Minimizing the Impact of Dirty Data in Veterinary Pharmacovigilance

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What is dirty data? Dirty data is a 21st century word that Wikipedia defines as "inaccurate, incomplete or erroneous data, especially in computer systems or databases." In other words, it is simply data that contains errors.

Unclean data can even be incorrect data associated with a field such as words in a numeric field, data that contains spelling or punctuation errors, or even data that has been duplicated or not allowed in the database. For instance, in the Center for Veterinary Medicine's (CVM) guidance for industry concerning data elements for submissions, the CVM points out that for electronic submissions free text fields may not include any special symbols (i.e. # " ' ö ñ é â Ç).

WHAT IS THE IMPACT OF DIRTY DATA?

Dirty data not only impacts the accurate assessment of individual case safety reports, but it also leads to an inaccurate assessment concerning the effectiveness or risk of the product in question. It can create delays in the detection of safety signals and jeopardize the safety of our patients. Additionally, an organization can incur significant costs and time expenditures associated with trying to clean up or convert bad data. Ultimately, this corrupted data can lead to the risk of regulatory actions, such as requiring changes in product labeling, design, packaging or distribution. It could result in safety alerts being issued or even product recalls requiring additional studies to demonstrate the product's safety prior to it being allowed back on the market. Between the recall, alerts and additional testing, it could cost pharmaceutical companies millions of dollars.

HOW DO WE MITIGATE THESE POTENTIALLY DISASTROUS EFFECTS?

First, let's review, at a high level, the processing of spontaneous adverse event data, which is a fairly standard process. The event information from any number of sources, such as consumers and veterinarians, to regulatory authorities is collected by a company representative. The data is then entered, coded, evaluated and reported. Ultimately, the data is used in many downstream processes, including individual case safety reports, aggregate report preparation, signal detection and trending (SDT) activities and the development of profile and labeling information. It is often even fed back into R&D and marketing activities.

In order to minimize the effects of dirty data, it is imperative that all individuals involved in the adverse event processing lifecycle be educated on the same training, quality and compliance guidelines, standard operating procedures and working practices. There are as many potential sources of dirty data as there are steps in the process or fields in the database. Some of these include errors in initial contacts (from adverse events (AE) to the wrong manufacturers), events

reported that are not actually events and errors in reporting (duplicate reporting).

INTRODUCING PANASITICIDE - THE NEW "WONDER DRUG"

Haven't we all dreamed of the panacea for our four-legged family members? Imagine a single tablet that controls all of the common parasites. Panasiticide, developed and manufactured by Veterinarians Engineering Treatments Pharmaceutical Company, is an imaginary flavored, chewable tablet given monthly that kills adult fleas and ticks, prevents canine heartworm disease and treats the adult stages of whipworms, roundworms, hookworms and tapeworms in dogs. The product has a novel mechanism of action that is not yet well understood – actually it is not yet discovered. The most common AEs seen with Panasiticide are vomiting, diarrhea, anorexia, pruritus and ataxia. Panasiticide received its approval from the FDA in April 2012.

To facilitate the discussion, the following narrative was pulled at random from the Veterinarians Engineering Treatments Pharmaceutical Company's safety database:

01-May-2014: Owner reported dog received 2 doses of Panasiticide. With the first monthly dose, the dog developed vomiting and diarrhea 12 to 24 hours post dosing. When the dog was redosed with Panasiticide, the owner reported that within a couple of hours the dog had a fit and was scratching uncontrollably. Concerned, the owner took the dog to the regular veterinarian. The veterinarian performed a physical examination and blood work. On physical examination, the veterinarian found the dog had 2 puncture wounds on the side of the chest and was painful in that area. The owner reported the dog had recently been in a fight with a housemate. Blood work showed PCV of 27, normal total proteins and a slightly low T4. The veterinarian prescribed antibiotics and a NSAID. The dog had recent history of antibiotics and prednisone use for an allergic reaction.

One of the major problems for those of us working in drug safety is the lack of complete information. After reading through the previous narrative, it is apparent that there are several issues, but let's take a closer look at a few in more detail.

Solid guidance and training for the people on the front line collecting adverse event data would allow for a clearer understanding of the information needed to make a complete and accurate assessment of potential adverse drug reactions. A lack of this understanding can result in a case narrative, as just seen.
In this case, essential follow up questions were not asked, and the information obtained at the time of the report was insufficient at best. The Panasiticide narrative states that "within a couple of hours the dog had a fit and was scratching uncontrollably." What exactly is a fit? Was it an episode of marketed agitation, or could it have been a seizure? The narrative also states that the "blood work showed PCV of 27 and total proteins were normal." Was the PCV normal? Can we assume it wasn't? Without a qualifier for the PCV value, either SI or %, it is impossible to tell.

The dog had recently been on antibiotics and prednisone for an allergic reaction. How recently? Was the dog on either at the time of Panasiticide dosing? What type of allergic reaction? The answer to these questions would help to determine if confounding factors played a role in the events reported.

All of these are questions that could have potentially been clarified at the time of the initial call if the agent receiving the call understood how the facts in the narrative impacted the overall assessment of the causal relationship between the adverse event and the suspect product.

In this example, the information provided only leaves us with more questions. Again, awareness of what constitutes adequate or quality information would have alleviated the problems discussed.

A CLOSER LOOK AT CODING PROBLEMS

Another potential source of dirty data is discrepancies in assigning VeDDRA codes. The greatest challenge in VeDDRA coding is consistency, especially throughout large international organizations. Some of the more common causes of VeDDRA coding errors are inappropriate code selection and under and over coding.

Here we have two examples of inappropriate code selection:

» EXAMPLE 1: Our narrative states that "on physical examination, the veterinarian found the dog had 2 puncture wounds on the side of the chest and was painful in that area." The VeDDRA code selected was *thoracic pain*, which codes up to the preferred term (PT) of *thoracic irritation*, which falls under the system organ class (SOC) of *respiratory tract disorder.* None of these terms are an accurate reflection of the medical condition described. A more appropriate code would have been *localized pain NOS,* which codes up to the PT of *localized pain* and is in the SOC of *systemic disorders.* Although the *thoracic pain* code is more specific, it is also misleading, as there were no respiratory tract signs described in the narrative.

» EXAMPLE 2: The narrative reports "when the dog was redosed with Panasiticide, the owner reported that within a couple of hours the dog had a fit and was scratching uncontrollably." The VeDDRA code selected was *fit,* which codes up to the PT of *convulsion* and falls under the SOC of *neurologic disorders.* Is this an accurate representation of what actually happened with the dog? We can't be sure the code is correct, but now we have assigned a VeDDRA code that potentially puts this case into the serious classification. Is the code an accurate reflection of the idea represented in the narrative? That is a very important but unanswered question.

Another problem is under coding or missed VeDDRA codes. No reported event should be excluded from the coding assigned to the case. The dog was reported to have had a PCV of 27, which was interpreted as 27 SI or international system units, a normal finding; therefore, the event was not VeDDRA coded. What if the PCV was 27%? This would have been an abnormal finding, and the code would have been missed.

Events not described in the narrative should not be VeDDRA coded. Our narrative implicitly states the "T4 value was slightly low." The VeDDRA code applied was *hypothyroidism,* which is a misrepresentation of the facts in the narrative. Here, only the reported abnormality of a low T4 should have been coded and not the inferred diagnosis that such a test result could imply.

CONSIDERING CAUSALITY ASSESSMENTS

Causality assessments are open to personal interpretations, making the process a likely source of inconsistencies or more dirty data. Here our assessors used the ABON method of causality:

ABON is the most commonly used method of applying causality assessment to individual case reports, and it does provide a list of factors to be considered; however, without guidance surrounding the factors, the resulting assessments can be haphazard.

Our sample narrative reports "the dog experienced vomiting and diarrhea 12 to 24 hours post dosing." It also mentions a "recent history of antibiotics and prednisone use for an allergic reaction." Assessor #1

gave both events a causality of A because Panasiticide is known to cause both vomiting and diarrhea, and neither could have been caused by the antibiotics or prednisone because the use was described as historical. On the other hand, assessor #2 gave both events a causality of O1 because the antibiotics and prednisone were described as given in the recent past and could have been active in the dog's system at the time of the events.

Depending on the assessor's interpretation, the description of *recent history* could indicate 1 day or 1 month in the past. Both have very different implications for the assessment of suspect product relatedness.

PREVENTING DIRTY DATA

The development of a best practices guide and associated training on the guide will set a uniform standard for the entire adverse event processing lifecycle. The guide could be a tabbed binder with specific sections dedicated to the best practices of each subject of interest such as sections for data collections, data entry, VeDDRA coding conventions and guidance on the selection of causality assessments. Each section would outline specific steps and detailed instruction on how to perform each task. Many organizations have already established at least some guidance on these subjects. The key is having the guidance in an easily-assessable, user-friendly format.

Regular and thorough QC of individual case safety reports is a required next step. For example, it is a great idea to have an independent QC person who performs random QC on a certain percentage of cases. These individuals would be specially trained to perform the QC checks and follow a check list – maybe a PDF document attached to each case in a database or a standard QC form. The findings are recorded and can then be used to identify specific areas where retraining would be beneficial. Specific QC instruction to emphasize data needed for certain product lines could be given, the customizable options are endless.

Once any errors are found, they can be quickly corrected. Random QC is essentially an additional preventative against dirty data.

To alleviate the problem of inadequate or insufficient data, it is best to start from the beginning (when the event information is initially received). Coaching call center staff in skills such as call control and interview techniques, along with the detailed instruction in the best practices guide, not only cuts down on the dirty data but also has the added benefit of expediting call handling time. For the best practices section on data collection, a list of predetermined questions would be included. Again, product or product line specific questions could be developed. Call center or sales staff then has pointed questions to key in on details of interest.

» EXAMPLE: Instead of asking open ended questions (i.e. "Is your pet on any other medications?"), the guide could instruct detailed questions be asked (i.e. "Do you give your pet heartworm or flea and tick prevention?").

Obviously, merely asking the question does not guarantee answers but more often than not, a pointed question can stimulate the reporter's memory.

With time and experience, the series of questions becomes committed to memory, as the individual learns precisely what information is required.

In addition, providing call center or sales staff a high-level overview of pharmacovigilance and case processing activities serves to increase their awareness of the essential data elements needed to make accurate evaluation of cases. For most people,

understanding why they are being asked to perform activities reinforces the practice.

VEDDRA CODING CONCERNS

The proper coding of adverse events determines the quality of outcomes for data mining and signal detection efforts, which ultimately affects everything from product labels to regulatory actions to consumer confidence. Due to the widespread implications of inaccurate VeDDRA coding, organizations must develop VeDDRA coding guidelines, such as the European Medicines Agency's "Guidance notes on the use of VeDDRA terminology" or other points to consider documents.

VeDDRA guidance should note that when selecting codes, priority should be given to the verbatim terms used by the reporter. However, the guidance should be emphasized that when attempting to code ambiguous or improper terms, it is more important to select a code that best reflects the reported medical condition or sign described as opposed to the verbatim language. This means ensuring the code makes sense medically and falls into the appropriate related system organ class. A reference list of chosen VeDDRA terms that correspond to labeled or expected adverse events for each product could be provided to aid consistency in term selection. This list could be in the form of a laminated, quick-reference card which not only ensures uniformity but also speeds case processing time.

METHODS FOR PERFORMING CAUSALITY ASSESSMENTS

There are three general methods for performing causality assessments - Expert judgment, Algorithms and Probabilistic. All methods, to some degree or another, rely on knowledge of the veterinary medicinal product (VMP) or class of medications, availability of information on the time between the VMP and the event, dechallenge/rechallenge and the existence or lack of other potential causes of the event.
The type and severity of the reaction can help determine the most appropriate approach, but in general, confusion over the terms used to classify the likelihood of association of the event to the VMP must be mitigated by providing detailed guidance on the use of the terms.

Which method is used is a matter of individual choice, but regardless of the method chosen, detailed guidance should be provided for any criteria considered.

Again, laminated cards with a flow chart or a specific list of weighted questions could be included in the best practices guide, and with repeated use of such aids, the process will become habitual.

It is understood that there is no single best or most reliable method of performing causality assessment; however, research and experience have shown that the establishment of detailed guidance and procedures can at least make consistency an achievable goal. In addition to the specific recommendations made to mitigate the effects of dirty data, routine systematic analysis of aggregate data must be the standard. The analysis must be conducted form multiple modes or the data can be misleading. A standard review period could be every quarter, but a review could certainly be performed more often, depending on the particular issues for the product or class of products. At Drug Safety Alliance, the review period and depth of review varies depending on the individual client's scope of work.

For example, we might begin by reviewing overall case numbers for a specific time period, say quarter one 2014. We then compare the numbers to the corresponding time period for the previous year. The same analysis is performed for the numbers of serious and non-serious cases between the 2 time periods. If the numbers are relatively consistent and the product is fairly stable, the analysis could conceivably stop there; however, if a more thorough review is desired, for

instance, because the product is one of special interest or an evaluation of the efficacy of a recently instituted best practices guide is sought, the review would be more comprehensive.

In such cases, the review would then concentrate on the specific AE numbers (i.e. reviewing the most common AEs and those of interest such as lack of efficacy and the associated events). This review would compare the findings from our time period of interest with previous similar time periods.

If any significant issues were discovered at that level of review, a more detailed review would occur. Individual case reports would be examined, and depending on the reason for the investigation (i.e. increase in the number of reported lack of efficacies), the cases would be evaluated to ensure that they truly met the established criteria of LOE classification, such as consistency with the labeled use of the product. If a noticeable increase in the number of serious cases with an A or B causality were seen, again, a certain percentage or number of those cases would be reviewed individually. If indeed there was continued reason for concern, then a need for further investigation has been identified. However, if the cases are found to be flawed in some way, then the source of the inconsistency could be identified, ideally before the time of aggregate reporting. Specific trainings could be conducted to address the issue.

CONCLUSION

Mitigation of the effects of dirty data can be achieved simply by standardization of the adverse event processing cycle. This consistency can be achieved through the development of best practices for the high risk steps of the process and through consistent review of the data on both an individual and aggregate level. Again, there is no way to completely eliminate dirty data, but by applying these practical approaches, an organization can hope to capture more precise data and thus more accurate and reliable understanding of products and increased product stewardship.

NOTES

1 WHO, The Importance of Pharmacovigilance: Safety Monitoring of medical products, 2002.

2 Lindquist M. Data Quality Management in Pharmacovigilance. Drug Safety 2004; 27 (12) 857-870.

3 European Medicines Agency. Recommendation on harmonising the approach to causality assessment for adverse events to veterinary medicinal products. 10-Oct-2013.

4 Agbabiaka TB, Savovic J, Ernst E. Methods for Causality Assessment of Adverse Drug Reaction. Drug Safety 2008; 31 (1) 21-37.

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ABOUT US

Founded in 2000 and acquired by UDG Healthcare in 2012, as part of its Ashfield Division, Drug Safety Alliance, Inc. (DSA) is a global leader in safety and risk management services supporting pharmaceutical, biotech, medical device, consumer health and animal health organizations. Uniquely focused on pharmacovigilance, DSA provides comprehensive outsourced solutions and modified services to augment existing safety departments. DSA is headquartered in Research Triangle Park, North Carolina. For more information, please visit www.DrugSafetyAlliance.com.

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