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# The quality System in Good Pharmacovigilance Practices (GVP) Good statistical practices regarding the quality control of lots applied to the cases processing

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## ABSTRACT

This paper shows that pharmaceutical companies and CRO often fail to respond to the recommendations of Good Pharmacovigilance Practices (GVP) by highlighting the lack of efficiency of the quality control (QC) process applied to the pharmacovigilance cases processing. The paper summarized the sampling acceptance statistical theory behind the good statistical practices regarding QC of lots and show that these principles can be easily implemented to set up an optimized QC system ensuring the quality of safety case processing in Pharmacovigilance units.

## INTRODUCTION

Good Pharmacovigilance Practices (GVP) have been established by experts from the European Medicines Agency (EMA) and from European Member States to improve the performance of pharmacovigilance activities by setting a set of measures/guidelines in the European Union with the ultimate aim of ensuring safety for patients. GVP guidelines describe how to set up a quality system in pharmacovigilance to ensure the Quality, but don't give any directives about the quality control (QC) procedures of pharmacovigilance activities. Pharmacovigilance activities are grounded on the safety cases processing. Our paper propose (1) an overview of the current practices in terms of safety case processing assessing the risks of acceptance of cases with errors in Pharmacovigilance databases, (2) a description of the GSP regarding the QC of lots and (3) how these statistical principles can be easily implemented to set up an optimized QC system ensuring the quality of safety case processing, and then improve the practices and be compliant with the GVP recommendations.

## GVP AND QUALITY SYSTEM IN PHARMACOVIGILANCE (PV)

### OVERVIEW OF THE PV ACTIVITIES WITHIN THE PHARMACEUTICAL INDUSTRY

PV can be defined as the process of identifying and responding to drug safety issues[1] or in other words as the processes and science of monitoring the safety of medicines and taking action to reduce risk and increase benefits[2]. The overall aims of PV within the industry are mainly:

1. as for the regulatory agencies, to minimize risks for patients by identifying previously unrecognized drug hazards, elucidating pre-disposing factors, refuting false safety signals and quantifying risk in relation to benefit [3]
2. Minimize the risks for the company
3. Meet global regulatory requirements

The task most common to all safety departments in the pharmaceutical companies is the reporting of adverse events (cases) to health authorities according to regulatory requirements. Based on pharmacovigilance policies, regulations and guidance documents, the process can be summarized as follows[4]:

1. Creation of individual case from multiple source of safety information such as clinical trials, safety call centers, spontaneous reports, literature searches, internet monitoring (forum), …
2. Processing of each case and assessment of its relationship to the investigational product
3. Reporting to the regulatory authorities and other stakeholders, either as an expedited report or as a part of an aggregate report

Each case becomes thus a part of the total safety data set for the medicinal product concerned.

In addition to the processing of individual case safety reports, drug safety departments collate, evaluate and report aggregate analyses of safety cases in order to detect safety issues and assess benefit/risk ratio. As required by the International Conference of Harmonization (ICH), periodic safety update reports (PSURs) are submitted to the

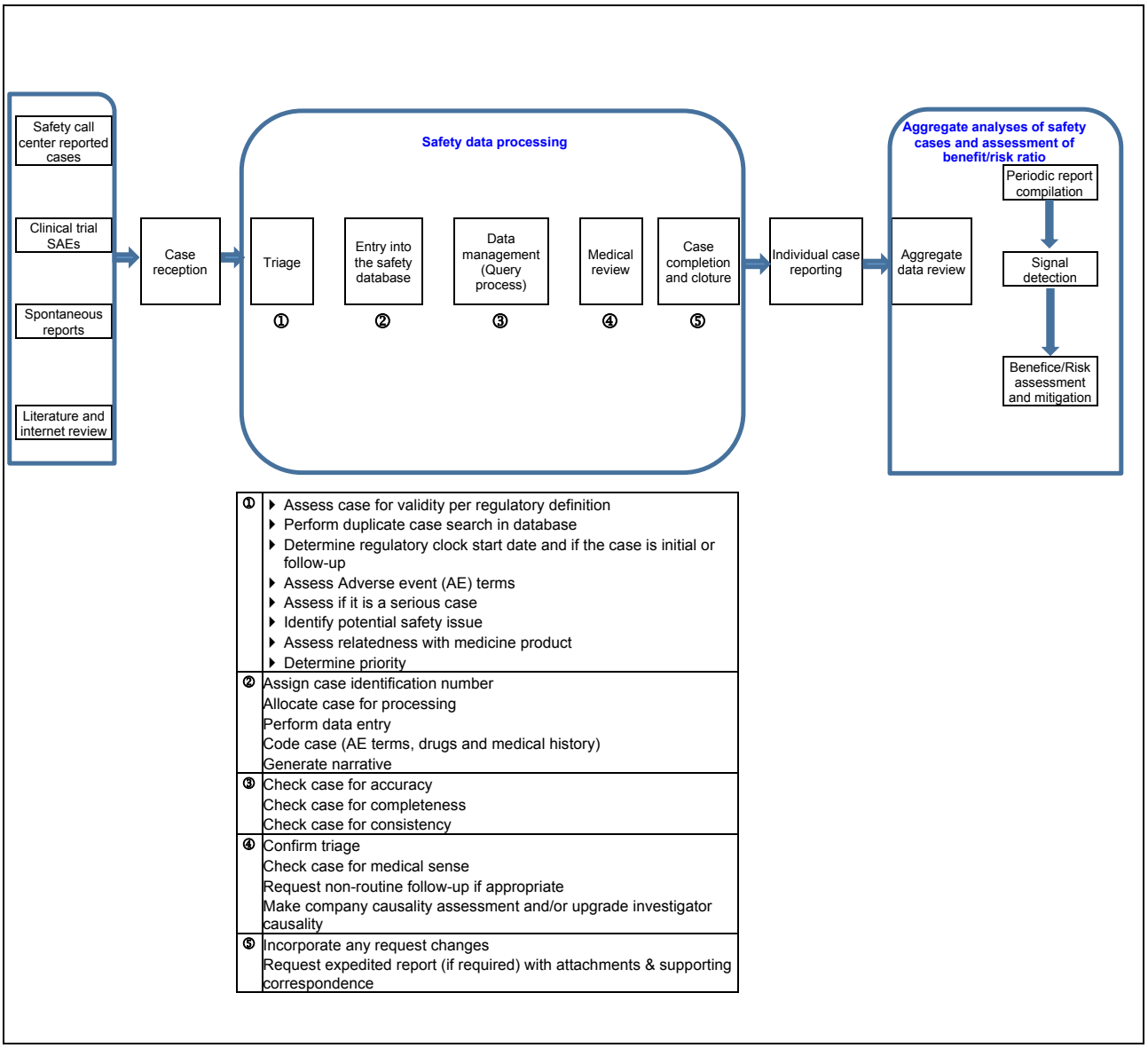
regulatory authorities (ICH E2-c). The safety issues are addressed to mitigate the risk associated with a medicinal product. PSURs present then the worldwide safety experience of a medicinal product at defined times post-authorization, in order to:

- report all the relevant new information from appropriate sources;
- relate these data to patient exposure;
- summarize the market authorization status in different countries and any significant variations related to safety;
- create periodically the opportunity for an overall safety re-evaluation;
- indicate whether changes should be made to product information in order to optimize the use of the product (ICH, 1996).

The PV process may then lead to modifications in clinical trials, changes in products labeling, implementation of a risk mitigation plan or the discontinuation of the development or use of the marketed product[4], [5].

The main activities associated with pharmacovigilance are summarized below in Figure 1.

**Figure 1: Summary of the Pharmacovigilance workflow**



#### THE QUALITY SYSTEM IN GOOD PHARMACOVIGILANCE PRACTICES (GVP)

Health agencies, in particular the American Food and Drug Administration (FDA) and European Medicine Agency (EMA) have detailed requirements on how to set up a quality system in pharmacovigilance to ensure the Quality. In European Union, this is detailed in module VI of the guidelines on GVP: Management and Reporting of Adverse Reactions to Medicinal Product (in application since July 2012):


| |
|---|
| 1. Quality planning: establishing structures and planning integrated and consistent processes (ex: Clear written standard operating procedures) |
| 2. Quality control: every stage of case documentation such as data collection, data management (correct data entry and coding), case validation,… should be verify for compliance, quality and integrity of data (source data have to be recorded and stored) |
| 3. Quality assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out (audit system). |
| 4. Quality improvement: correcting and improving the structures and processes and the carrying out of those processes as necessary |

See http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf

So in each PV unit a quality management system including a quality policy, approved standard operating procedures (SOPs), quality control (QC) procedures, key performance indicators (KPI), jobs description and training plans should be in place covering the entire PV process. This quality management system has to ensure that all PV activities are conducted in conformity with the highest ethical standards and relevant regulatory requirement and contractual obligations to any partners.

GVP insist on the need for better planning and completing quality controls of PV activities but without giving any directives about the way of implementing them.

The case processing and more specifically the cases data capture and management activities form the basis for adequate and good pharmacovigilance. We need then with a high priority to define the best quality control system to ensure the quality of safety case processing.

## QUALITY LEVEL OF CURRENT PRACTICES IN TERMS OF SAFETY CASE PROCESSING

#### HOW IS THE QUALITY LEVEL OF THE SAFETY CASE PROCESSING IN THE PHARMACEUTICAL INDUSTRY?

Data published on health authorities' inspections performed on the processing of individual case safety reports highlight the weakness of the current CRO and pharmaceutical companies' practices in terms of safety case processing. As an example, we can refer to the data related to findings in the inspection performed by the UK Medicines and Healthcare products Regulatory Agency (MHRA) during the period of April 2011 to March 2012. Safety case processing and related issues represented:

- 53% of the critical findings (37% of critical findings were related to reference safety information, 11% were issues regarding the spontaneous case processing and 5% concerned clinical trials PV)
- 35% of major findings (19% of major findings were related to spontaneous case processing, 12% to reference safety information and 4% to clinical trials PV)
- 24% of minor/other findings (13% of these findings were related to spontaneous case processing, 7% to reference safety information, 3% to clinical trials PV and 1% to literature searches)

Among the common findings examples provided by MHRA, the lack of QC of data entry and of expedited reporting decision are listed.

See http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con175416.pdf (Pharmacovigilance Inspection Metrics Report - April 2011 to March 2012) and http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con015700.ppt (Common inspection findings) on the MHRA website.

The following examples can be provided as an illustration of poor quality control of cases processing activities:

- Similar cases coded differently or incorrectly
- Important missing information in the MedWatch/CIOMS I/E2B file present in the source document
- Cases not independently re-checked
- Serious AEs misclassified as non-serious because of a lack of medical review of non-serious spontaneous AEs

Based on the observations made by the inspectors of Health Authorities, it seems obvious that we cannot consider that the quality level of the safety case processing in the pharmaceutical industry is satisfying and then that the current practices in terms of safety case processing and QC activities have to be reconsidered.

**THE CURRENT PROCESS OF QUALITY CONTROL OF SAFETY CASES BASED ON CASE STUDY**

The following case study describes the current QC practices of one major global biopharmaceutical company within the local PV unit located in Belgium.

- *Definition*

  1 lot is defined by the total number of safety cases processed during a defined period of time by a given Pharmacovigilance Assistant.

  The PV unit is composed of 15 Pharmacovigilance Assistants.

  1 monthly lot is composed of about 34 safety cases.

- *Description of the QC performed according to the pharmaceutical PV SOP*

  A QC is performed every months in every lots produced by selecting in a random way a not fixed number of safety cases to be controlled within a given lot. Let's $N_i$, i=1 to 15, represents the number of cases controlled a given month for the Pharmacovigilance Assistant n°i.

  The number of safety cases controlled every month varies from 1 lot to the other one. Generally, it is included between 2 and 5 ($N_i$, i=1 to 15, $2 \leq N_i \leq 5$).

  For these monthly QCs, the acceptance limit and action taken are the following one:

  - If in a given lot, the number of significant findings is 0 or 1, the concerned PV Assistant is considered as being a "good" performer and no specific action is taken
  - If in a given lot, the number of significant findings is ≥2, the concerned PV Assistant is defined as being a "bad" performer and the following specific action are taken regarding the concerned PV Assistant:
    - ⇨ During the 2 following months, in an systematic way, 5 safety cases processed by this PV Assistant are randomly selected to be controlled
    - ⇨ But no specific actions are taken to control the remaining safety cases in the lot: the risk of having encoded in the safety database safety cases having significant errors may be quite high.

- *Obvious comments and conclusion regarding these practices*
  - Depending of the number of cases controlled in a given lot, the acceptance error rate may vary from 20% to 50%. **So the variability is important and the accepted error rate can be very high when there are few controlled cases**. The risk to have accepted "bad" safety cases may be very high in some situations.
    - ⇨ ***Rough recommendation n°1*:**

      Rather than to fix an absolute acceptance limit expressed as a fixed *number of cases, whatever the number of controlled cases is, why not to fix a relative acceptance limit expressed in %, 25% for example? In this case, a lot can be declared "acceptable", if the controlled sample contains:*
      - *0 case with significant findings if the controlled sample size is ≤ 3*
      - *Only 1 case with significant findings if the controlled sample size is >3 and ≤ 5*
  - In the current process, no action is taken regarding a given lot assessed as being "bad" based on monthly QC results. So for a given controlled lot including at least 2 cases with significant findings among the controlled cases, the probability is high that among the other cases, a not insignificant number of cases present major errors too. It will be then useful to control and correct more cases in the incriminated lot in order insure that the global accepted error rate in the entire lot stays in the planned acceptable limit, let us put it to 25 %.

    Illustration: Suppose that for a given lot, 5 cases were controlled out of the 34 processed during the month and that 2 cases with major errors were found, the probability for the overall error rate on the whole lot to be > 25 % for the incriminated PV Assistant can be computed based on the Bayes formula:

$$Pr(A|B) = \frac{Pr(B|A).Pr(A)}{Pr(B)} = \frac{Pr(B|A).Pr(A)}{Pr(B|A).Pr(A) + Pr(B|\overline{A}).Pr(\overline{A})}$$

    With
    - A = The overall error rate on the whole lot is > 25% (that is there are more than 8 cases with major errors among the 34 cases) ; $\overline{A}$ = The overall error rate on the whole lot is ≤ 25%
    - B= 2 cases among 5 selected cases present significant findings

    We suppose that $Pr(\overline{A}) = Pr(A) = 0.5$ which means that a priori a given PV Assistant has a probability=0.5 to be a "bad" performer.

    We can then calculate Pr(The overall error rate on the whole lot is > 25% / 2 cases out of 5 with significant errors were observed) = 0.61

    - ⇨ ***Rough recommendation n°2:***

      To decrease the risk having accepted cases with major errors within a given lot identified as being "bad" according to the initial QC (QC1), select a second sample of cases within the same lot and perform a second QC (QC2).

If on the set QC1 + QC2, the accepted errors rate is ≤ the accepted level, correct the identified errors and consider the QC process for the lot is ended. Otherwise, perform a 3rd QC (QC3),.. etc., if needed until the whole lot will have been controlled.
This process insures that the acceptance level of quality is obtained at the lot level.

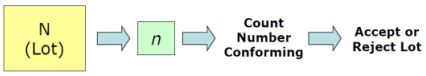
This case study illustrates that even within global major pharmaceutical companies, QC performed at the time of the safety cases processing is not sufficiently efficient, so that a not insignificant number of safety cases with probable errors are recorded in the safety database and submitted to the medical review.
According to the GVP recommendations, the quality control system of the safety case processing has to be improved to ensure the overall quality of safety database without performing a 100% QC of lots that would be very expensive and time consuming.

## APPLICATION OF GOOD STATISTICAL PRINCIPLES (GSP) IN TERMS OF QC OF LOTS TO IMPROVE THE QC SYSTEM OF THE SAFETY CASE PROCESSING

### REMINDER: WHAT ARE THE GOOD PRACTICES REGARDING QC OF LOTS?[6], [7], [8], [9]

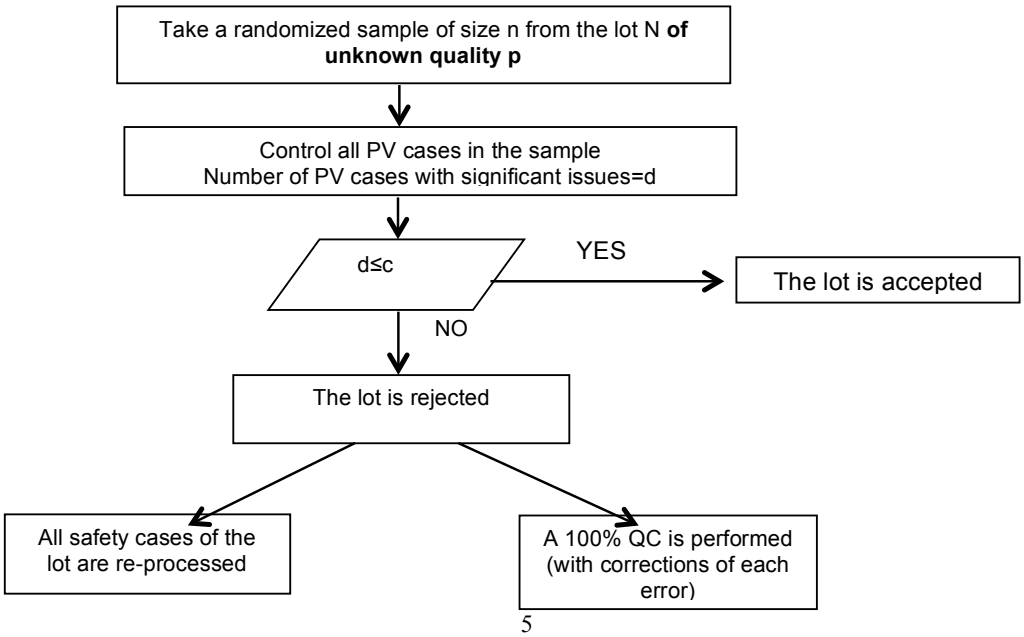
GSP regarding QC of lots represents a compromise between doing no control at all and doing 100% QC.
It is based on acceptance sampling, i.e., a QC technique, where a random sample is taken from a lot, and upon the results of appraising the sample, the entire lot is either rejected or accepted. The acceptance sampling theory was created during the Second World War by Dodge and Romig. When applied to safety case processing, rejected an entire lot would mean that a 100% QC will be performed on the rejected lot with correction of detected errors or an independent PV Assistant would have to re-process all monthly safety cases of the rejected lot and then a new QC will have to be performed.
The purpose of an acceptance sampling is to judge whether the quality level of a lot is within the level that has been predefined.

- *Principles of acceptance sampling*
  The scheme by which representative samples will be selected from a population and tested to determine whether the lot is "acceptable" or not is known as an acceptance plan or sampling plan.



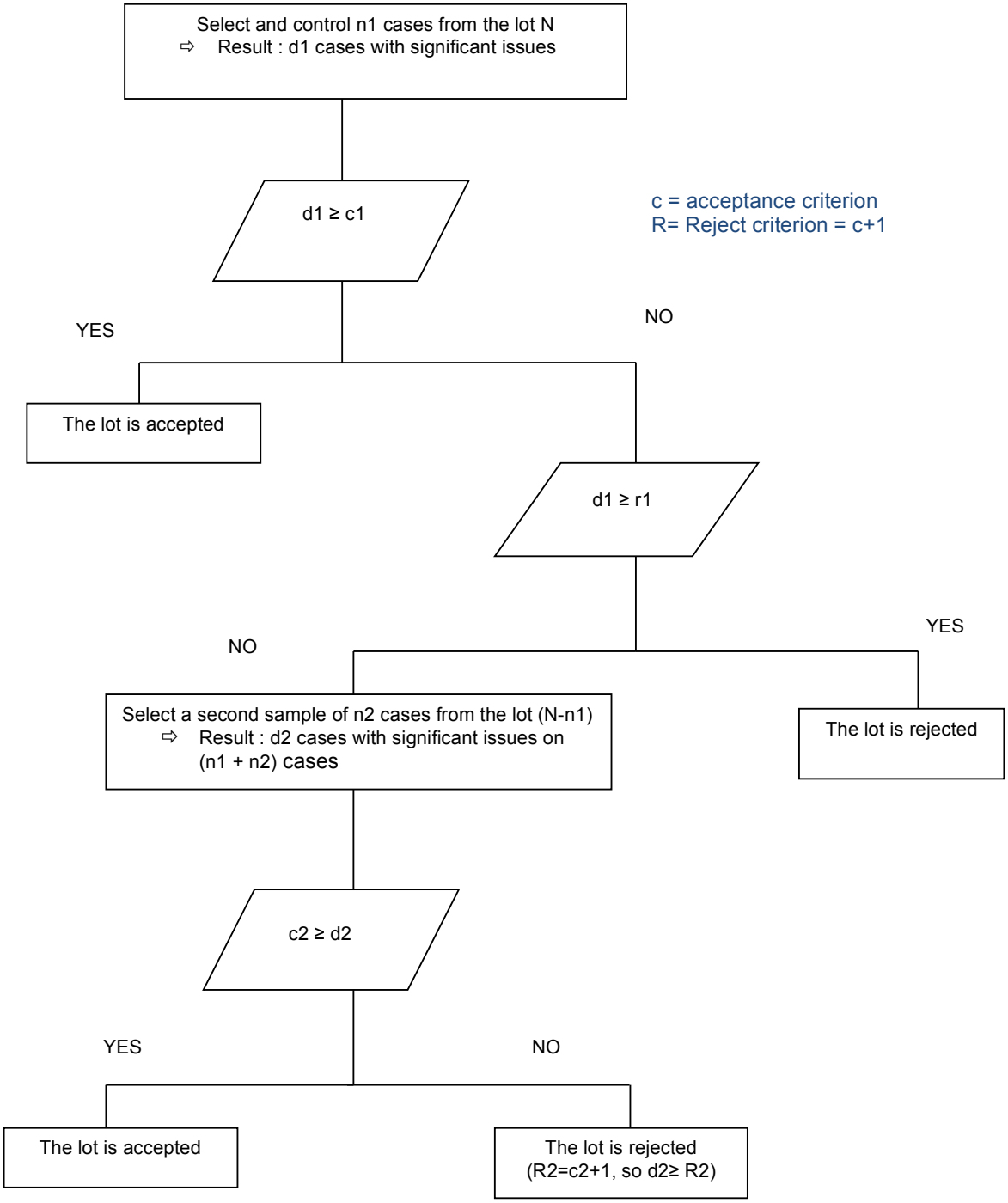

A Sampling plans can be single, double or multiple.
A *single sampling* plan consists of a sample of size n and an acceptance number c. The procedure operates as follows: select n items at random from the lot. If the number of defective items (i.e. safety cases with errors), in the sample set, d, is ≤ c the lot is accepted. Otherwise, the lot is rejected.
The single plan procedure is as follows:

**Figure 2: The single sampling procedure**



*Double sampling plan*: the principle is identical but a second "chance" is given before rejecting the lot by considering a second sample.

**Figure 3: The double sampling procedure**



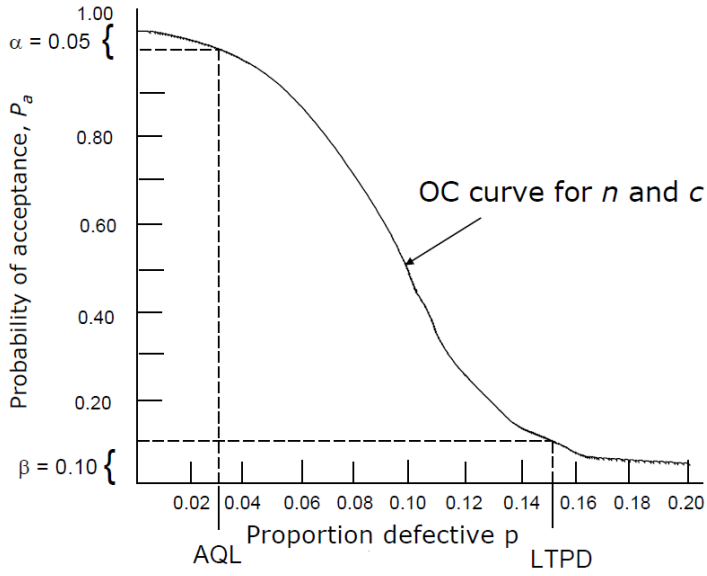
*Multiple sampling plan*: the principle is identical to the double plan. It consists to select and control several samples.

- *How acceptance sampling works?*
- *Definitions*
  - Acceptance quality level (AQL) = the smallest percentage of defective that will make the lot definitely acceptable. It is the quality level corresponding to the baseline requirement of the customer. The producer (PV assistant) would like to design sampling plan such that there is a high probability of accepting a lot that has a defect level ≤ AQL
  - Lot tolerance percent defective (LTDP) = the quality level that is unacceptable to the customer (PV responsible). The LTPD is a designated high defect level that would be unacceptable for the consumer. The consumer would like the sampling plan to have a low probability of accepting a lot with a defect level ≥ LTPD
  - Producer's & Consumer's risks due to mistaken sentencing

    Type 1 error = $\alpha$ = P (reject good lot) = Producer's risk (5% is a common value for $\alpha$). It is the probability for a given (n, c) sampling plan of rejecting a lot that has a defect level equal to the AQL.

    Type 2 error = $\beta$ = P (accept a bad lot) = Consumer's risk (10% is a typical value for $\beta$). It is the probability for a given (n,c) sampling plan, of accepting a lot with a defect level equal to the LTPD.
  - Operating Characteristic (OC) Curve: the curve plots the probability of accepting the lot (Y-axis) versus the lot fraction of percent defectives (X-axis).

**Figure 4: OC curve**




OC curves can be calculated using a binomial distribution, an hypergeometric distribution [Pa=Pr(r defectives found in a sample of n], a Poisson formula [Pr(r defectives in n)=P(r)=$((np)^r e^{-np})/r!$] and Larson nomogram.

The OC curve is the primary tool for displaying and investigating the properties of a sampling plan: the number c and sample size n are most important factors in defining the OC curve.

When p1=AQL and p2=LTDP are fixed as well as $\alpha$ and $\beta$, n and c can be defined (by using the Larson nomogram for example)

- *In practices, how can we define easily the sample plans and the associate rules?*

Based on the supporting theory summarized above, statistical tables were built and published in the different norms allowing determining the LTPD, the AQL and the size required for the acceptance sample: see MIL STD 105 E, MIL-S-19500, MIL-M-38510, NFX 06-022 , ISO 2859,...Standards.

From these tables, the control plan and its rules can be defined.

Remark: in these tables, the LTPD of a sampling plan is the level of quality routinely rejected by the sampling plan. A confidence interval is associated to the LTPD. Typically, a 90% confidence interval is used.

So the LTPD is generally defined as the percent defective (number of defectives per hundred units X 100%) that the sampling plan will reject 90% of the time. In other words, this is the percent defective that will be accepted by the sampling plan at most 10% of the time. This means that lots at or worse than the LTPD are rejected at least 90% of the time and accepted at most 10% of the time. If the lot fails the sampling plan, we can state with 90% confidence that the quality level of the lot is worse than the LTPD (defective rate > LTPD) and if a lot passes the sampling plan, then we can state with 90% confidence that its quality level is ≥LTPD

**Figure 5: Extract of the LTPD Sampling table based on the Mil-S-19500 and Mil-M-38510**[9]

| *Max % Defective* | *20%* | *15%* | *10%* | *7%* | *5%* | *3%* | *2%* | *1.5%* | *1%* | *0.7%* | *0.5%* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Acceptance Number (c); rejects=c+1** | **Minimum Sample Size Needed** | | | | | | | | | | |
| **0** | 11 | 15 | 22 | 32 | 45 | 76 | 116 | 153 | 231 | 328 | 461 |
| **1** | 18 | 25 | 38 | 55 | 77 | 129 | 195 | 258 | 390 | 555 | 778 |
| **2** | 25 | 34 | 52 | 75 | 105 | 176 | 266 | 354 | 533 | 759 | 1056 |
| **3** | 32 | 43 | 65 | 94 | 132 | 221 | 333 | 444 | 668 | 953 | 1337 |
| **4** | 38 | 52 | 78 | 113 | 158 | 265 | 398 | 531 | 798 | 1140 | 1599 |
| **5** | 45 | 60 | 91 | 131 | 184 | 308 | 462 | 617 | 927 | 1323 | 1855 |

*This table indicated that a sample of n=18 cases to be controlled are required for a LTPD set to 20% and for an AQL set to 1. In this case, the lot is rejected if there are 2 or more cases found presenting significant issues.*

So by using acceptance sampling methods, the QC of the safety cases processing can be easily improved becoming more rational and much better able to control and reduce the errors rates in the safety databases.

## MITIGATION OF THE RISKS OF ACCEPTANCE OF CASES WITH ERRORS IN PHARMACOVIGILANCE DATABASES: REDUCED CONTROL, STRENGTHENED CONTROL

The review and interpretations of the quality controls results at periodic times can allow a classification of the PV Assistants and controls level adapted (reduced, unchanged or strengthened) to each PV assistant depending on preceding controls and risks levels.
If the performances of a PV Assistant are assessed as being “doubtful” based on the quality of the produced cases, strengthened control should be applied to the lots processed by this PV assistant. At the opposite, if results of the quality control are good and stable over the time for a given PV assistant, it can be decided to use a reduced control plan for this PV assistant.
By setting such risk-based QC, the overall processes and individual human activities will be improved and the QC system optimized.

## CONCLUSION

GVP insist on the need for better planning and completing quality controls of pharmacovigilance activities. The case processing is a critical step of PV since PV in the industry is backed up with the cases data capture and management activities. The current quality control process is very often not sufficiently efficient since inspectors of health agencies detect errors in safety cases recorded in the safety databases and highline major or critical findings related to the case processing and its QC. So to be in line with the GVP, it is quite important to define better quality control system to ensure the quality of safety case processing.
The good statistical practices regarding QC of lots can be easily implemented to set up an optimized QC system for the case processing. We recommend then to PV units of CRO or pharmaceutical company to:

- Use acceptance sampling methods and more specifically opt for a double or multiple sampling plans
- Define what a « significant issue » is
- Define LTPD and AQL depending on the acceptable error rate that can be accepted (several % errors rate depending on the Risks can be defined)
- Determine the size of the samples to be controlled based on LTPD and AQL. This can be done by using published tables in norms such as 2859 or MIL XXX
- Define the strengthened control plans according to risks (required by « Bad » performances and/or junior team and/or sensible projects, …) and reduced control plans for « Good » performers or less sensible projects

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