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Clinical Data Publication

## Clinical data publication (Policy 0070) report Oct 2016- Oct 2017

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### Executive summary

The first year of implementation of EMA's clinical data publication policy (Policy 0070) has been productive, starting with the initial publication of two clinical dossiers in October 2016 followed by a steady increase as experience was gained. As of 20 October 2017, clinical data corresponding to 54 regulatory procedures for 50 medicines, including orphan, biosimilar and generic medicines, as well as medicines for use in children, were publicly available on the Clinical Data Publication (CDP) website. This amounts to over 3,000 clinical documents, totalling more than 1.3 million pages.

This first year has served to embed the business processes, positively engage with stakeholders and ultimately publish clinical data provided as part of centralised regulatory applications on the publicly accessible CDP website. This has been achieved while at the same time protecting commercially confidential information (CCI) and personal data.

The majority of the clinical data relates to the approval of new medicines, but there are also clinical data for medicines already authorised and for which an extension of their clinical use has been sought. Published data attracted a total of more than 3,600 users, resulting in over 22,000 document views and in excess of 80,000 document downloads for non-commercial research purposes.



There has been full compliance with the policy in the first year. The amount of CCI redactions in the documents published was very low, in only 0.01% of total pages published.

In addition, applicants anonymised their clinical documents in accordance with the EMA guidance and different methodologies were applied with the aim of maintaining as much data utility as possible, as outlined in each individual anonymisation report. The next phase will involve working with applicants to improve the quality of the anonymisation reports as more experience is gained.

The establishment of the technical anonymisation group (TAG) will facilitate further development of best practice in the anonymisation of the clinical reports. All this has been made possible through close interaction with stakeholders; from support to applicants with the pilot scheme, through to presentations at external meetings and regular webinars. There has also been very valuable collaboration with our international regulatory partners, including visits hosted for international colleagues.

Transparency is a key feature of the work of the Agency. Preliminary feedback from users of the website has shown satisfaction with the data published, with most respondents to an online survey agreeing that the initiative has begun to achieve its goals of increasing public trust in EMA's decision-making and of allowing the secondary analysis of clinical data. In order to fully gauge the wider and longer term impact of Policy 0070, EMA plans to repeat the survey over the next years. Looking to the second half of 2018 and beyond, the continuation of the proactive publication of clinical data under Policy 0070 will have to take due account of the next phases of the EMA Brexit preparedness business continuity plan (BCP), launched to enable EMA to undertake its relocation to the new host Member State.

## 1. Introduction

The European Medicines Agency (EMA) is committed to the principle of transparency. Through implementation of its flagship policy on the publication of clinical data, also known as Policy 0070<sup>1</sup>, EMA is the first medicines regulatory authority worldwide to give open access to the clinical data submitted by pharmaceutical companies in support of marketing authorisation applications.

EMA set out on this initiative in the belief that:

- public trust and confidence in EMA's scientific and decision-making processes would be enhanced;
- duplication of clinical trials could be avoided;
- innovation and development of new medicines would be encouraged;
- public availability of the scientific data would enable independent secondary analysis of the scientific data reviewed by the Agency's scientific committees to determine medicines' benefits and risks, which was expected to lead to public-health benefits.

Policy 0070 covers clinical data submitted to EMA on or after 1 January 2015 as part of marketing authorisation applications (MAAs), as well as for 'Article 58' applications for medicines for use outside the European Union<sup>2</sup>. Clinical data submitted as of 1 July 2015 in the context of extensions of indication or line extensions applications also fall within the scope of the policy, as do all corresponding withdrawn applications. The launch of the second phase of the policy (concerning the publication of

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<sup>1</sup> EMA's Policy 0070, entitled 'European Medicines Agency policy on publication of clinical data for medicinal products for human use', was developed in accordance with Article 80 of Regulation (EC) No 726/2004, and adopted by EMA's Management Board on 2 October 2014.

<sup>2</sup>[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000157.jsp&mid=W.C0b01ac05800240d1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp&mid=W.C0b01ac05800240d1)

individual patient data) is yet to be decided. EMA developed a new CDP website (<https://clinicaldata.ema.europa.eu>) specifically to provide access to the published clinical data, with the first clinical data being published on 20 October 2016.

This report provides an overview of the first year of operation of Policy 0070 since its implementation began on 20 October 2016. It provides figures on the information published, the amount of CCI redacted and the anonymisation techniques used by industry to protect personal data. It also details the industry support measures put in place by the Agency, as well as its interaction with stakeholders.

## 2. Project implementation

### *Overview of procedures in first year*

Table 1 gives an overview of the 54 procedures published in the first year and the clinical reports and anonymisation reports published on the clinical data portal. **Annex 1** of this report contains the full list of procedures with the details of each of the applicants/marketing authorisation holders along with the publication dates. The 54 procedures can be grouped by the different legal bases for the submitted applications: 21 full initial applications, 12 generic, 2 hybrid, 1 biosimilar and 18 post-authorisation applications for addition or modification of therapeutic indication. Within these legal bases there are various other product or procedure attributes that can apply, such as 2 withdrawn applications, 9 orphan indications, 6 paediatric indications and 2 procedures from SMEs. Table 1 shows the different combinations presented in the dataset; for example taking the SME column, one marketing authorisation application from an SME and one extension of indication for an SME with a paediatric indication.

**Table 1.** Application types published in first year

Type application		Withdrawn (W)	Orphan (O)	Paediatric (P)	SME (S)
Legal basis					
Total	54	2	9 <sup>a</sup>	6 <sup>b</sup>	2 <sup>c</sup>
Stand alone and mixed	21	2	5 - O		1 - S
			1 - O - P		
Generic	12			1 - P	
Hybrid	2				
Biosimilar	1				
Extension of indication	18		2 - O	2 - P	
			1 - O - P		
				1 - P - S	

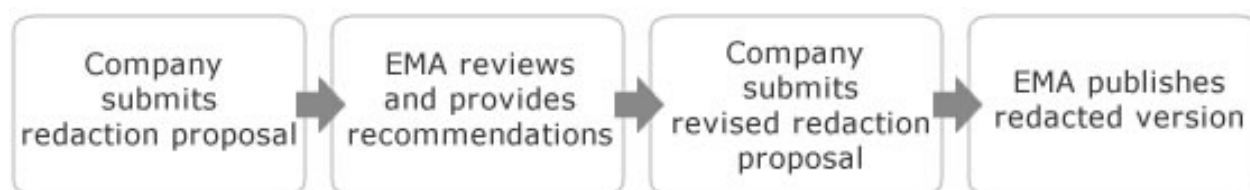
<sup>a</sup> 9 medicinal products including orphan indications in total – from the MAAs, five contained only orphan indication(s) and one included a paediatric and orphan indication (*which is the same product as the paediatric product with the orphan indication in the next column under paediatric*); for extension of indications there were two orphans and one orphan which also had a paediatric indication

<sup>b</sup> 6 medicinal products including paediatric indications in total - one MAA with a paediatric and orphan indication; one generic with a paediatric indication; for extension of indications there were two paediatric; one paediatric which was from an SME, one paediatric which also had an orphan indication

<sup>c</sup> 2 procedures from SME companies - one MAA from an SME and one extension of indication for a paediatric indication

## **Overview of process**

Procedures falling within the scope of policy 0070 are addressed in chronological order. Currently the clinical data publication (CDP) team contact companies six months in advance of the proposed submission date for their procedure, to allow sufficient time to prepare the initial redaction proposal package. The flowchart below summarises the process. The published external guidance document [EMA/90915/2016](#) provides a more detailed overview of each of the individual steps in the process<sup>3</sup>.



## **Validation**

All procedures go through an internal validation step. The internal validation checklist was published to provide assistance to companies in preparing their submissions. In this first year, 14 procedures (26%) failed validation and had to be re-submitted. One applicant had 5 individual applications that failed validation out of the 14 procedures that failed. The main issues encountered in order of increasing frequency are:

- the declaration that the application is a true and complete copy of the original, was missing in the cover letter;
- the anonymisation report was not included or was incomplete;
- issues with the justification tables and proposed CCI redactions; out of scope (pages were removed incorrectly, incorrect labelling)
- redaction labels not applied or incorrectly applied.

The most common reason was that the naming convention for the documents was not followed.

In accordance with the documented procedure, applicants/marketing authorisation holders were requested to resubmit the proposal package until a valid package was received.

## **Final redaction document package**

In the reporting period, 19 procedures (35%) failed to submit final redaction packages that were suitable for publication. The main issues encountered in order of increasing frequency are;

- revision of the anonymisation report required;

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<sup>3</sup> The operational start-up to implement the policy began in July 2016, when EMA began processing CHMP opinions from September 2015, the first procedures with a CHMP opinion under the policy. Because of limited resources to deal with this volume of opinions, it has not been possible for EMA to publish clinical data within 60 days of the European Commission Decision as foreseen in Policy 0070. EMA is working steadily to address this issue.

- data sharing statement included in the anonymisation report; cover letter incorrect;
- in-scope pages removed, not anonymised, or missing;
- the CCI outcome was not correctly implemented;
- the naming convention for documents was not followed;
- out of scope issues related to labelling missing or documents submitted that are not part of the package.

The most common reason was that the protected personal data (PPD) redactions were not applied or incorrectly applied.

In accordance with the documented procedure, applicants/marketing authorisation holders were requested to resubmit the final package until a valid package was received.

### ***Guidance and procedural documents***

During this first year many internal and external checklists, procedure overview and standard templates were developed to ensure consistency and maintain record keeping for the documents submitted under the policy. These will be revised as appropriate.

Validation checklists and a new template for the anonymisation report for generic medicinal products, where there are no patient identifiers, were published as part of the updated guidance annexes.

The external guidance for industry has been updated to clarify issues that arose in implementing the policy and a separate question-and-answer document was drafted to address specific issues that commonly arose in meetings with applicants to prepare for the submission of a document package. It is intended that this question-and-answer document will be updated on a regular basis.

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2017/04/WC500225881.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/04/WC500225881.pdf)

### ***Pilot support to industry***

A pilot scheme was implemented to provide support to each company with their first procedure published in line with the policy. Under this pilot, the Agency provides extensive support on an individual basis regarding the process, explanations on CCI redaction and personal data anonymisation, in or out of scope documents and on specific queries regarding the individual application. Out of all the applicants/marketing authorisation holders with clinical data published in the first year, 33 applicants availed of the additional support offered by EMA for their first submission; only 6 applicants declined the offer. Applicants/marketing authorisation holders were invited to submit any questions related to their procedure, justification tables for CCI and draft anonymisation reports, and examples of clinical study reports (CSRs) for review. Face-to-face meetings (6 occasions), teleconferences (16 occasions) or responses in writing only (11 occasions), were provided based on the choice of the applicant. Applicants who made use of the pilot were twice as likely to successfully pass validation as those who declined the support provided by the pilot. This pilot support will continue to be offered to applicants for their first submission and the knowledge gained will then be applied in subsequent submissions. While no pilot is offered for the second or subsequent submission, applicants may still submit any questions on their data package.

## ***Support to micro, small and medium sized enterprises (SMEs)***

The Agency provides a license tool, free of charge, to SMEs submitting clinical data for the purpose of the CDP policy. The license is valid for a period of 12 months to allow companies enough time to prepare the final redacted version. This incentive is to support SMEs effort to co-operate with the Agency in the implementation of CDP.

The SME office has individually contacted all SMEs in advance of the start of the process to inform them of this incentive. The SME office aims to contact SMEs around 3 months in advance of the formal request from the Documents Access and Publication Service. To date the two SME applicants/marketing authorisation holders with procedures published in this first year have not required the license tool offered by EMA.

### ***Compliance with phase 1***

Documents have been published in line with the policy. Industry was compliant in all applications falling under the scope of the policy, providing documents for publication as requested, including for withdrawn medicinal products. The co-operation from industry, along with the additional assistance offered by the CDP team for the first procedure (pilots), addressing questions as they arise and showing a flexible approach has resulted in full compliance in the first year.

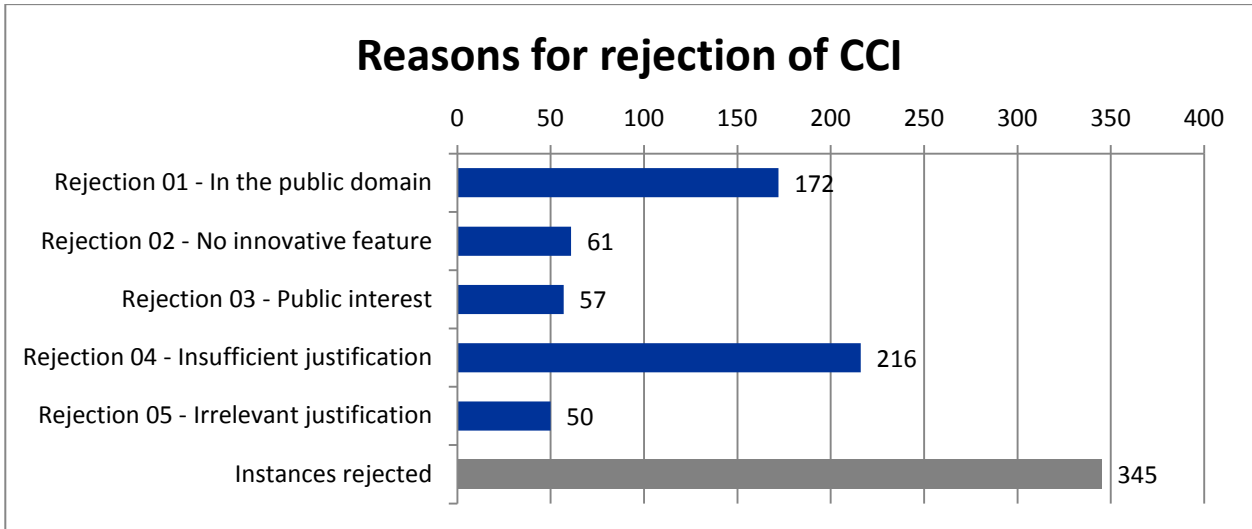
## **3. Commercially confidential information**

CCI shall mean any information contained in the clinical data submitted to the Agency by the applicant/marketing authorisation holder (MAH) that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the applicant/MAH. The Agency does not divulge CCI. Chapter 4 in the published external guidance for industry provides detailed information on the identification and redaction of CCI.

Of the 54 **procedures** published in the first year, 28 proposed CCI in some documents within the package for redaction in the initial submission (52% of the total). Redactions justified on the basis of CCI were accepted by EMA for 19 of the 54 procedures published, which equates to **35%**.

However if we look at the total number of **documents** published (3,279), CCI redactions were proposed in 145 of them but only accepted in 48 documents, which shows that **1.46%** of the published documents contain CCI. Turning to the number of **pages** published (1,308,244), 134 pages were redacted, which equates to **0.01%** of the total pages published.

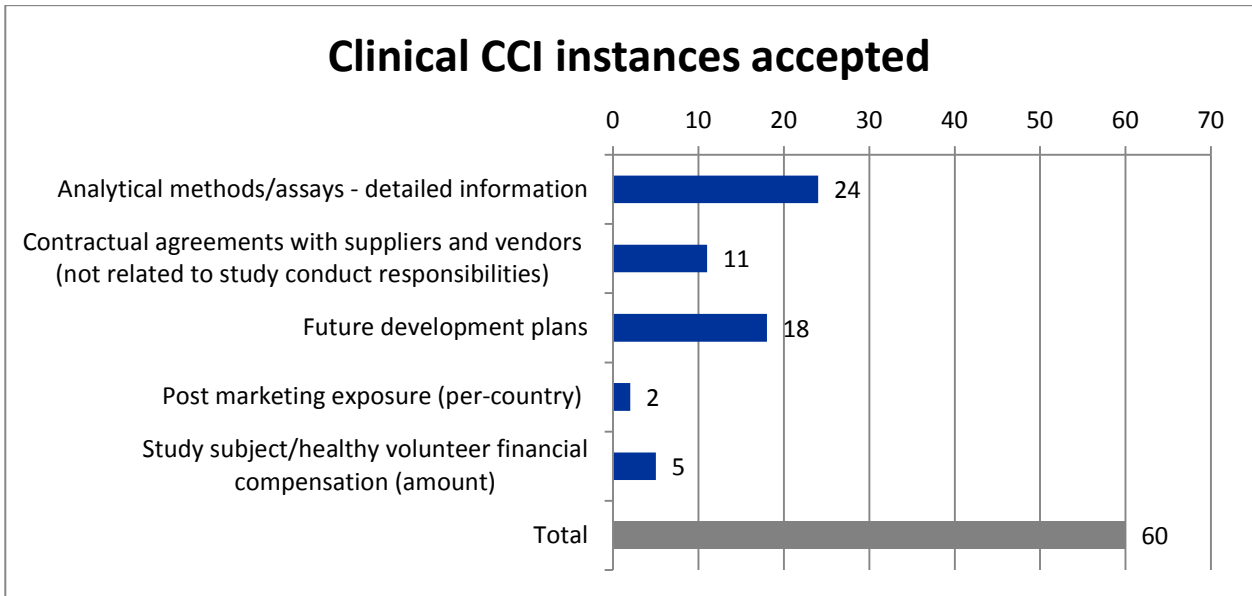
The number of instances where CCI was proposed in those 145 individual documents was 454. Of those 454 instances, 24% were accepted and 76% rejected. An instance is defined as a single CCI proposal per individual document regardless of how many times it appears in that individual document.



**Figure 1** Reasons for rejection of CCI

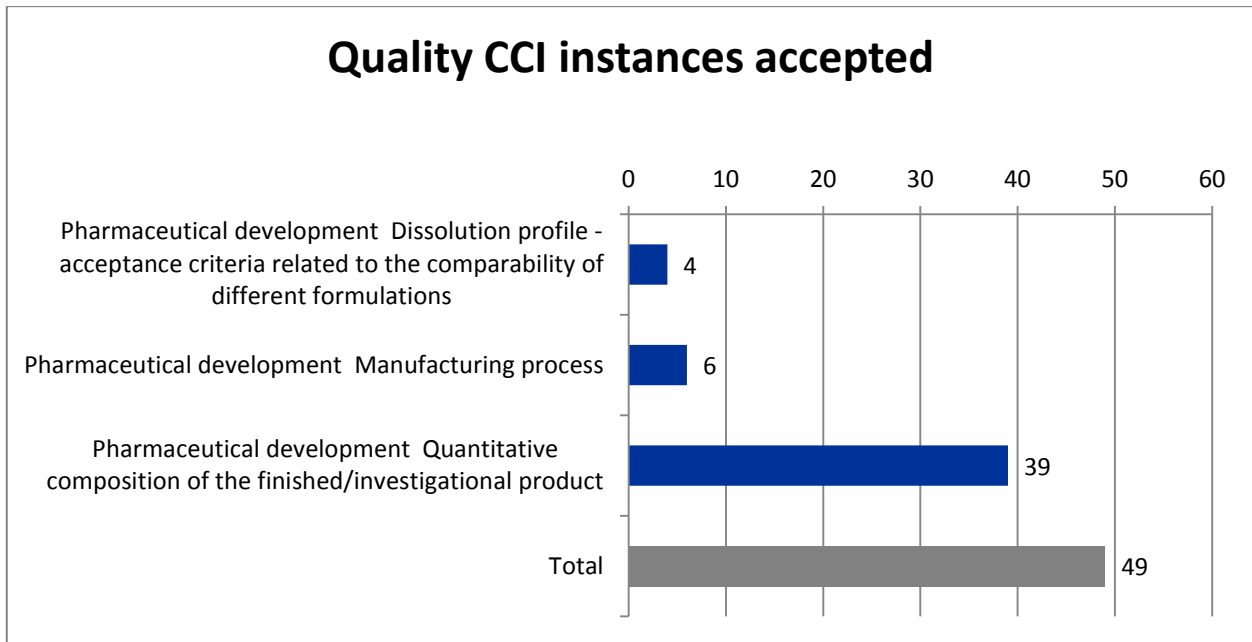
The reasons for rejection are presented in Figure 1 above. The external guidance (EMA/90915/2016) chapter 4 provides more details on the different rejection codes. The most common reason was insufficient justifications (rejection code 04) put forward. The second most common reason was that the information is already in the public domain (rejection code 01) indicating that this is not checked routinely prior to submitting the justification tables. There may be multiple reasons for rejection for any one instance where a CCI redaction is proposed.

CCI redactions accepted have been divided into two categories; **quality** or **clinical**. More CCI of a clinical nature was redacted in the published documents, 55% clinical as opposed to 45% quality.



**Figure 2** Instances of clinical CCI accepted

In the **clinical** instances, the five most commonly accepted CCI redactions, starting with the most frequently seen: detailed information on analytical assays or methods; future development plans; contractual agreements with suppliers and vendors; the amount of financial compensation given to study volunteers; or post marketing exposure per country. This is presented in Figure 2 above.



**Figure 3** Instances of quality CCI accepted

In the **quality** instances, the three main reasons for the acceptance of CCI redactions, starting with the most frequently seen, were: pharmaceutical development; the quantitative composition of the finished/investigational product; details of the manufacturing process; the dissolution profile - acceptance criteria related to the comparability of different formulations. In total, 49 instances of quality CCI were accepted as shown above in Figure 3.

In **Annex 2** of this report, the breakdown of the detailed reasons for both the acceptance and the rejection of CCI proposals are presented.

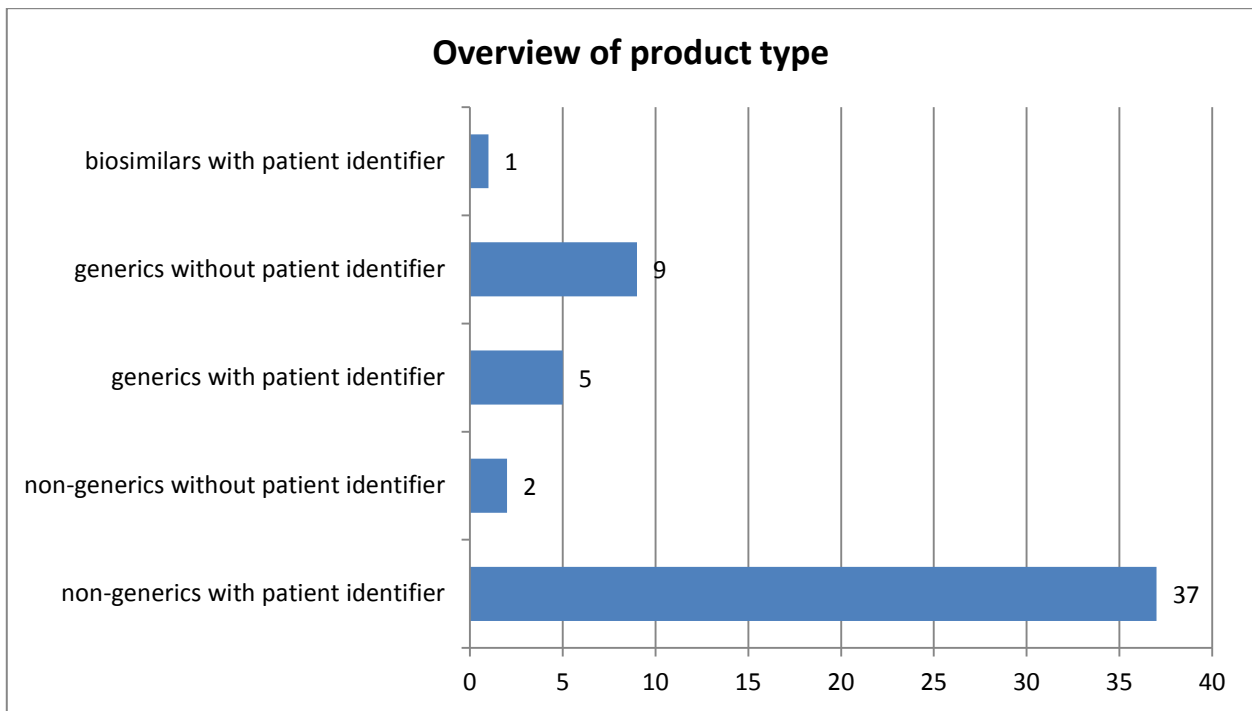
## 4. Anonymisation

Policy 0070 guidance on anonymisation was developed to ensure adequate personal data protection and compliance with the applicable EU legislation in this area. Chapter 3 of the external guidance covers this subject in detail and reviews different methodologies for anonymising the clinical documents whilst at the same time ensuring data utility is maintained. The guidance provides recommendations and individual applicants are responsible for ensuring that the anonymisation process chosen does not allow the re-identification of individuals. Two options are outlined in the guidance to ensure that the data is anonymised, based on the 05/2014 opinion of the Article 29 working party: fulfilment of the three criteria or conducting a risk assessment. The different anonymisation techniques lead to different levels of data utility in the anonymised reports.

The anonymisation process to be followed is set out in both the guidance and the template for the anonymisation report provided to applicants. Direct (elements that permit direct identification) and quasi (variables that may indirectly identify patients) identifiers are defined in the data set. Possible adversaries and plausible attackers of the data are identified and the risk of re-identification is evaluated. Data utility must be carefully considered; if the anonymisation of the clinical reports renders them unsuitable for secondary analysis, the data utility is compromised. The methods and outcome of the anonymisation process, chosen by the applicant as the most suitable technique for their data set, are documented in the anonymisation report published. Special consideration needs to be given in the case of rare diseases and small populations to ensure adequate data protection.



Within the 54 procedures published in the first year there were 37 MAAs or extension of indication applications with patient identifiers and 2 without patient identifiers as bibliographic data was provided. For the generic applications 5 had patient identifiers and 9 had no patient identifiers. One biosimilar application was published which contained patient identifiers. This is shown in Figure 4 below.

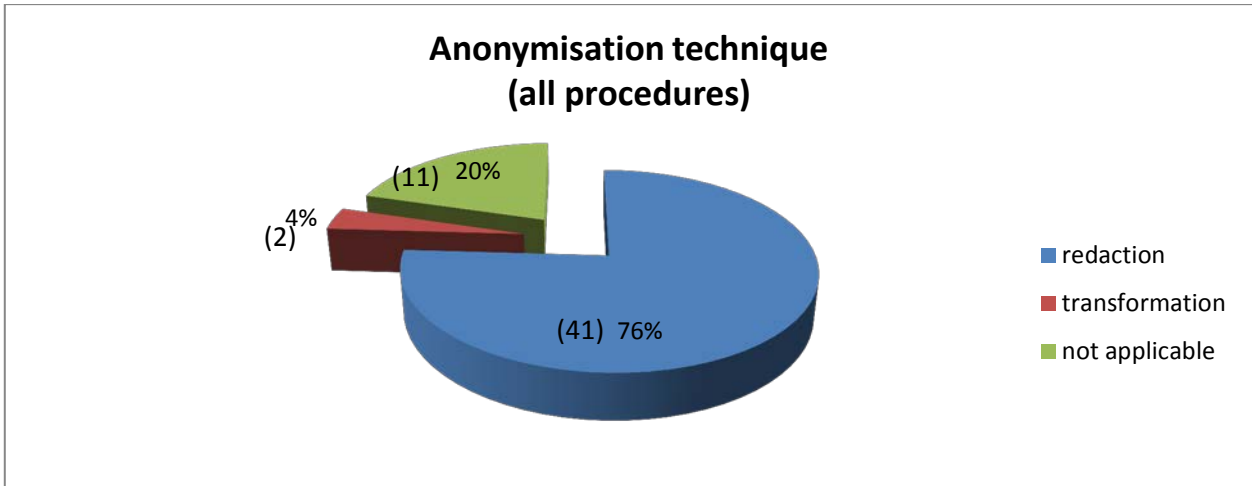


**Figure 4** Overview of product types

The non-analytical approach to anonymisation was chosen in 24 procedures, the analytical approach in 8 procedures; 11 procedures had no patient identifiers and therefore did not need to anonymise their reports and in a further 11 procedures the approach taken was not documented by the applicants/MAHs.

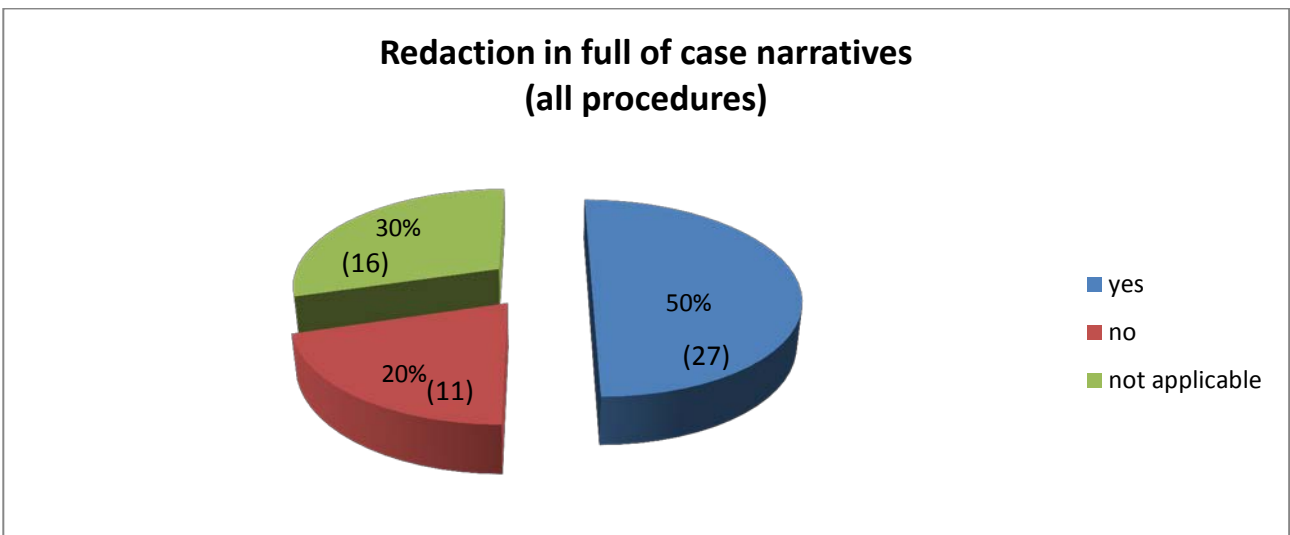
For the risk assessment 11 procedures had no patient identifiers and did not need any risk assessment; fulfilment of the three criteria (no possibility to single out an individual, link records or infer information about individuals) as outlined in the guidance was chosen on 5 occasions; a qualitative risk assessment on 34 occasions and the quantitative approach on 4 occasions where the risk threshold recommended in the guidance of 0.09 was selected on each occasion.

Figure 5 below shows the main anonymisation technique chosen for each of the 54 procedures, either redaction of the personal data (applied in the majority of procedures 76%) or transformation of the data – 4% of cases.



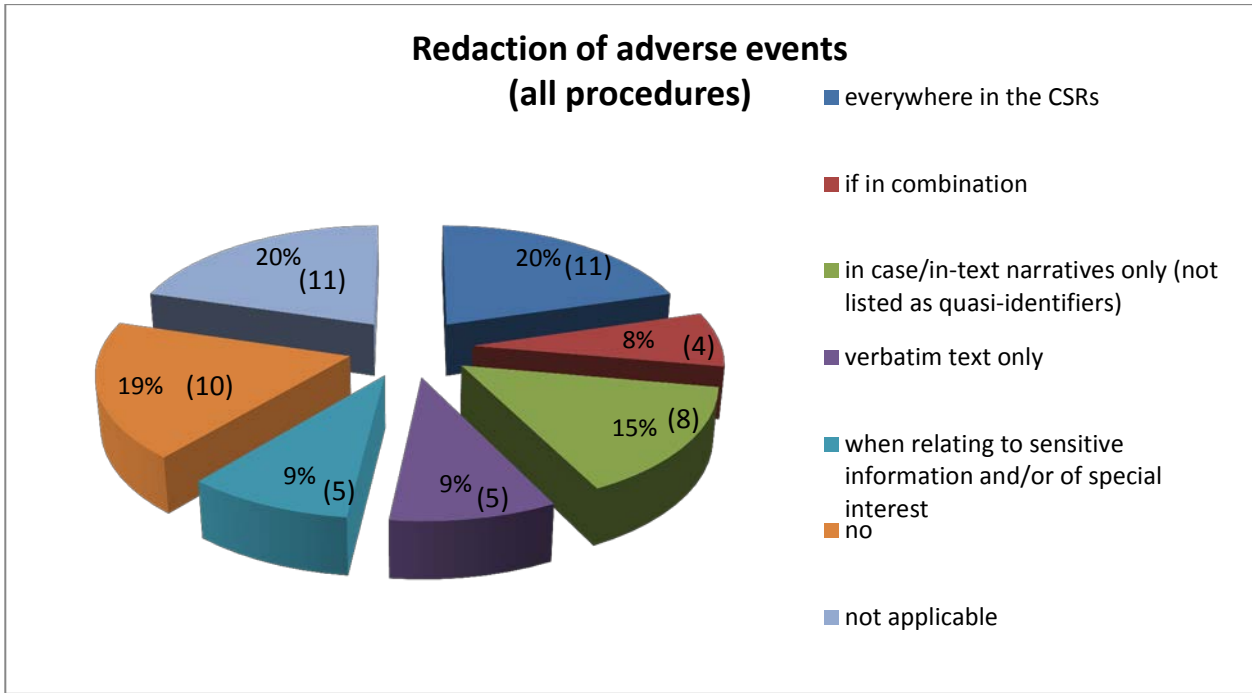
**Figure 5** Anonymisation technique chosen

**Case narratives** (Figure 6) were redacted in full in 27 (50%) of the 54 procedures published, and only partially redacted in 11 (20%) procedures. The remaining 16 (30%) procedures had either no patient identifiers present in the data set, or were generic applications with no case narratives present. Redacting case narratives in full limits the data utility of the reports and this should be addressed and justified within the data utility section of the anonymisation report template.



**Figure 6** Case narratives redaction

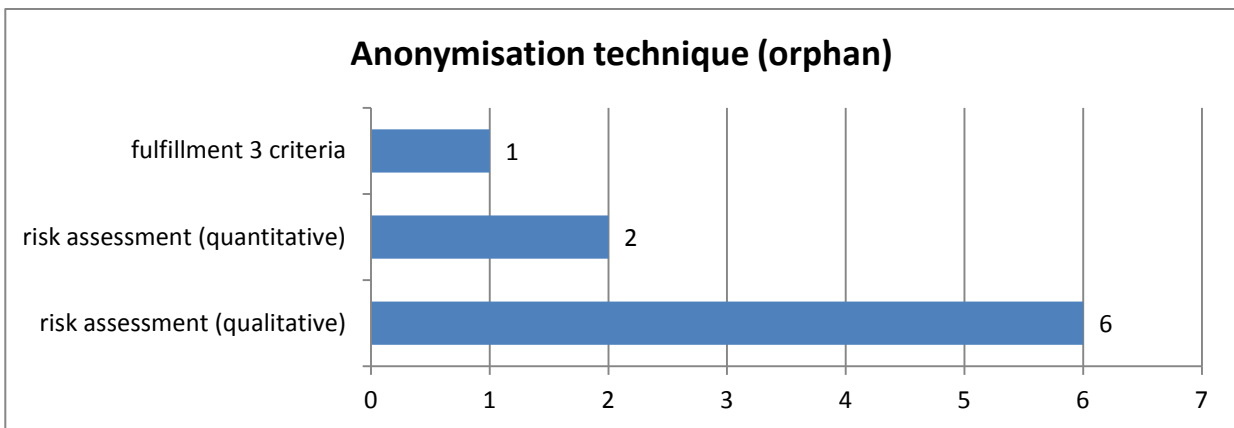
The approaches taken to the **adverse reactions** listed in the CSRs were: 11 procedures redacted them in their entirety; 4 redacted where they were presented in combination; in 8 procedures they were redacted in case/in-text narratives only (not listed as quasi-identifiers); in 5 procedures they were redacted when present in verbatim text; in a further 5 procedures they were redacted when relating to sensitive information and/or of special interest; for 10 procedures there was no redaction and for the 11 procedures where there are no patient identifiers there were no adverse reactions listed. This is presented in Figure 7 below. Therefore a variety of approaches to redaction of adverse reactions has been seen in the published reports to date.



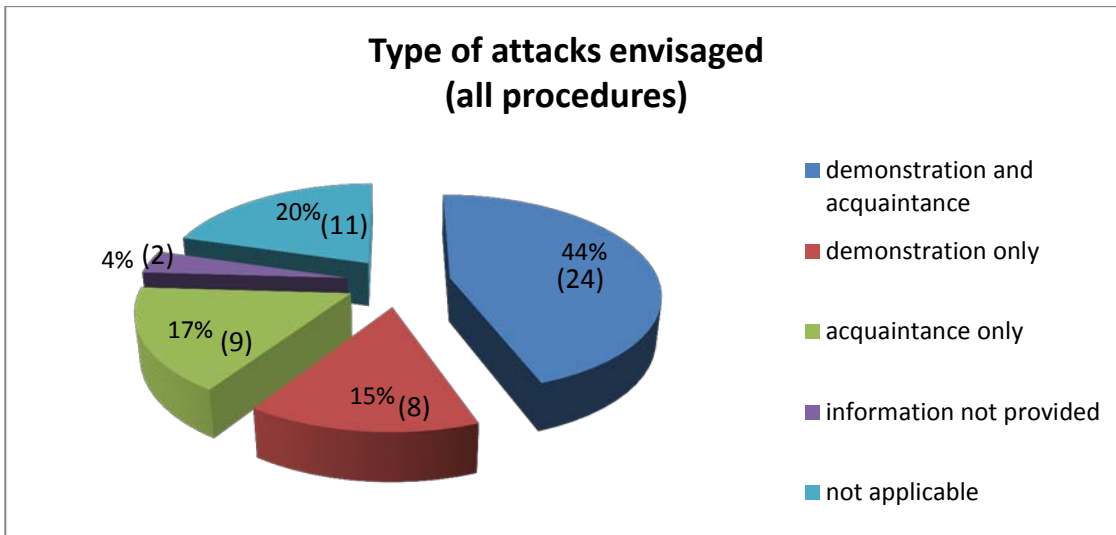
**Figure 7** Adverse reactions redaction

The **uniqueness** of the subjects' variables in all 54 procedures was taken into account in 19 procedures, not taken into account in 24 and not applicable in the 11 procedures without patient identifiers.

The anonymisation for **Orphan** indications was reviewed in more detail as a specific group. There were 9 procedures for orphans in the first year. The method chosen for anonymisation was redaction in 8 procedures and transformation in 1 only. Case narratives were redacted in full for 7 procedures. The risk assessment conducted, illustrated in Figure 8 below, was: fulfilment of the three criteria for 1 procedure, a qualitative approach for 6 procedures, and for 2 procedures a quantitative risk assessment using the threshold of 0.09 - as recommended in the EMA guidance. Overall this outcome is in line with the approach taken for all procedures – redaction was the preferred method and mainly a non-analytical qualitative approach was taken to the risk assessment. Case narratives were redacted in full for the majority as orphan indications have inherently a higher risk of re-identification of individuals.



**Figure 8** Anonymisation technique orphans



**Figure 9** Possible adversaries attackers identified

In the anonymisation report applicants/MAHs are requested to identify possible adversaries and plausible attacks on the data and to evaluate their impact on the risk of re-identification. Figure 9 above lists the possible **adversaries** and plausible attackers of the data listed in each of the procedures published. Each of these scenarios has a different risk and this is evaluated within the anonymisation report published. The most common attack envisaged was a demonstration (showing that an attack is possible) and acquaintance attack.

In **annex 3** of this report further detailed review of three different subsets of the procedures published including (1) non-orphan and non-generics and biosimilar, (2) generics and (3) orphans is provided.

### **Reporting patient re-identification**

Applicants/MAHs are expected to submit only fully anonymised versions of clinical study reports for publication. Users of the clinical data publication website, accessing published clinical reports undertake by accepting the terms of use, not to seek to re-identify the trial subjects or other individuals from the clinical reports. There is a re-identification alert procedure outlined on the clinical data publication website. Although no instances of patients' re-identification were reported, in 2017 one technical issue was reported to the Agency. The concerned document package provided by the MAH for publication contained a non-locked redaction, resulting in a see-through redacted version being published. On the day following publication, the Agency was notified by a member of the public and the documents were removed within a few hours and subsequently the MAH provided a new final package with the redactions locked. An impact assessment for this generic procedure was conducted and deemed that there was negligible risk of patient re-identification. The overall outcome showed that the procedure in place works well to prevent the re-identification of individuals and documents were removed within 48 hours of first publication.

### **Technical anonymisation group**

The technical anonymisation group (**TAG**) was established to help further develop best practices for the anonymisation of clinical reports, in the context of the Agency's policy on the publication of clinical data. The group includes members from academia, industry, patients and healthcare professionals with expertise in areas such as data protection, experts involved in the development of standards and

guidance for anonymisation and re-analysis of clinical data. EMA established the group following a public call for applications launched in March 2017.

The group will consider experience to date with EMA's publication of clinical reports. In particular, it will look at:

- patient re-identification and any privacy risks in the light of new technological developments;
- the scientific utility of the published clinical data as a function of the anonymisation methodology used;
- whether it is possible to successfully conduct a secondary analysis of the anonymised clinical data.

The first TAG meeting took place during the second year of the operation of Policy 0070 and full details on the composition of the TAG, meetings and minutes are provided on the EMA website

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_001880.jsp&mid=WC0b01ac0580c77e78](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001880.jsp&mid=WC0b01ac0580c77e78)

## 5. Measuring success

To provide initial feedback on how well the initiative to publish clinical data is meeting its intended aims, and to gather preliminary information on user experience during the first few months of operation, EMA carried out a survey of users of the clinical data website in mid-2017, eight months after launch. When the survey was first published on 8 June 2017, 23 dossiers were available on the website; 46 were available by the time the survey ended on 15 September 2017.

The online survey consisted of eight voluntary questions, which took around 10 minutes to complete during internal testing. It asked users to give their reasons for accessing the data, how easy they found the data and the website to use, and their level of agreement with EMA's reasons for developing the policy. The survey was linked from the EMA corporate<sup>4</sup> and clinical data websites. EMA also emailed the survey to its list of academic and healthcare-professional organisations.

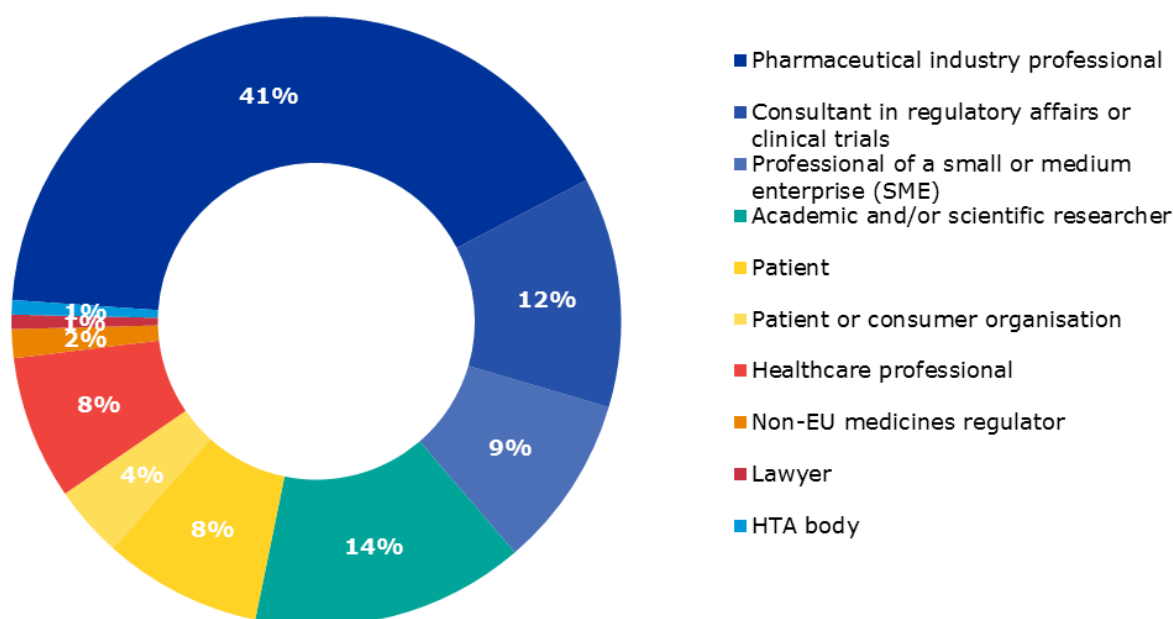
### ***Survey results***

There were 131 respondents, all of whom could be included in one of the categories below (indicated in figure 10<sup>5</sup>). About two thirds (62%) were affiliated to the pharmaceutical industry (pharmaceutical industry professional, consultant in regulatory affairs or clinical trials and professional of an SME), the stakeholder group most directly concerned by Policy 0070. Other sizeable respondents groups included academic or scientific researchers (14%) followed by patients (8%), healthcare professionals (8%), and patient or consumer organisations (4%).

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<sup>4</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

<sup>5</sup> In total, 12 respondents identified themselves as 'other'. These respondents were invited to describe their affiliation in their own words by completing a free-text field. Analysis of these descriptions enabled all of these respondents to be included within one of the final stakeholder groups shown in Figure 1.



**Figure 10** Survey responders per user group (out of a total of 131)

Of the 131 respondents, 118 (90%) gave a reason for accessing the data on the clinical data website, with the different stakeholder groups showing noticeable differences<sup>6</sup>. In general, responders from the groups related to the pharmaceutical industry explained that they used the data to check for compliance with the Agency's requirements for clinical study reports, to benchmark against other companies (e.g. for product development, report writing and transparency) and to be aware of competitors' activities. Typical quotes from these responders are given in table 2.

**Table 2** Reasons for accessing clinical data: pharmaceutical industry

User group	Quote
Pharmaceutical company professional	"To check the compliance of EMA Policy 0070 and strategies followed by sponsors"
Consultant in regulatory affairs or clinical trials	"To get inspiration for my clinical data disclosure tasks"
Professional of an SME	"Competitor review, state of the art information gathering"

Academia were more concerned with data access for research purposes: one responder explained that he or she accessed the data for "research in data disclosure." In contrast, patients cited information and awareness, giving "to follow up clinical trials" as one example, while healthcare professionals tended to express an interest in assessing the evidence relevant to their medical practice.

Overall, 100 (76%) responders stated that they had accessed the clinical data. Of these, 87 (87%) reported that the data are in an understandable format, with only 7% disagreeing; 75 (75%) reported that the data are useful, very useful or extremely useful, with only 8% saying they are not useful. There were few clear differences between user groups. The main reasons for dissatisfaction with the

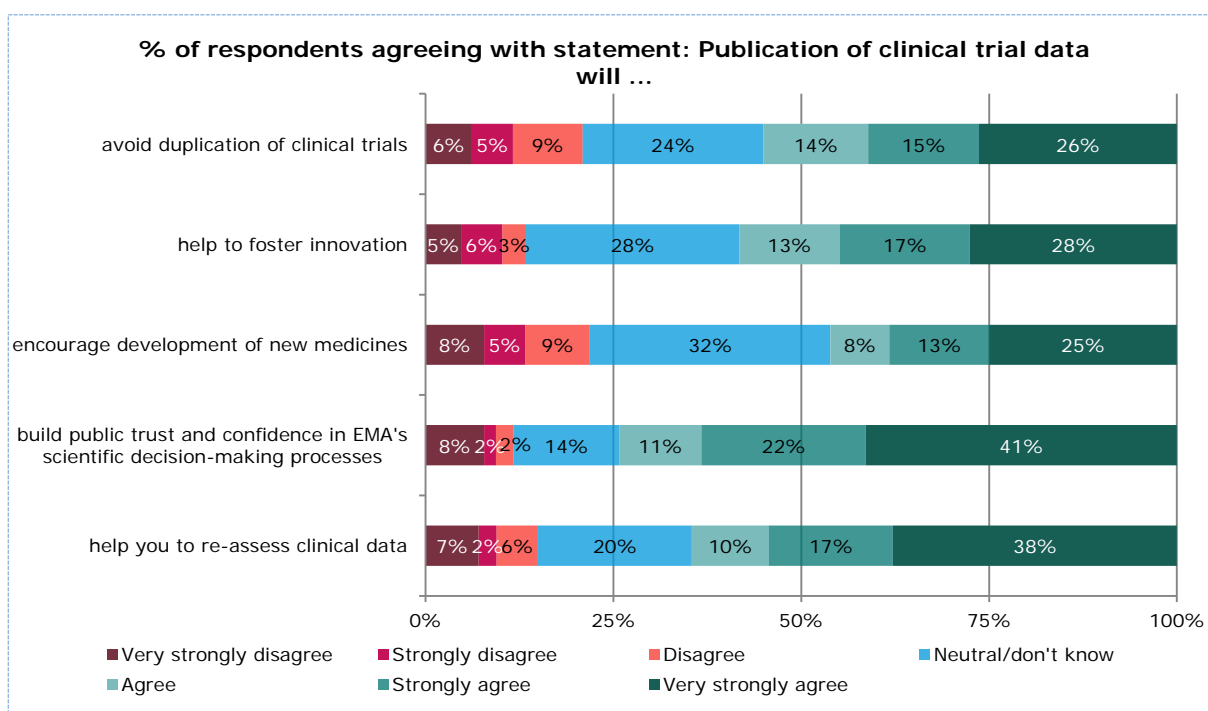
<sup>6</sup> Responses were analysed using word clouds indicating the frequency of use of all words in the responses provided by the different stakeholder groups revealed noticeable differences (see Figure 17 in annex IV).

data included anonymisation, the absence of individual patient line listings (IPLLs) and issues with the way the files are published. These included 'unhelpful' titles, the existence of several documents for each individual clinical study report, and difficulty navigating the documents.

Users were asked to what extent they agreed with five statements encapsulating EMA's reasons for developing Policy 0070:

- Publication of clinical data by EMA will help to avoid the duplication of clinical trials.
- Publication of clinical data by EMA will help to foster innovation.
- Publication of clinical data by EMA will help to encourage development of new medicines.
- Publication of clinical data by EMA will help to build public trust and confidence in EMA's scientific decision-making processes.
- Publication of clinical data by EMA will help you to re-assess clinical data.

Agreement with these statements was high, with a majority of the respondents agreeing with four of them and low levels of disagreement (see figure 3). Agreement was particularly high for two statements: that the data's publication will build public trust and confidence in EMA's processes; and that it will allow the re-assessment of clinical data.



**Figure 11** Level of agreement with EMA's reasons for developing the policy

The more neutral response to other statements is likely to be due to the novelty of the initiative. One responder stated that, "it is too early to judge on some of these justifications; the survey should be repeated at a later point in time."

Overall, 50% of responders reported that the website was easy or very easy to use, finding it simple and user friendly, particularly the 'help' page and 'latest news' section. Responders found the search function very useful, along with the download and export functions, while pharmaceutical industry

professionals stated that the anonymisation reports were very helpful. Possibilities for future improvements included increasing awareness of and access to the published data, and broadening the scope of Policy 0070 to include individual patient data and applying the policy to older marketing authorisation applications, as well as improving ease of use of the website and the published documents themselves.

### ***Survey findings***

The results of the survey speak in favour of EMA's decision to develop and implement Policy 0070, particularly as it is seen to increase trust in EMA's regulatory activities and facilitate third-party reassessment of the published clinical data. They showed that, at least in the first few months of availability, the main users of the website represented the pharmaceutical industry. This is unsurprising, given that these stakeholders are directly concerned by the policy, although their positive reaction to the website is encouraging.

Users representing the pharmaceutical industry tended to refer to policy compliance, benchmarking (product development, report writing and transparency) and awareness of competitors' activities when asked to explain why they were using the website to access clinical data. On the other hand, academia were more concerned with access to data for research purposes, while patients cited information and awareness, and healthcare professionals expressed an interest in assessing the evidence relevant to their medical practice.

## **6. Meetings with stakeholders**

### ***Webinars***

Webinars with different stakeholders started in 2015 before the implementation of the policy and in the first year of implementation took place to discuss revisions to the external guidance and emerging issues. Regular webinars with industry were held in this first year of operation of the policy. EMA consulted industry stakeholders on procedural aspects and principles for redaction of CCI and anonymisation of personal data. The original guidance for industry was published in March 2016 before the first submissions under policy 0070. The first webinar in this reporting period with industry associations was held on 9 December 2016 to update on initial experience with implementation and explain the proposed changes to the external guidance. Subsequent webinars with industry stakeholders were held on 23 March 2017 and 29 June 2017 to further discuss specific issues. The external guidance was updated after each of these webinars and the summary of changes published also. The agenda and documents discussed at the industry webinars are published at the EMA web site "[support for industry on clinical data publication](#)".

### ***Anniversary publication***

The Agency published a [press release](#) to mark the first anniversary of the implementation of the policy with some background details and a snapshot of the data published in the first year.

## **7. International co-operation**

A central pillar of EMA's strategy to protect public health is the strengthening of collaboration at international level to promote harmonisation of regulatory requirements, sharing of information and addressing common challenges. The Agency works with our international partners to share our



experience in clinical data publication and to examine opportunities for harmonisation. As part of this co-operation an overview of the exchanges with international partners is presented below.

### ***FDA***

In October 2016, FDA hosted a visiting expert from EMA for 2 weeks to exchange experience on transparency issues and present the principles and background to the implementation of Policy 0070.

### ***Health Canada***

The EMA hosted a one week visit from a colleague from Health Canada in June 2017 who spent time with the CDP team reviewing the processes in place and sharing information on the implementation plans for clinical data in Health Canada.

### ***Japan***

The EMA hosted a visiting expert from the Japanese Ministry of Health, Labour and Welfare for 5 months starting in September 2017. The Japanese authority publishes a summary of clinical data but not the clinical study reports for authorised innovative medicines and is developing guidance in publication of clinical data.

These visits enhance international co-operation in the field of clinical data publication and enable sharing of best practice and allow for development of standardised processes to publish anonymised clinical data. The contacts are maintained via subsequent bilateral exchanges between the different Agencies.

## **8. Next steps**

Looking to the second half of 2018 and beyond, the next phase of EMA's Brexit preparedness BCP will have to be taken into account. EMA is currently preparing for its relocation to the new host Member State and the UK's withdrawal from the EU regulatory system. The Agency launched the first phase of its BCP in 2017 and as a result work in some areas has been temporarily reprioritised, suspended or postponed to resource Brexit preparedness activities and safeguard core activities. The second half of 2018 as well as 2019 will see a further reduction in the operation of EMA's proactive publication of clinical data in line with a revised prioritisation of its activities to take due account of the consequences of the relocation. The Agency will do its utmost to resume the proactive publication of clinical data to the level outlined at the start of the policy once the relocation is complete.

## Annex 1 – list of procedures published in first year (20 October 2016-19 October 2017)

Product name	Active substance	Procedure number	MAH	Publication date
Kyprolis	Carfilzomib	EMA/H/C/003790/0000	Amgen Europe B.V.	20/10/2016
Zurampic	Lesinurad	EMA/H/C/003932/0000	Grunenthal GmbH	20/10/2016
Armisarte	Pemetrexed diacid monohydrate	EMA/H/C/004109/0000	Actavis Group PTC ehf	24/11/2016
Caspofungin Accord	Caspofungin acetate	EMA/H/C/004134/0000	Accord Healthcare Ltd	24/11/2016
Praxbind	Idarucizumab	EMA/H/C/003986/0000	Boehringer Ingelheim International GmbH	21/12/2016
Tarceva	Erlotinib	EMA/H/C/000618/II/0043	Roche Registration Limited	21/12/2016
Palonosetron Hospira	Palonosetron	EMA/H/C/004069/0000	Hospira UK Limited	30/01/2017
Aripiprazole Mylan	Aripiprazole	EMA/H/C/004236/0000	MYLAN S.A.S	31/01/2017
Cubicin	Daptomycin	EMA/H/C/000637/II/0053/G	Merck Sharp & Dohme Limited	27/02/2017
Empliciti	Elotuzumab	EMA/H/C/003967/0000	Bristol-Myers Squibb Pharma EEIG	28/02/2017
Coagadex	Human coagulation factor X	EMA/H/C/003855/0000	Bio Products Laboratory Limited	28/02/2017
Palonosetron Accord	Palonosetron	EMA/H/C/004129/0000	Accord Healthcare Ltd	16/03/2017
Amlodipine-Valsartan Mylan	Amlodipine / valsartan	EMA/H/C/004037/0000	MYLAN S.A.S	16/03/2017
Descovy	Emtricitabine / tenofovir alafenamide	EMA/H/C/004094/0000	Gilead Sciences International Ltd	21/04/2017

Product name	Active substance	Procedure number	MAH	Publication date
IDELVION	Albutrepenonacog alfa	EMA/H/C/003955/0000	CSL Behring GmbH	28/04/2017
Zonisamide Mylan	Zonisamide	EMA/H/C/004127/0000	Mylan S.A.S	02/05/2017
TAGRISSO	Osimertinib	EMA/H/C/004124/0000	AstraZeneca AB	05/05/2017
Ferriprox	Deferiprone	EMA/H/C/000236/II/0103	Apotex Europe BV	05/05/2017
Pemetrexed Fresenius Kabi	Pemetrexed	EMA/H/C/003895/0000	Fresenius Kabi Oncology PLC	18/05/2017
Giotrif	Afatinib	EMA/H/C/002280/II/0012	Boehringer Ingelheim International GmbH	18/05/2017
EndolucinBeta	Lutetium (177 lu) chloride	EMA/H/C/003999/0000	ITG Isotope Technologies Garching GmbH	01/06/2017
Alprolix	Eftrenonacog alfa	EMA/H/C/004142/0000	Swedish Orphan Biovitrum AB (publ)	02/06/2017
Rasagiline Mylan	Rasagiline	EMA/H/C/004064/0000	MYLAN S.A.S	02/06/2017
Bortezomib Hospira	Bortezomib	EMA/H/C/004207/0000	Hospira UK Limited	12/06/2017
OPDIVO	Nivolumab	EMA/H/C/003985/II/0002	Bristol-Myers Squibb Pharma EEIG	21/06/2017
OPDIVO	Nivolumab	EMA/H/C/003985/II/0008	Bristol-Myers Squibb Pharma EEIG	21/06/2017
Halaven	Eribulin	EMA/H/C/002084/II/0028	Eisai Europe Ltd.	22/06/2017
Strimvelis	Autologous cd34+ enriched cell fraction that contains cd34+ cells transduced with retroviral vector that encodes for the human	EMA/H/C/003854/0000	GlaxoSmithKline Trading Services	29/06/2017

Product name	Active substance	Procedure number	MAH	Publication date
	ada cdna sequence			
Flixabi	Infliximab	EMA/H/C/004020/0000	Samsung Bioepis UK Limited (SBUK)	30/06/2017
Lonsurf	Trifluridine / tipiracil	EMA/H/C/003897/0000	Les Laboratoires Servier	07/07/2017
Zinbryta	Daclizumab	EMA/H/C/003862/0000	Biogen Idec Ltd	17/07/2017
Pandemic influenza vaccine H5N1 AstraZeneca	Pandemic influenza vaccine (h5n1) (live attenuated nasal)	EMA/H/C/003963/0000	AstraZeneca AB	21/07/2017
Avastin	Bevacizumab	EMA/H/C/000582/II/0086	Roche Registration Limited	24/07/2017
Humira	Adalimumab	EMA/H/C/000481/II/0149	AbbVie Ltd.	25/07/2017
Enzepi	Pancreas powder	EMA/H/C/002070/0000	Allergan Pharmaceuticals International Ltd	25/07/2017
Zavicefta	Ceftazidime / avibactam	EMA/H/C/004027/0000	Pfizer Ireland Pharmaceuticals	26/07/2017
Taltz	Ixekizumab	EMA/H/C/003943/0000	Eli Lilly Nederland B.V.	02/08/2017
Victoza	Liraglutide	EMA/H/C/001026/II/0038	Novo Nordisk A/S	02/08/2017
Ruconest	Conestat alfa	EMA/H/C/001223/II/0031	Pharming Group N.V	10/08/2017
Gazyvaro	Obinutuzumab	EMA/H/C/002799/II/0007	Roche Registration Limited	10/08/2017
Bortezomib SUN	Bortezomib	EMA/H/C/004076/0000	Sun Pharmaceutical Industries Europe B.V.	25/08/2017
Afinitor	Everolimus	EMA/H/C/001038/II/0048	Novartis Europharm Ltd	01/09/2017
Darzalex	Daratumumab	EMA/H/C/004077/0000	Janssen-Cilag	04/09/2017

Product name	Active substance	Procedure number	MAH	Publication date
			International NV	
Zepatier	Elbasvir / grazoprevir	EMA/H/C/004126/0000	Merck Sharp & Dohme Limited	05/09/2017
Kyprolis	Carfilzomib	EMA/H/C/003790/II/0001/G	Amgen Europe B.V.	07/09/2017
HyQvia	Human normal immunoglobulin	EMA/H/C/002491/II/0021	Baxalta Innovations GmbH	12/09/2017
Docetaxel SUN	Docetaxel	EMA/H/C/004086/0000	Sun Pharmaceutical Industries Europe B.V.	13/09/2017
OPDIVO	Nivolumab	EMA/H/C/003985/II/0003	Bristol-Myers Squibb Pharma EEIG	19/09/2017
Qtern	Saxagliptin / dapagliflozin	EMA/H/C/004057/0000	AstraZeneca AB	20/09/2017
Odefsey	Emtricitabine / rilpivirine / tenofovir alafenamide	EMA/H/C/004156/0000	Gilead Sciences International Ltd	28/09/2017
Humira	Adalimumab	EMA/H/C/000481/II/0147	AbbVie Ltd.	29/09/2017
Revestive	Teduglutide	EMA/H/C/002345/II/0020	Shire Pharmaceuticals Ireland Ltd	04/10/2017
Nordimet	Methotrexate	EMA/H/C/003983/0000	Nordic Group B.V.	04/10/2017
Mysildecard	Sildenafil	EMA/H/C/004186/0000	Mylan S.A.S	06/10/2017
Total	54			

## Annex 2 – Commercially Confidential Information

In the first year of Policy 0070, 24% of instances of CCI proposals made by applicants/marketing authorisation holders were accepted and in 76% of cases these were rejected.

A detailed breakdown of the reasons for the acceptance of CCI proposals is presented below for both quality and clinical information.

### Quality

All CCI accepted related to pharmaceutical development - 49 instances in total were accepted. The detailed reasons for acceptance are illustrated below in Figure 12.

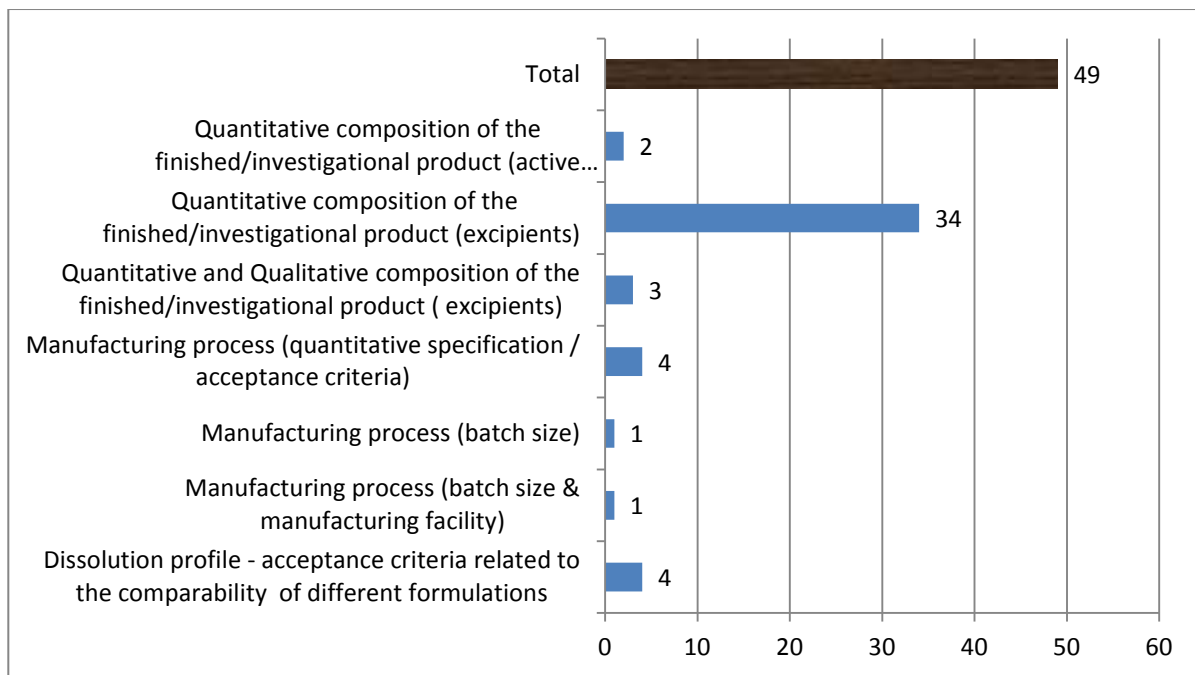
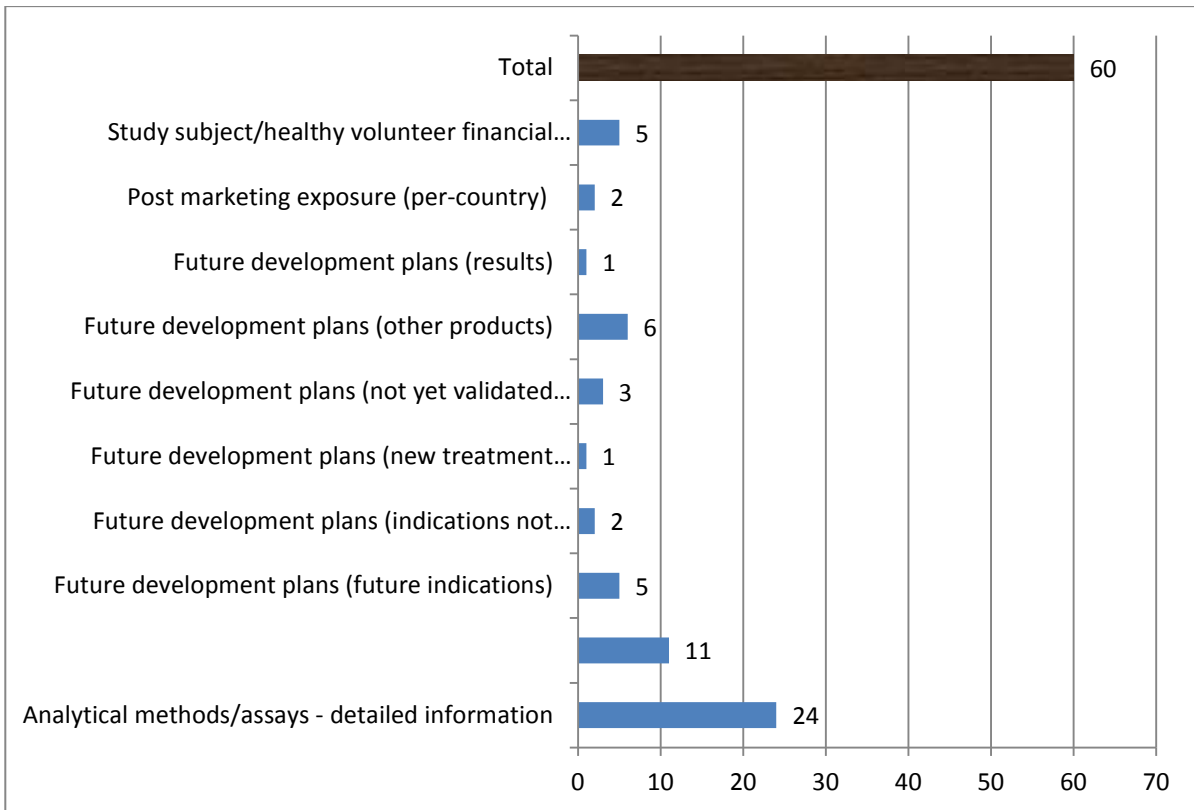


Figure 12 Quality CCI accepted – pharmaceutical development – detailed reasons

### Clinical

There were 60 instances in total where clinical CCI was accepted. The detailed reasons for acceptance are illustrated in Figure 13.



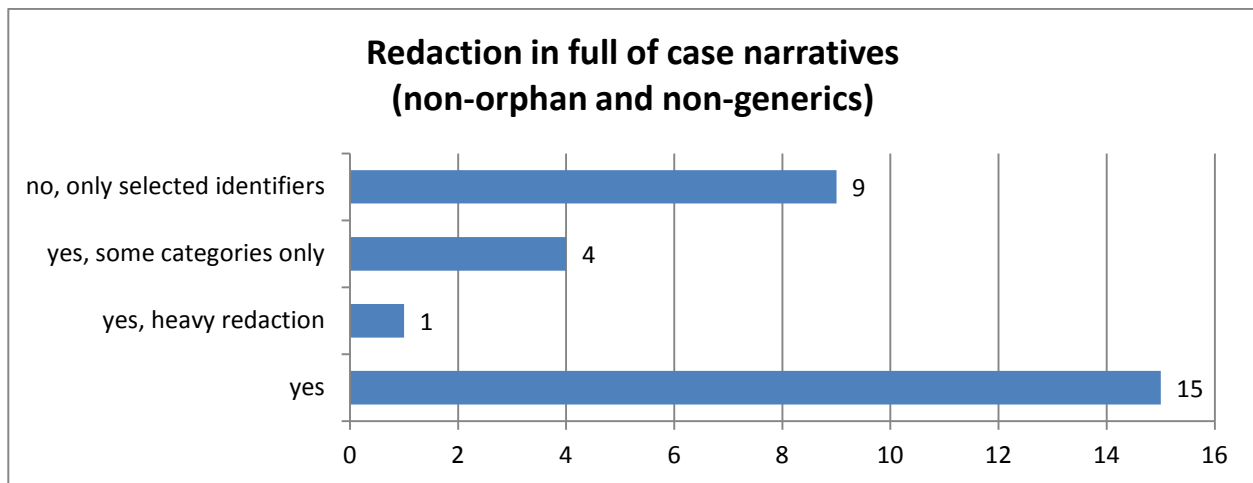
**Figure 13** Clinical CCI accepted – detailed reasons

## Annex 3 – Anonymisation

### **(1) Non-orphan and non-generics and biosimilar (29 of 54 procedures published)**

In this subset of procedures some additional analysis is presented below for how case narratives and adverse reactions were addressed within the clinical reports. Within these 29 procedures, 26 provided a qualitative risk assessment; 2 provided quantitative risk assessments and 1 fulfilled the three criteria. Redaction was the method of anonymisation chosen in 28 cases and redaction and transformation in 1 procedure. The size of the population was taken into account in 21 of these procedures.

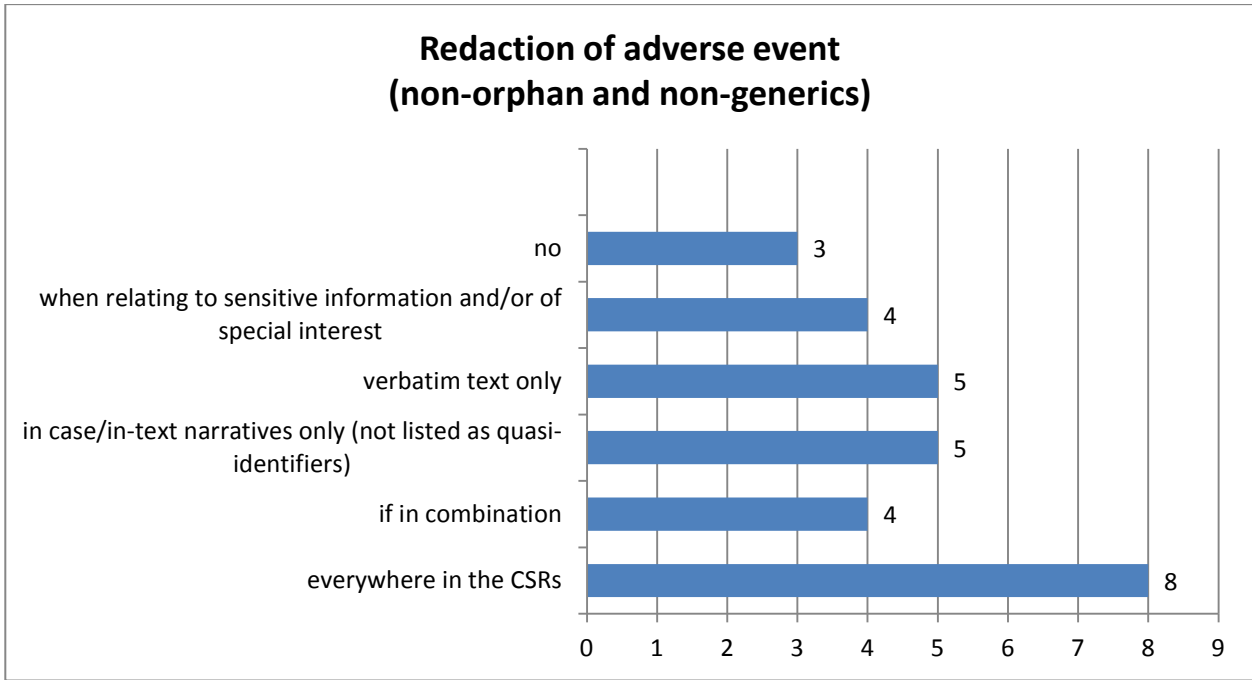
Redaction in full of the case narratives was seen in 15 procedures as shown in Figure 14.



**Figure 14 - Case narratives redaction non-orphan non-generics**

The redaction of the adverse events is presented in Figure 15. Adverse events were redacted throughout the CSRs in their entirety in 8 procedures, with selective redaction in other procedures and no redaction of any adverse events in 3 procedures only.





**Figure 15** – adverse events redaction non-orphan non-generics

**(2) Generics**

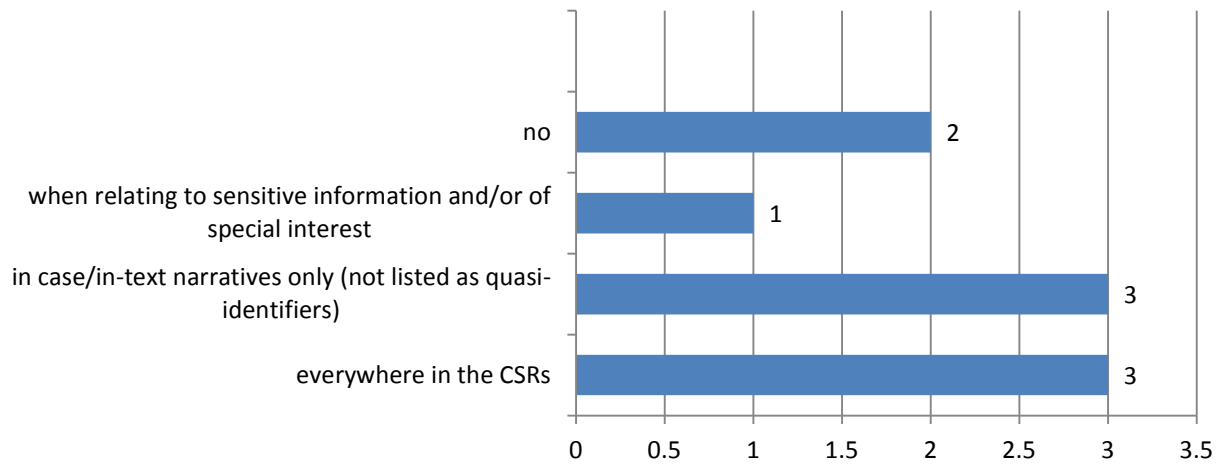
There were 5 generic procedures with patient identifiers in the first year of publication. Two provided a qualitative risk assessment and three fulfilled the three criteria. Redaction was the anonymisation method of choice in all 5 cases. Case narratives were not included in the clinical study reports.

**(3) Orphan**

There were 9 orphan procedures in the data set. Six provided a qualitative risk assessment, two a quantitative risk assessment and one fulfilled the three criteria. Redaction was the method of anonymisation chosen in eight cases and transformation in one procedure. Case narratives were redacted in full in seven of the clinical study reports and only selected identifiers redacted in two procedures. Demographic data and medical history were redacted in full for all procedures. The size of the population was taken into account in eight of the procedures.

The redaction of adverse events for the nine orphan procedures is presented in Figure 16.

### Redaction of adverse events (orphan)



**Figure 16** - Adverse events redaction orphans

