturer/Sup-plier information; Subject ID numbers; Dates related to SAEs	Yes (527)	Abbre-viated CSR	Contact information; Investigator and study administrator names

CSR=clinical study report; EMA=European Medicines Agency; FDA=United States Food and Drug Administration; HC=Health Canada; LDV=ledipasvir; RBV=ribavirin; SAE=serious adverse event; SOF=sofosbuvir; TGV=tegobuvir; VDV=vedroprevir.

[a]CSR bodies were compared, not CSR appendices, such as protocols, sample case report forms, and statistical analysis plans.

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Appendix Table 6

Timeline of milestones for our information requests to the European Medicines Agency, Health Canada, and the US Food and Drug Administration

Agency	FDA	FDA (days)	EMA	EMA (days)	HC	HC (days)
Initial request	December 17, 2014	0	November 14, 2016	0	February 27, 2020	0
Request acknowledged	December 19, 2014	2	November 15, 2016	1	n/a	n/a
Decision on expedited processing request	December 22, 2014	5	n/a	n/a	n/a	n/a
Decision on request	n/a	n/a	November 18, 2016	4	n/a	n/a
Appeal filed-expedited processing	January 26, 2015	40	n/a	n/a	n/a	n/a
Appeal decision-expedited processing	February 19, 2015	64	n/a	n/a	n/a	n/a
Request for reconsideration of appeal filed	April 1, 2015	105	n/a	n/a	n/a	n/a
2nd appeal decision-expedited processing	April 3, 2015	107	n/a	n/a	n/a	n/a
Court filing	June 25, 2015	190	n/a	n/a	n/a	n/a
Initial court decision	September 20, 2016	643	n/a	n/a	n/a	n/a
Initial data production	September 19, 2016	642	December 1, 2016	17	n/a	n/a
Agreement to narrow request	November 29, 2016	713	n/a	n/a	n/a	n/a
Final data production	June 22, 2017	918	July 10, 2019	968	July 31, 2020 (Harvoni) February 12, 2021 (Sovaldi)	155 (Harvoni) 351 (Sovaldi)

EMA=European Medicines Agency; FDA=United States Food and Drug Administration; HC=Health Canada.

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Appendix Box 1

Information requested from the US Food and Drug Administration under the Freedom of Information Act

1. All data submitted in relation to the new drug application ("NDA") for sofosbuvir and the sofosbuvir/ledipasvir combination from the earliest trials onward, including, but not limited to:
   - patient-level safety and efficacy data;
   - case report forms;
   - informed consent forms;
   - adjudication forms;
   - toxicity and dosage information;
   - pharmacology data and formulation;
   - records generated by international experience regarding sofosbuvir.
2. All records submitted in support of any associated accelerated NDAs or supplemental NDAs for these drugs.
3. All study protocols submitted along with the raw pre-market approval and post-market adverse event data for sofosbuvir and the sofosbuvir/ledipasvir combination.
4. All records regarding the Breakthrough Therapy Designation priority review of sofosbuvir and the sofosbuvir/ledipasvir combination.
5. All records related to trials and design of trials for sofosbuvir and the sofosbuvir/ledipasvir combination, whether the trial design was approved or not approved.
6. All correspondence between HHS or FDA and the company or companies developing sofosbuvir and the sofosbuvir/ledipasvir combination, including both Gilead Sciences and Pharmasset, that concern any aspect of the FDA approval process.
7. Any other raw clinical trial data regarding sofosbuvir and the sofosbuvir/ledipasvir combination submitted by Gilead Sciences to the FDA in support of FDA approval.
8. All records, including the Clinical Study Reports, regarding trials of sofosbuvir and the sofosbuvir/ledipasvir combination alone or in combination with another drug or drugs (e.g., ribavirin and/or interferon), including, but not limited to, the following trials:
   - SPARE Trial;
   - ELECTRON Trial;
   - FUSION Study;
   - FISSION Study;
   - POSITRON Study;
   - VALENCE Study;
   - NEUTRINO Study;
   - PHOTON-1 Study;
   - ION-1 Study;
   - ION-2 Study; and
   - ION-3 Study.

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