SHORT COMMUNICATION

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Individual Case Safety Reports – How to Determine the Onset Date of an Adverse Reaction

A Survey

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Abstract

Background: The building blocks of a pharmacovigilance system depend primarily on good quality individual case safety reports (ICSRs), which are stand-alone summaries describing one or more suspected adverse reactions that occur while a subject is taking either an investigational or marketed medicinal product and may require expedited reporting to regulatory authorities. For regulatory reporting purposes, the information of an ICSR is usually captured on forms such as MedWatch 3500/3500A, CIOMS I, Vaccine Adverse Event Report System (VAERS) or Adverse Events Following Immunization (AEFI). ICSRs that are sent electronically must meet the standards for electronic transmission specified in the International Conference on Harmonisation (ICH) E2B (R2) guideline. In filling out these regulatory forms, there are some areas of ambiguity. One of these is what the 'date of event' (MedWatch) or 'reaction onset date' (CIOMS) is interpreted to be.
Objective: The aim of the survey was to determine the uniformity of responses for the onset date of an adverse reaction.
Methods: A pilot and three surveys of pharmacovigilance professionals were undertaken between February and July 2009 to determine the range of responses for the onset of an adverse reaction. A narrative of a subject admitted to hospital with a diagnosis of pneumonia was presented and the respondent was asked to pick the date of onset of the adverse reaction.
Results: The total number of respondents was 129. The results of the surveys indicated there was considerable variation in responses. These differences were based on different perspectives regarding the suspected adverse reaction. Some viewed the 'reaction' to be the first onset of signs and symptoms (even if nonspecific), others considered the onset of the reaction to be the date of the diagnosis, while others considered the date to be when the reaction became serious.
Conclusion: By means of a survey, we have illustrated an example of the variability of determining the onset date of a suspected adverse reaction, and recommend that a criterion for onset time, i.e. beginning of signs or symptoms

of the event, or date of diagnosis, be chosen as the standard. Once decided, this information should be incorporated into the company's case assessment documentation and staff appropriately trained, thus ensuring consistency across cases and minimizing the time spent in determining what date to use.

Background

The individual case safety report (ICSR) is a stand-alone summary of one or more suspected adverse reactions that occurs while a subject is taking either an investigational or marketed medicinal product (drug, biological, herbal, nutraceutical or vaccine), and often requires expedited reporting to regulatory authorities. The quality of an ICSR depends on the accuracy and completeness with which specific information is obtained about a case and entered onto a database. This information includes patient identifiers (e.g. age, sex and race), the suspected adverse reaction in question, the suspect product(s), any relevant laboratory findings/tests, medical history and concomitant medications. An integral part of the ICSR is the narrative description of the suspected adverse reaction. A well crafted narrative provides a time-sequenced summary of all the relevant information that helps to determine the 'weight of evidence' for or against a causal relationship between the adverse event and medicinal product.[1,2] The way the elements of a case are assembled determines the content of the cumulative line listings, which is the basis for aggregate safety reports and signal detection procedures.

The ICSR serves several key purposes, primarily forming one of the key data sources for signal detection. Regulatory agencies worldwide mandate prompt notification of suspected unexpected serious adverse reactions (SUSARs). The definitions of 'unexpected', 'serious' and 'adverse reactions' are found in guidance documents from the International Conference on Harmonisation (ICH).[1,2] However, the CIOMS Working Group V has already showed variability in determining seriousness and expectedness, even for terms such as 'total blindness for 30 minutes' and 'suicidal threats'.[3]

For regulatory reporting purposes, the information in an ICSR is usually captured on the MedWatch 3500/3500A forms used in the US or the CIOMS I form used in the EU and many countries worldwide.[4-6] Adverse events involving vaccines are captured on the Vaccine Adverse Event Report System (VAERS) form in the US and the Adverse Events Following Immunization (AEFI) reporting form in Canada.[7,8] ICSRs that are sent electronically must meet the standards for electronic transmission specified in the ICH E2B(R2) guideline.[9]

Therefore, several questions arise:

- When completing a regulatory reporting form, how much is enough to ensure adequate quality?
- Are all the case features of equal weight or are certain features less important than others?
- How do we decide a case is complete?

Not only can collecting unnecessary information be inefficient and costly, but in addition, redundant and irrelevant data can obfuscate signals. In filling out these regulatory forms, there are some areas of ambiguity; one of these is what is the 'date of event' (MedWatch) or 'reaction onset date' (CIOMS). Specifically, one of the authors noted one question came up time and time again – ''what is the reaction onset date – when the initial signs and symptoms of the reaction start, when there is a diagnosis, or when the reaction becomes serious?'' This is one of the 'grey' areas, i.e. it can be interpreted in different ways, and the authors decided to perform a survey to assess the range of responses. The objective of our survey was, therefore, to determine the uniformity of responses for the onset date of an adverse reaction.

Methods

In February 2009, an informal pilot survey was developed by one of the authors (MK) and sent by email to six other individuals who had at least 10 years' experience in drug safety/pharmacovigilance. The survey question was:

A 54-year-old male develops cough and cold on 1 March 2008; 1 week later (8 March 2008) he is diagnosed with pneumonia and 2 days later (10 March 2008) he is hospitalized for his pneumonia.

What is the 'date of event' (MedWatch) or 'reaction onset date' (CIOMS) that should be entered on the form?

Answer 1: 1 March 2008

Answer 2: 8 March 2008

Answer 3: 10 March 2008

Following these initial responses, this question was then modified by excluding the 8 March 2008 answer to create a simpler binomial choice, and between February and July 2009 the revised survey was given three different times in training courses given in the EU to a mixture of pharmacovigilance professionals, mainly from industry, attending training courses in Hatfield and Guilford, UK (Survey I and II, respectively), and Verona, Italy (Survey III).

Results

Table I is a summary of the findings from the pilot survey and findings from each of the three surveys tabulated both separately and combined.

These results show that there was a wide range of responses within and across surveys, including the pilot survey of experienced drug safety/pharmacovigilance professionals. Although response number 2 was not included in surveys I–III, some participants wrote 8 March 2008 as their answer.

Discussion

Throughout the pharmaceutical industry, millions of case reports are produced each year based on ICH guidelines, with the main focus on identifying cases eligible for expedited case reporting within 7 or 15 days, and most of these are sent to regulatory authorities electronically. The purpose of the ICH E2B (R2) document is to standardize the data elements for the transmission of ICSRs; this drives the approach to data entry. However, not all data elements within a case report are easy to identify in a precise numeric way. CIOMS V addressed issues such as what are the minimum criteria to make a case valid for expedited reporting (not to be confused with what is a case) and how to mitigate the risk of missing cases that are either serious and unexpected.[3] However, although there is excellent guidance about how to perform follow-up, there is no discussion on how to define quality elements once the information is received. Indeed, the authors are not aware of any published guidance about this or publically available benchmarking data.

Date of Onset of an Adverse Reaction

Because the temporal association between the exposure of the suspect product and the

Table I. Results of the survey[a,b]

Survey	Answer 1 *1 March 2008* [n (%)]	Answer 2 *8 March 2008* [n (%)][c]	Answer 3 *10 March 2008* [n (%)]	Did not provide specific answer [n (%)]
Pilot (n = 7[d])	2 (29)	3 (43)	2 (29)	0
Survey I [Hatfield, UK] (n = 52)	25 (48)	7 (13)	14 (27)	6 (12)
Survey II [Gilford, UK] (n = 47)	33 (70)	1 (2)	8 (17)	5 (11)
Survey III [Verona, Italy] (n = 23)	11 (48)	0	10 (43)	2 (9)
Combined results of surveys I–III (n = 122)	69 (57)	8 (7)	32 (26)	13 (11)

a The question posed in the survey was: "A 54-year-old male develops cough and cold on 1 March 2008; 1 week later (8 March 2008) he is diagnosed with pneumonia and 2 days later (10 March 2008) he is hospitalized for his pneumonia. What is the 'date of event' (MedWatch) or 'reaction onset date' (CIOMS) that should be entered on the form?"

b Percentages may not equal 100% due to rounding.

c Answer 2 was only included in the initial pilot survey; in surveys I–III some participants wrote 8 March 2008 even though this choice was not listed.

d The authors were part of the seven responders to the pilot survey.

development of the adverse reaction is an important factor in determining causality, we decided to perform an informal survey of opinions from pharmacovigilance professionals. Although the authors were part of the initial seven responders to the survey, the survey question was sent out separately by email to each participant. The answers from the other five responders remained unknown to the others, thus ensuring answers remained uninfluenced by the responses of the other participants. Surveys I–III were handed to pharmacovigilance professionals and, to minimize the risk that responses could have been influenced by the responses from the rest of the group, i.e. 'group opinion bias', respondents completed the forms under supervision and conferring was strongly discouraged. However, in the 'real-world setting' the individual responsible for a case will often ask colleagues for their advice during preparation of the ICSR regarding matters of uncertainty, so even if there was 'group opinion bias' this does not significantly distort results for our purposes.

The onset of the reaction is key information in case causality assessment. However, in the context of case management, how precise should this be? From these survey results, the onset date of the 'event/reaction' is ambiguous. This confusion arises because there is uncertainty about the 'event as opposed to the reaction' (i.e. non-specific signs and symptoms vs a specific diagnosis), and a different perspective between the medical and regulatory categorization of a suspected adverse reaction. In this example, the 'suspected adverse reaction' is pneumonia. Cough and cold (1 March 2008) reflected the beginning process of a condition that resulted in pneumonia (answer number 1), but 'cough and cold' is not specific to pneumonia. The 'suspected adverse reaction' of pneumonia was not diagnosed until 8 March 2008 (answer number 2). Since expedited regulatory reporting is required for SUSARS, the reaction of pneumonia was not deemed serious, based on regulatory criteria, until the subject was hospitalized on 10 March 2008 (answer number 3). One might also consider that the case could have been serious prior to hospitalization based on the criterion of 'medically important' (i.e. an event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition of serious).[1] 'Medically important' because it relies on medical judgement can be equally ambiguous, but the limited case details provided no indication of a change in the signs, symptoms and status of the subject from 1 March 2008 (the beginning of signs and symptoms) to 8 March 2008 (date of diagnosis). Therefore, depending on what perspective was used in assessing the case, there could be, and were, three different answers. One could argue that from a medical perspective (which is most relevant for causality assessment), date of the first most plausible signs and symptoms or diagnosis of the reaction would be most suitable, yet many would use the date when a suspected adverse reaction turned serious as the onset date. But does a difference of 9 days affect individual or aggregate case causality? However, with the compliance emphasis on regulatory reporting, it is easy to understand why some interpret adverse reaction start date as only when an adverse reaction becomes serious in the regulatory sense.

Existing guidances and regulations do not provide clear instruction on how to determine the onset date. Instructions for filling out the MedWatch form for 'date of event' (section B3 on the form) include the following: ''provide the actual or best estimate of the date of first onset of the event. If day is unknown, month and year are acceptable. If day and month are unknown then year is acceptable.''[4,5] The problem from the responses seen above is the 'event' is interpreted differently. Although the US FDA say 'best estimate' rather than a precise figure, much time can be spent deliberating on these issues with no consensus, as shown in the survey results shown above. More important, in our experience, within a pharmaceutical company (particularly when a contract research organization is involved), a lot of time and thought is used in attempting to answer questions such as these, i.e. questions that do not require precise answers to aid causality assessment. This is at a time of great financial pressures when a drug safety unit can ill afford to

divert attention from other important aspects of the ICSR.

As one component of causality assessment, assuming the condition being treated has not been aggravated, temporality of an adverse reaction after a suspect drug has been administered is best thought of in terms of the following: first dose, rapid (within minutes), early (within a few hours), intermediate (days), late (weeks) and delayed (years). Admittedly, if a suspected adverse reaction shows consistent clustering for reaction onset dates this is an important factor for determining causality, although it is but one factor. In addition, as mentioned in section B.2.i.7 of ICH E2B (R2) under the 'User Guidance' section:

''The major uses of intervals are to cover circumstances where both the dates are known but the interval is very short (e.g., minutes, such as in anaphylaxis), and when only imprecise dates are known but more information concerning the interval is known. Dates, if available, should always be transmitted in the appropriate fields rather than intervals.''[9]

Thus, when referring to 'days' as time to onset for an adverse reaction, arguably our position is consistent with ICH guidance that precision is 'nice to have' when available and obvious to interpret.

Other Important Issues

Based on the authors' experience, the following are other important areas prone to deficient quality in ICSRs:

- missing therapy dates for suspect product(s), making it impossible to determine if there is a temporal relationship between the product and the event/reaction;
- insufficient or contrary information about biological plausibility (such as laboratory data or other tests) in support of the diagnosis of the event/reaction;
- a poorly written narrative that negatively impacts understanding of the case;
- poor quality and incomplete case information, especially for spontaneously reported postmarketing safety reports, which is well recognized.[10]

These deficiencies led to the development of guidelines for submitting ICSRs for publication.[11] However, we are concerned that this negative attitude about the quality of spontaneous reports can be a self-fulfilling prophesy and that, intrinsically, spontaneous reports are not poor quality if there is adequate attention to all components of the process. Understanding which areas of a case report are prone to poor quality should stimulate companies to shape training courses to help staff maximize the quality of information obtained from the reporter and the way it is subsequently managed. An example of a proactive approach is training frontline staff with questionnaires for adverse reactions of interest that worry regulatory agencies, such as drug-induced liver injury or Stevens-Johnson syndrome. In this way, those staff who are the first to be contacted are best placed to elicit key case details.

The narrative portion of the ICSR should then tell the 'complete story' of the event from 'beginning to end', i.e. summarizing all the relevant information according to the sequential timeframes when key events/findings happened. Even with the lack of clarity or uniformity of responses shown in the survey results above, a well crafted narrative that contains all the relevant information of the event, including the sequence of events from the onset of the non-specific signs/symptoms of cough and cold to the progression of pneumonia and subsequent hospitalization would allow the reviewer to assess the case regardless of what onset date was provided in the box on the MedWatch/CIOMS forms. Guidance on how to write a well crafted narrative and what to include was published by the CIOMS Working Group V and is a good reference to follow.[3] More recently, the FDA has developed 'Patient Profile Viewer' as a better way of demonstrating how case components relate to each other to maximize the use of such data. However, this is more appropriate for the substantial narratives obtained in clinical trials.[12]

With respect to the question we posed, for regulatory reporting, to minimize the confusion regarding what the onset date is since no standard currently exists, we recommend that the pharmacovigilance department determine and specify what criterion will be used for onset. The choices include the following:

1. The date of first onset of 'medically relevant' signs and symptoms associated with the suspect reaction. 'Medically relevant' means those signs/symptoms typically associated with the suspected adverse reaction, i.e. 'cough and cold', in the example above rather than, for example, 'toothache'.
2. The date of diagnosis.
3. The date the suspected reaction met one or more serious criteria.

(Note: It is the authors' opinion that criterion 1 or 2 be used. We do not recommend option 3 because we feel this information does not help in the medical understanding/assessment of the case, i.e. the fact that the subject was hospitalized is important, not when the case met serious criteria.)

Once it has been decided which criterion to use, this information should be incorporated into the company's case assessment documentation and staff appropriately trained, thus ensuring consistency across cases and minimizing the time spent in determining what date to use.

Because not all cases are the same, and in order to manage those case components that matter, through pharmacovigilance planning, case managers should be proactive in defining variability in criteria for quality completeness of case information, to address ambiguous aspects of ICSRs. Variation is a fundamental reality of pharmacovigilance. Approaches to minimize variation should be a design feature of any quality pharmacovigilance system that needs to be routinely assessed to determine effectiveness.[13]

We believe that the Good Manufacturing Practice (GMP) concept of Design Space should be studied, as described in ICH Pharmaceutical Development Q8, for clues on how to better define the relationship of variation to quality. Design Space describes the linkage between the process inputs (input variables and process parameters) and the critical quality attributes of a process.[14] Thus extrapolating the 'Design Space' concept to case management, we would look at the complexity with which pieces of data are fed into the process and then define how these data elements can be managed within a certain range of variability. This is applicable to concepts such as adverse events or adverse reactions of special interest. If the case load of a well selling product is examined, there are often certain groups of cases that are repetitive, reflecting well known adverse reactions for a product. By using the 'Design Space' analogy, the process can be streamlined to capture and record case information in a predetermined way without managing each case on its own merits (of course, you still need to be vigilant for severe or unusual examples and can set boundaries that should not normally be exceeded). The best examples of this are injection site reaction for a vaccine and application site reaction for a product patch. Predefining what acceptable variation in these cases is should improve efficiency as well as more easily identify those outliers that do not fit the normal pattern.

Conclusions

With the understandable current focus on making a case suitable for electronic reporting, there is little published advice on how to practically reconcile the unpredictability of information, especially when received spontaneously, with the structured E2B format. We are concerned that there is too much emphasis on quantity at the expense of quality, in the sense that rarely have we found companies prospectively planning for the inevitable variation in case processing. By means of a survey, we have illustrated an example of this variability of determining onset date of a suspected adverse reaction, and recommend that a criterion for onset time, i.e. beginning of signs or symptoms of the event, or date of diagnosis, be chosen as the standard. Once decided, this information should be incorporated into the company's case assessment documentation and staff appropriately trained, thus ensuring consistency across cases and minimizing the time spent in determining what date to use. For other issues, there is no gold standard as to what is a good quality case report. In those companies with a significant postmarketing workload, appropriate senior and qualified pharmacovigilance managers should predetermine an acceptable range of criteria for determining datapoints, such as onset date, and incorporate this into a training programme. The process should be defined in such a way so as to obtain as complete

case information as is scientifically appropriate. We suggest the variability of case report layout can be defined within the equivalent of 'Design Space', remembering the importance of a well crafted and medically informative narrative in helping determine causality. This can be applied throughout the process for the increasingly popular concepts of adverse reactions of special interest.

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