EDITORIAL

Drug Saf 2012; 35 (6): 429-435
0114-5916/12/0006-0429/$49.95/0

Good Pharmacovigilance Practice and the Curate's Egg

I. Ralph Edwards

Uppsala Monitoring Centre, Uppsala, Sweden

In February this year, the European Medicines Agency (EMA) placed on the Internet the first seven Good Pharmacovigilance Practice (GVP) modules, out of a full set of 16, for public consultation; the remainder will be available over the next few months.[1] The consultation time is over, and I did not make any comments directly for reasons that are clear: the size and complexity of the documents; the cross referencing needed for consistency in the details; and that there is less than half of the full GVP available now. The GVP is coincident with new, important EU Directives (Directive 2010/84/EU)[2] and Regulations (Regulation [EU] No 1235/2010)[3] amending existing legislation that were adopted in the EU in December 2010. These are comprehensive developments in pharmacovigilance (PV) and need serious, critical reflection.

1. Some General Comments

First, I must explain the curious title. The 'curate's egg' is a metaphor for something that has both good and bad aspects, and it relates to the first impression I had as I tried to read the 272 pages of the modules. I thought, 'I cannot get my head round all this and its implications particularly considering the new regulations' and then, as I read further, I thought, 'there is some very good guidance and information here'. I came to realise that in fact this GVP covers nearly all of what one might think is theoretically relevant to the practice of PV, but stated at an information level that raises queries in almost every section, whether those be questions of correct understanding, practical implications or indeed broader implications of how PV will develop in the future. One particular shadow to considering content and context in the GVP is the warning that the words 'shall' and 'should' mean: … *all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb ''shall''. Guidance for the implementation of legal requirements is provided using the modal verb ''should''*[4] (note the use of usually!). This brings me back to the curate's egg. The origin of this was a cartoon in the English magazine '*Punch*' on 9 November 1895 called ''True Humility''. It showed a downtrodden looking curate taking breakfast in his bishop's house. The bishop says, ''I'm afraid you've got a bad egg, Mr Jones.'' The curate replies, ''Oh, no, my Lord, I assure you that parts of it are excellent!'' This also suggested that it is easy to defer to power and even not to admit to an unpalatable truth. If the GVP were not from an authority backed by Directions and Regulations one could accept it as helpful guidance much more easily, and not go looking for hidden meanings and dissecting the precise wording for its regulatory inferences. 'Good '*X*' Practice' guidelines have proved themselves very useful, and it is worth considering the reasons for this success. Perhaps the starting point was Good Laboratory Practice (GLP), and thereafter, Good Clinical Practice (GCP) has made a strong impact on improving the ways of doing things. Laboratories are confined environments, and the work and equipment used in that work are also well defined. Much is known *and validated* about optimal

operations that lend themselves to standard operating procedures (SOP) and algorithms – each time one follows the rules one will get the same answer. GCP adds a level of complexity because of human interaction, but even then a controlled clinical trial is just that – controlled. Nevertheless, potential for human errors and unanticipated, and therefore uncontrolled, variability is greater. PV is a very complex area with large amounts of data of different kinds, in differing locations that is reviewed using different analytical approaches and different professional expertise; there is a decision making and communication aspect of the work that is extremely important and requires flexibility for the impact of PV to be relevant to clinical practice and patients' expectations. All this needs careful overview, coordination and audit but also using experience and intuition. The EMA draft GVP recognizes all of this and it seems that there are Modules that cover a huge amount of information, and yet… . And yet, there is not enough practical, crystal-clear guidance for a G*'X'*P, and far too much breadth in the overall subject for this to be possible. Perhaps most importantly, there is little validation of the best practice in PV and no mention of how to handle some of the obvious challenges in PV. For example, there is concern expressed about under-reporting and poor quality of ICHRs (individual case harm reports; ICSRs), but there is no advice about how to improve it so, whilst exacting standards for data management once ICHRs and other information are received are important, they do not address the key issue. It is both instructive to compare this GVP with the US FDA Guidance on PV (2005)[5] and also to consider the EU Volume 9a (2008).[6] The FDA guidance is still their latest document on PV and is 23 pages of the FDA's views on the latest good practice in PV produced in an overall advisory style: quite different in tone. The new EU GVP is a development on Volume 9a which was 229 pages about PV, and now seems likely to become double that length when the new GVP is completed (only 4 years later). PV is an evolving discipline and does not lend itself to the kind of didactic approach. This new 'GVP' could really be the basis for a curriculum for a PV professional (e.g. for the EU qualified person – QPPV) to learn what may be useful, as a reference and guideline, for the specific different areas covered in the Modules.

Considered as a detailed GVP for the whole of PV, even when the content of remaining modules is considered, the coverage is patchy. The EMA uses the WHO definition in its Introduction to the GVP:[7]

''Pharmacovigilance has been defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. In line with this general definition, underlying objectives of the applicable EU legislation for pharmacovigilance are:

- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.''

Taking the last paragraph of the Introduction gives the overall objective of the GVP against which it should be judged. In a recent critical article I argued that the public criticisms of PV performance were as follows:

''… progress in ameliorating the problem (PV performance for public health has been slow: *decisions, with no protocol* (although risk management plans are a great step forward), *with obscure materials and methods used for making decisions, with very limited* (publicised) *reasoning and discussion, and little or no follow up and audit of the results. Problems include under-reporting, poor quality reports, underuse of the latest communications technology and suboptimal individual feedback to reporters. Assessment of causality is poor, impeding decision-making. After signal detection, more active measures to assess the risk to public*

health are needed. Other essential factors include precision about the ways in which data are prepared and transformed into databases, *the recognition of secondary effects, which may be more obvious than the primary effect, but not so easy to link causally*, and cognisance of all kinds of interactions. Areas that should be developed include pharmacoepidemiology, knowledge finding (through data mining), and communication and systems technology. The general way forward seems clear: a rigorous way of documenting all the steps, from getting reports of harms into regulatory databases to assessing their effects on public health, is essential *and should be publicly reviewed for weaknesses. In turn, matters would be much improved by input on benefit/harm perceptions from patient groups, influencing decisions about what should be the true targets for regulatory and pharmacovigilance activities, avoiding second guessing by regulators.'*[8]

In essence, I think the main weaknesses of PV (the areas in italics above) are related to decision making, its transparency, and the communication and public audit of the effects of PV on public health. The GVP modules, so far, mainly concern how data will be managed by industry. This gives us a GVP for industry and national regulatory agencies, but nothing for the essential steps taken within the EU organizations apart from the formation of a new committee – the Pharmacovigilance Risk Assessment Committee (PRAC). In my view, the functions of the EMA and EudraVigilance should be audited by the public as much as industry. There is evidence[9-12] that makes it quite clear that the ongoing concerns about drug safety relate not to the collection of safety data, but to delays in making decisions and the avoidable medication errors that still occur, and which, at least to some extent, are related to poor communication. The idea of open peer review of regulators seems to be anathema, but industry is forced to do everything according to extensive pro-active bureaucracy, whether or not the requirements are evidence-based in terms of their impact on the performance of good PV. One observation regarding the Modules on data management and IT systems is that, in the plethora of detail about systems, there is scant attention in the GVP to improving the amount and quality of reports of problems with drugs (ICHR) submitted. Certainly the topic is mentioned, but little is said about how to engage health professionals and patients in the global drug safety endeavour. Once again this is not just a responsibility of industry, indeed it is mainly a failure of regulatory agencies largely because of their lack of resources, to promote drug safety as a public responsibility. Some of my concerns above may be dealt with more exhaustively in the future modules (these are outlined in table I).

This is a problem with the EU public review procedure of the GVP. It is not possible to make a fully considered comment on the totality when we only have less than half the modules. All one can say is that there is a major bureaucratic system being further developed for the quality performance

Table I. Proposed Schedule for Release of the Remaining GVP Modules for Public Consultation[13]

Module number	Module title	Date of release for public consultation
III	Pharmacovigilance inspections	Q3 2012
IV	Pharmacovigilance system audits	Q3 2012
X	Additional monitoring	Q2 2012
XI	Public participation in pharmacovigilance	Q4 2012
XII	Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication	Q4 2012
XIII	Incident management (may be included in module XII: to be confirmed)	Q4 2012
XIV	Referral procedures for safety reasons (may be part of GVP or notice to applicants: to be confirmed)	Q3 2012
XV	Safety communication	Q3 2012
XVI	Risk-minimisation measures: selection of tools and effectiveness indicators	Q3 2012

GVP = Good Pharmacovigilance Practice; **Q*x*** = quarter *x*.

and documentation of the data management and underlying IT networks to get information from the industry to regulators. Whilst this might be important, one result is likely to be that the QPPV will concentrate more on closely audited activity, such as data management, rather than making good use of the data as a basis for good decision making. This might be avoided by experienced people and adequate resources, but even the signal detection process is more about sharing signal information between five groups, which seem to have overlapping described responsibilities.

2. Some Detail

In an editorial it is not feasible to go into depth over details in each Module, but GVP Module IX is the main one that deals with what should be *actively done* with data rather than just its collection and management. It is the only one I shall consider in any detail as an example. Module IX is about signal detection and management, which must be the key function of PV together with further investigation of signals and their use to promote patient safety. But this is also the most confusing Module.

It starts with a definition of a signal that has much merit, particularly reminding us that a signal is new information that is important for safety and should be investigated further. The definition uses 'verification' relating to further investigation but the Module uses 'verification' as meaning that the data in the signal should be checked and then uses 'validation' for assessing whether the signal is true in other ways. This is confusing to start with, and section IX.B.3.3 seems to be an almost redundant section that only reinforces the definition of a signal: a 'valid' signal is really just a signal. According to the Module, the Marketing Authorization Holder (MAH) and the regulatory agencies will be looking for signals and then documenting their validation, all of which they share with the EMA. Section IX.B.3.7 refers to exchange of information but stipulates only on 'validated' signals. This seems reasonable except that experience shows that there may be different opinions about what is a signal based on assessments of different data and its strengths. Even with definition and explanation this is likely to happen. It is where there is doubt about whether an early signal should be pursued that information exchange and other views are likely to help. This is where paragraph IX.B.3.3 is of little help, because each of the well known items that are used in evaluating a signal are value judgements: what is a 'severe' reaction, what is a 'similar' case in the literature? Signals have different degrees of probability according to the completeness of relevant data, the strength of the causal argument and the severity and seriousness. These are different dimensions, and this is where professional judgement is required. The main question is who will make this judgement? If the national regulator or the MAH, after evaluation, decides the data do not constitute a signal they must document their reasoning but that means only that it can be audited retrospectively; but the signal is then missed, from someone else's different value perspective. On the other hand, a 'valid' signal is examined over and again, according to this Module, by five different groups.

If the national PV regulators and the QPPV can perform this first, critical decision-making task pretty well on their own, why does it take so many further steps to confirm their positive findings of 'valid' signals? Moreover, paragraph IX.B.3.5 on Signal Assessment is oddly brief compared with the other sections, particularly considering the importance and complexity of epidemiology.

When the 'valid' signals (with or without epidemiological information?) are made available to all parties, the Module defines the roles of no less than five groups that are going to be involved in 'valid' signals. These are the MAH, the national regulatory agencies, the EMA, the new PRAC and the Committee for Medicinal Products for Human Use (CMPH). Section IX.C gives details of the responsibilities of each of the groups, but in spite of every one of them being concerned with validation of signals (''Signal management in the EU regulatory network should be a shared responsibility of the Agency, national competent authorities, the Pharmacovigilance Risk Assess-

ment Committee (PRAC) and the marketing authorisation holders. The detection of signals shall be based on a multidisciplinary approach and shall be supported by statistical analysis within EudraVigilance [IM Art 23(3)]. The identification of signals based on statistical analysis should be a matter of clinical judgment and subject to validation as detailed in IX.B.3.3."[14]) the MAH and the regulatory authorities have the responsibility for the actual work and the crucial early decision on what is a signal or not.

On the other hand, it is only the PRAC that gives the final recommendation for action to the CMPH, which has to accept the scientific decision of the PRAC.

("For the fulfillment of its pharmacovigilance tasks, approving risk management systems and monitoring their effectiveness, the CHMP and coordination group shall rely on the scientific assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee.").[15] This implies that the CMPH might only apply some political filter, in finally ratifying a decision, otherwise it is redundant in this role.

One good thing about the PRAC is that it appears that its deliberations will be truly transparent, but in a committee of around 30 people there is only one patient and one health professional represented and most of the others are appointed by each member state. This latter point is interesting since each national PV regulator should already have had input to the signal.

3. Summary

I am certainly not saying that the GVP is all bad. There is much very useful *guidance* there, but it is not a collegial document. It seems like a set of orders with tiers of backup authorities that will criticise everything, and at the back of everything mentioned there is the thought that any of the content might become the subject of EMA or PRAC audit. If I were a QPPV or the head of PV in a regulatory authority I would be tempted to say, 'If that's how they feel about my expertise I will just send them the information and let them get on with it.'

It all reminds me of John Ruskin (1819–1900), the English critical thinker and philosopher. In his book *On Art and Life* (1853), he makes the much-quoted comment: *"You must either make a tool of the creature, or a man of him. You cannot make both."* His point was in relation to Gothic architecture, where he claims that craftsmen had much more freedom to create decoration their way, under general direction only; whereas for Greco-Roman architecture, they were precisely instructed by the masters and had no individual freedom of expression.

PV is an art as much as a science at the signal detection step. Further evaluation for confirmation of the hypothesis and impact is science.

It can be readily argued that rigorous, uniform methodology is essential to safeguard individual and public health, after a hypothesis for a signal is formed. It can also be argued that there should be quality-assured data and information management throughout, but that is not PV.

In my view, the 'GVP' should not be called that because it should never have such an overall prescriptive authority, and it could perhaps be reorganized to reflect clearly the different strengths of influence. The document could be produced in three focussed sections (or three separate documents) clearly indicating different levels of authority:

1. *PV strategic management:* Mandatory systems that will ensure that PV is given a priority for all those stakeholders who must contribute, and descriptions of some ways to improve the current performance.
   - This involves reconsideration of the way regulatory PV is done, particularly how regulation may support health patients and health professions, as part of a team.
     - 'All stakeholders' therefore will include patients and health professionals as major players.
   - Strong regulation of data flow is only a part of strategy, and this will include both obtaining data and information, as well as performance monitoring *for impact* (i.e. what makes a real difference to public and individual health decisions).

- Detailed audit of *results of the decisions* will be the main outcome measurement, and not details of methodology.

2. *Project management and quality assurance in PV:* Methodology that is proven to be optimal in supporting PV, which must be quality assured (e.g. data and data management).
   - These functions will be audited in detail to ensure that all stakeholders get the same data and information.
   - This responsibility should be truly international and not just within a developed country network.
3. *PV health professional guidelines: safety and benefit-risk assessment and decisions:* Collegial guidelines and networks for sharing methodology and information about developing safety hypotheses and benefit-risk decisions.
   - The development of the signal hypothesis should not be proscribed.
   - Any signal (fulfilling the definition) from any stakeholder should be referred to the PRAC, who should make decisions on the next steps, utilizing expert advice as necessary.
     - A sub-committee could be set up to filter incoming work.
     - This would reduce bureaucracy and keep decision functions separate from any direct influence on the work of PV professionals.
   - The PRAC should have more patient and health professional members.
   - The PRAC would be audited by results as in (1) above, and their decisions subject to appeal.

Perhaps it is also time to take away the personal legal liability of the QPPV for all that goes wrong in PV!

Many will see this proposal as not very different from the GVP, but I think it makes clearer where freedom of thought can be separated from the quality systems that underpin creativity.

Comments on this editorial are welcomed by both *Drug Safety* and myself. Documents from major drug regulatory agencies can have a great impact on the practice and developing science of PV. In particular, I would like to hear other views than my own about this aspect of GVP guidelines.

Acknowledgements

The author has no conflicts of interest that are directly relevant to the content of this editorial.

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Correspondence: Professor *I. Ralph Edwards*, Uppsala Monitoring Centre, Box 1051, Uppsala SE 751 40, Sweden. E-mail: ralph.edwards@who-umc.org

