



**Good statistical practices regarding the quality control of lots
applied to the case processing**

Véronique CHAPALAIN, Head of Biometry

AGENDA



GVP AND QUALITY SYSTEM

- ▶ Overview of the PV activities within the pharmaceutical industry
- ▶ The Quality System in GVP

QUALITY LEVEL OF CURRENT PRACTICES OF SAFETY CASE PROCESSING

- ▶ How is the quality level of the safety case processing?
- ▶ Case study (current practices in terms of QC of safety case processing)

GSP IN TERMS OF QC OF LOTS APPLIED TO THE QC SYSTEM OF THE SAFETY CASE PROCESSING

- ▶ GSP regarding QC of lots
- ▶ Practical implementation

CONCLUSION

AGENDA



GVP AND QUALITY SYSTEM



► **Overview of the PV activities within the pharmaceutical industry** ☒

► The Quality System in GVP

QUALITY LEVEL OF CURRENT PRACTICES OF SAFETY CASE PROCESSING

GSP IN TERMS OF QC OF LOTS APPLIED TO THE QC SYSTEM OF THE SAFETY CASE PROCESSING

CONCLUSION

Pharmacovigilance in the pharmaceutical industry



Definition : Process of identifying and responding to drug safety issues

Pharmacovigilance (PV) = the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (OMS).



Overall objectives for pharmaceutical companies

- 1.Minimize the risks for the patients** by identifying previously unrecognized drug hazards elucidating pre-disposing factors, refuting false safety signals and quantifying risk vs Benefits
- 2.Minimize the risks for the company**
- 3.Meet global regulatory requirements**

Pharmacovigilance in the pharmaceutical industry



Task common to all safety departments

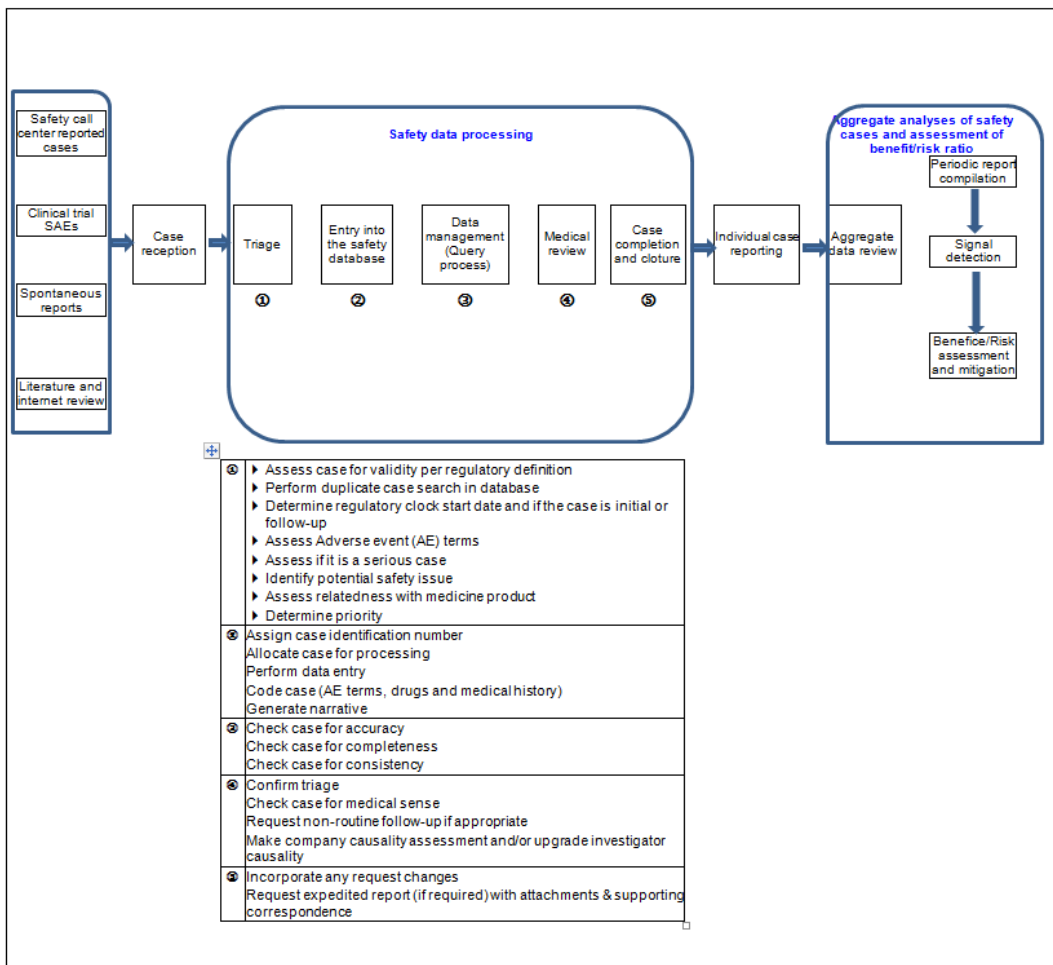
Report adverse events (AE) to health authorities according to regulatory requirements



Summary of the process

1. Creation of individual case from multiple sources of information (clinical trials, safety call centers, spontaneous reports, literature searches, internet forum, ...)
2. Processing of each case and assessment of its relationship to product
3. Reporting to the regulatory authorities and other stakeholders of individual case report
4. Collation, evaluation and reporting of aggregate analyses of safety cases in order to detect safety issues and assess the benefice/risk ratio
5. Submission of periodic safety update reports (PSURs) to the regulatory authorities (ICH E2c)

The Pharmacovigilance workflow



AGENDA



GVP AND QUALITY SYSTEM



► Overview of the PV activities within the pharmaceutical industry

► **The Quality System in GVP**

QUALITY LEVEL OF CURRENT PRACTICES OF SAFETY CASE PROCESSING

GSP IN TERMS OF QC OF LOTS APPLIED TO THE QC SYSTEM OF THE SAFETY CASE PROCESSING

CONCLUSION

What are the Good Pharmacovigilance Practices ?



A new set of guidelines for the conduct of PV in EU was developed to support the new legislation for PV applying in EU since July 2012. This new **guideline on Good Pharmacovigilance Practices (GVP)** is divided in chapters falling into 2 categories:

- ▶ modules covering major pharmacovigilance processes (**modules I to XVI**)
- ▶ product- or population-specific considerations

GVP have been established by experts from the EMA and from European Member States **to improve the performance of pharmacovigilance activities (by setting a set of measures/guidelines)** in the EU **with the ultimate aim of ensuring safety for patients.**

GVP apply to marketing-authorisation holders (MAH), the EMA and Health authorities in EU Member States and cover both medicines authorized centrally via EMA as well as medicines authorized by national agencies.

What are the Good Pharmacovigilance Practices ?



Most modules available in their final versions except modules XI, XII and XIV scheduled for release for public consultation in Q4 2014/Q1 2015, Q4 2014 and Q1/Q2 2015 respectively

Module I PV Systems and their quality systems	Module II PV Systems and their quality systems	Module III PV inspections	Module IV PV audits
Module V Risk Management system	Module VI Management and reporting of Adverse reactions to medicinal products	Module VII Periodic safety update reports	Module VIII Post-authorization safety studies
Module IX Signal management	Module X Additional monitoring	Module XI Public anticipation in PV	Module XII Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication
Module XIII Incident management <i>No more developed: original topics covered by Module XII</i>	Module XIV International cooperation	Module XV Safety communication	Module XVI Risk-minimisation measures: selection of tool and effectiveness indicators

The Quality System in GVP



GVP guidelines describe how to set up a quality system in pharmacovigilance to ensure the Quality (Module I):



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 Improvements: correcting and improving the structures and processes and the carrying out of those processes as necessary

The Quality System in GVP



In each PV unit, a quality management system should be in place covering the entire PV process and including:

- ▶ Quality policy
- ▶ SOPs
- ▶ Quality control (QC) procedures
- ▶ Key performance indicators (KPI)
- ▶ Jobs description
- ▶ Training plans
- ▶ Review plans of the system in a risk-based manner to verify its effectiveness and introducing corrective and preventive measures where necessary
- ▶ System audit plans

Quality Control guidelines in GVP ?



GVP insist on the need for planning and completing audit and quality controls of PV activities

e.g. Module VI (*Management and reporting of Adverse reactions to medicinal products – Rev 1 dated on 15/09/2014*)

§ VI.B.4. (Data management) “Correct data entry, including the appropriate use of terminologies, should be verified by **quality assurance auditing**, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency confirmed”.

§ VI.B.5. (Quality management) “Conformity of stored data with initial and follow-up reports should be verified by **quality control procedures**, which permit for the validation against the original data or images thereof”.

§ VI.C.6.2.4. (Data quality of individual case safety reports transmitted electronically and duplicate management). “marketing authorisation holders and competent authorities in Member States should have in place **an audit system**, which ensures the highest quality of the ICSRs transmitted electronically to the EudraVigilance database within the correct time frames, and which enables detection and management of duplicate ICSRs in their system”.

§ VI.App2.6. (Review and selection of articles) “ It is recommended that **quality control checks** are performed on a sample of literature reviews / selection of articles to check the primary reviewer is identifying the relevant articles”.

Quality Control guidelines in GVP ?



But GVP don't give any directives about the quality control procedures of pharmacovigilance activities.

Then, how to ensure the best quality control of activities such as:

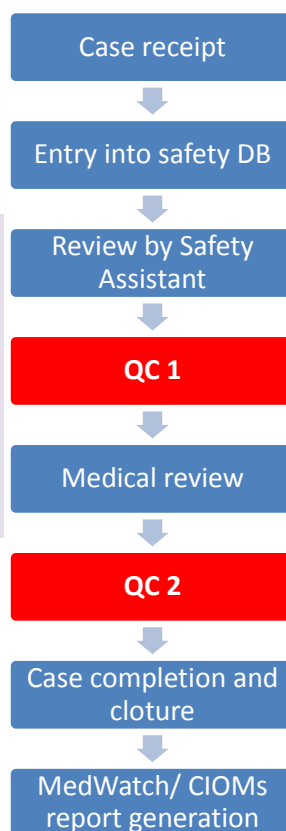
- ▶ Data management: data collection, data entry, data coding, case validation, case evaluation, case follow-up,...?
- ▶ Data recording management ?
- ▶ Literature screening ?

Basis for a good PV = the case processing (and more especially data capture and management activities)



High priority to define the best quality control system to ensure the quality of safety case processing

QC in case processing



QC 1 after data entry by PVA (check for accuracy, consistency and completeness)

- Confirmation of the triage assessment of regulatory reportability;
- Consistency of data-entry with source documents.
- Consistency with established report standards (ICH E2).

QC 2 after medical review by PVP (check for medical sense), focusing on

- Appropriateness of AE terms selected
- Seriousness classification
- listedness/expectedness classification of AE terms
- Outcome
- Coding
- Narrative
- Identification of safety signal
- ...

AGENDA



GVP AND QUALITY SYSTEM

- ▶ Overview of the PV activities within the pharmaceutical industry
- ▶ The Quality System in GVP

QUALITY LEVEL OF CURRENT PRACTICES OF SAFETY CASE PROCESSING



- ▶ **How is the quality level of the safety case processing?** 
- ▶ Case study (current practices in terms of QC of safety case processing)

GSP IN TERMS OF QC OF LOTS APPLIED TO THE QC SYSTEM OF THE SAFETY CASE PROCESSING

CONCLUSION

Current quality level of case processing within the Industry



Health authorities inspection reports show the weakness of the current practice of CRO and pharmaceutical companies regarding the case processing (1/2)

e.g. Findings in the inspection performed by the UK MHRA during the April 2011 – March 2012 period
(<http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con175416.pdf>)

Safety case processing and related issues =

- ▶ 53% of the critical findings
 - Reference safety information (37%)
 - Spontaneous case processing (11%)
 - Clinical trials PV (5%)
- ▶ 35% of major findings
 - Reference safety information (12%)
 - Spontaneous case processing (19%)
 - Clinical trials PV (4%)
- ▶ 24% of minor or other findings
 - Reference safety information (7%)
 - Spontaneous case processing (13%)
 - Clinical trials PV (3%)
 - Literature searches (1%)

Current quality level of case processing within the Industry



Health authorities inspection reports show the weakness of the current practice of CRO and pharmaceutical companies regarding the case processing (2/2)

e.g. Findings in the inspection performed by the UK MHRA during the April 2011 – March 2012 period

Some common findings examples showing the weakness of QC performed during the case processing:

- ▶ Similar cases coded differently or incorrectly
- ▶ Important information was missing in the MedWatch/CIOMS I/E2 B file present in the source document
- ▶ Cases not re-checked by an independent PV officer
- ▶ Serious AEs misclassified as non-serious because of a lack of medical review of non-serious spontaneous AEs



Quality level of safety case processing activities is not good
Current practices in terms of QC have to be reconsidered

17

AGENDA



GVP AND QUALITY SYSTEM

- ▶ Overview of the PV activities within the pharmaceutical industry
- ▶ The Quality System in GVP

QUALITY LEVEL OF CURRENT PRACTICES OF SAFETY CASE PROCESSING



- ▶ How is the quality level of the safety case processing?
- ▶ Case study (current practices in terms of QC of safety case processing) ☒

GSP IN TERMS OF QC OF LOTS APPLIED TO THE QC SYSTEM OF THE SAFETY CASE PROCESSING

CONCLUSION

Case study



Definition

- ▶ The case study refers to the QC 1 performed after Data Entry and Data Management of the safety cases according to one major global biopharmaceutical company SOP
- ▶ **1 lot** = whole cases processed during a defined period of time by a given PV Assistant (PVA)
- ▶ PV unit composed of 15 PVA
- ▶ Monthly lot composed of about 34 cases

Case study



Description of the QC performed

- ▶ Monthly QC performed on **all lots** by selecting in a random way a not fixed number of cases (varying from 2 to 5)
- ▶ Findings classified as "significant" or "non-significant " according to precise definitions
- ▶ Acceptance limit and action plan defined as follows for a given lot:

Results	Conclusion and action plan
 Significant findings: 0 or 1	PVA is a "good" performer; no specific actions are required
 Significant findings ≥ 2	PVA is defined as being a "bad" performer → Action plan: ➡ 5 cases controlled in a systematic way during the two following months ➡ But no specific control for the remaining cases of the lot

Case study



Comments and immediate recommendations (1/4)

► **Acceptance error rate for a given lot:** varies from 20% (5 cases are controlled) to 50% (2 cases are controlled)

- ➡ High variability
- ➡ Accepted error rate **may be very high** (e.g. in a clinical trial study accepted error rate for the clinical DB : $1\text{‰} - \sqrt{n} + 1$ patients controlled, n =total number of patients)

► **Risk to have accepted « bad » cases (i.e. cases with errors recorded in the DB): may be quite high** since no specific action is taken to review non-controlled safety cases even for PVA qualified as "Bad performer" regarding the QC result

Case study



Comments and immediate recommendations (2/4)

recommendation #1:

If the size of controlled lots is not fixed, fix an **acceptance limit expressed in %** and not as an absolute number of cases

e.g. if the relative acceptance limit is 25%, a given lot may be declared "acceptable" if

- the controlled sample contains 0 case with significant findings if the controlled sample size is ≤ 3

- the controlled sample contains 0 or 1 case with significant findings if the controlled sample size is > 3 and ≤ 5

Case study



Comments and immediate recommendations (3/4)

► What about a lot assessed as being "bad" during a monthly QC:

- ☞ For a given controlled lot including at least 2 cases with significant findings among the controlled cases, high **probability that among the other cases, a non insignificant number of cases present major issues too**

e.g.

Assuming that

- For a given lot, 5 cases were controlled out of 34 processed cases during the month
- 2 cases with significant findings were found
- We want to compute the probability for the overall rate on the whole lot to be $> 25\%$

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) ; $\bar{A}$ = The overall error rate on the whole lot is $\leq 25\%$; B = 2 cases among 5 selected cases present significant finding

— $\Pr(\bar{A}) = \Pr(A) = 0.5$

We can show that $\Pr(A|B) = \frac{\Pr(B|A) \cdot \Pr(A)}{\Pr(B)} = \frac{\Pr(B|A) \cdot \Pr(A)}{\Pr(B|A) \cdot \Pr(A) + \Pr(B|\bar{A}) \cdot \Pr(\bar{A})} = 0,61$

Case study



Comments and immediate recommendations (4/4)

recommendation #2:

to decrease the risk having accepted cases with major errors within a lot assessed as being "Bad" according to the initial QC (QC 1), **select a second sample cases** within the same lot and performed a second QC (QC 2) :

😊 On the set (QC1 + QC2), accepted error rate $\leq$ accepted level → Correct the identified errors and consider **the QC process for the lot is ended**

😓 On the set (QC1 + QC2), accepted error rate $>$ accepted level → Correct the identified errors but perform a QC3, ...**The QC process continues...**may be until the whole lot is controlled

Case study



Conclusion

► Even within global major pharmaceutical companies, QC process performed at the time of the safety case management may be not efficient: a not insignificant number of cases with "probable" significant findings are recorded in the safety DB and submitted to the medical review



According to the GVP recommendations, the QC system of the safety case processing has to be improved to ensure the overall quality of the safety DB **without performing a 100% QC of lots**

AGENDA



GVP AND QUALITY SYSTEM

- ▶ Overview of the PV activities within the pharmaceutical industry
- ▶ The Quality System in GVP

QUALITY LEVEL OF CURRENT PRACTICES OF SAFETY CASE PROCESSING

- ▶ How is the quality level of the safety case processing?
- ▶ Case study describing current practices in terms of QC of safety case processing

GSP IN TERMS OF QC OF LOTS APPLIED TO THE QC SYSTEM OF THE SAFETY CASE PROCESSING



- ▶ GSP regarding QC of lots ☒
- ▶ Practical implementation

CONCLUSION

Good Statistical Practices (GSP) regarding QC of lots



A compromise between doing no control at all and doing 100% QC

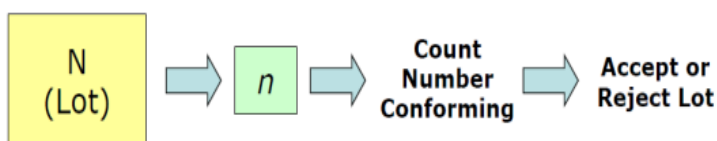
►Based on attribute **acceptance sampling**

➡A QC technique where a random sample is taken from a lot, and upon the results of appraising the sample, the **ENTIRE** lot is **accepted** or **rejected**.

➡The theory is not new: created during WW II by Dodge and Roming

►Principles of acceptance plan or sampling plan

Selection of a « representative » (random) samples from a population and test to determine whether the lot is « acceptable » or not



Good Statistical Practices (GSP) regarding QC of lots



- ▶ Regarding QC of safety case management activities performed by PVA, rejected an entire lot of cases processed by a given PVA =
 - ➔ A second PVA will have to **re-process all monthly cases** of the rejected lot
 - OR
 - ➔ A **100% QC of the non accepted lot would be performed** by an independent PVA with systematic correction of all detected errors

Good Statistical Practices (GSP) regarding QC of lots



► Acceptance test 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 (e.g. safety cases with significant findings) in the sample set is d and $d \leq c$, the lot is accepted
- If $d > c$, the lot is rejected

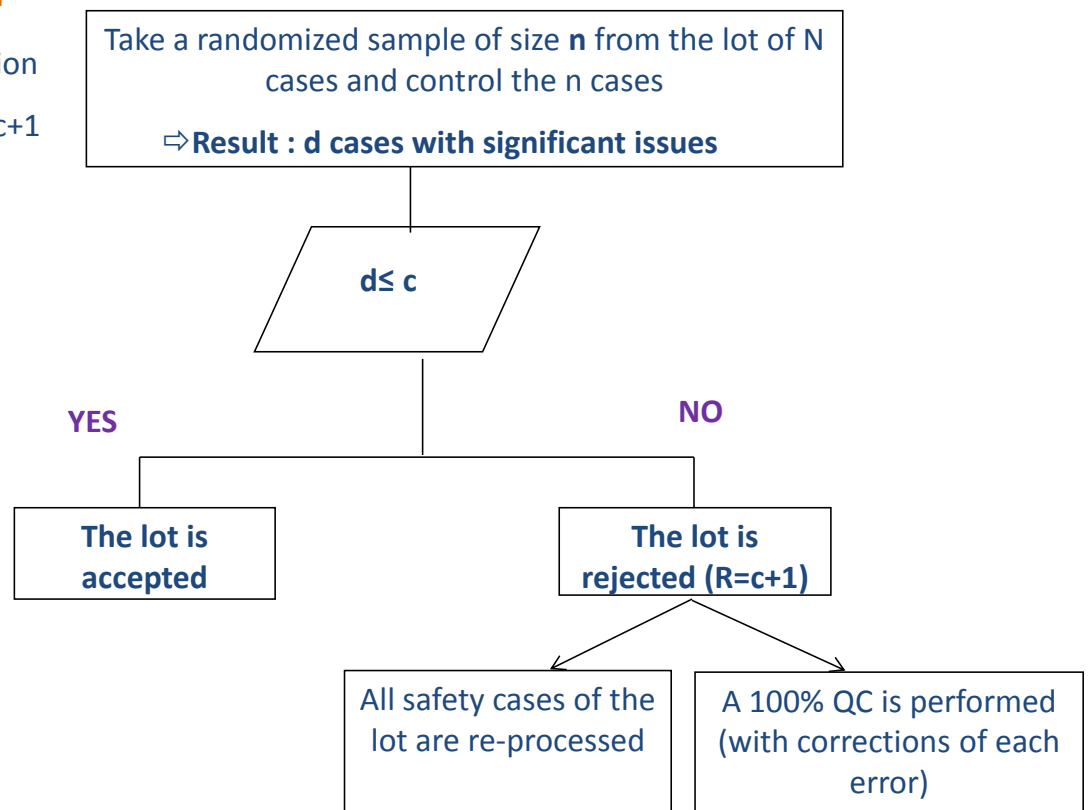
Good Statistical Practices (GSP) regarding QC of lots



Single sampling plan

c = **Acceptance** criterion

R = **Reject** criterion = $c+1$



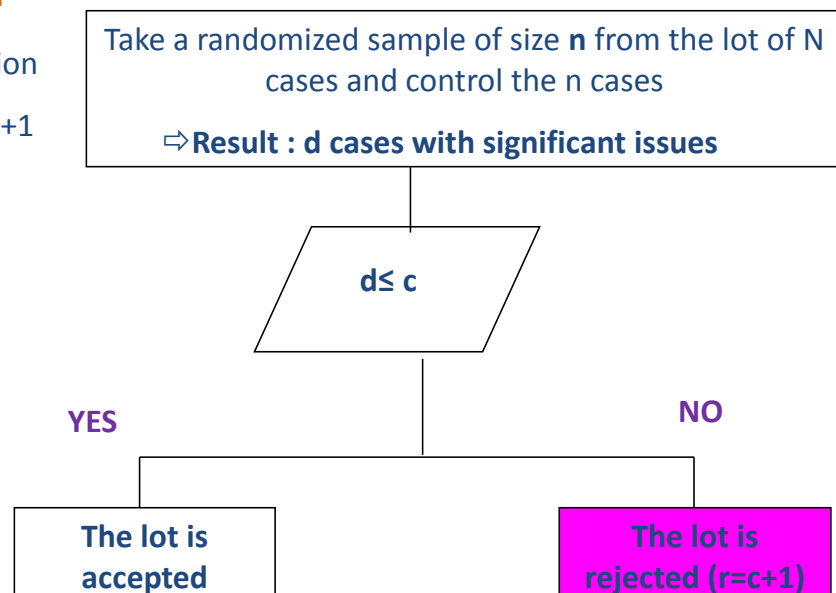
Good Statistical Practices (GSP) regarding QC of lots



Single sampling plan

c = **Acceptance** criterion

r = **Reject** criterion = $c+1$



What about if a second « chance » is given before rejecting the lot?
→ Considering a second random sample

It is the principle of a **Double acceptance plan**

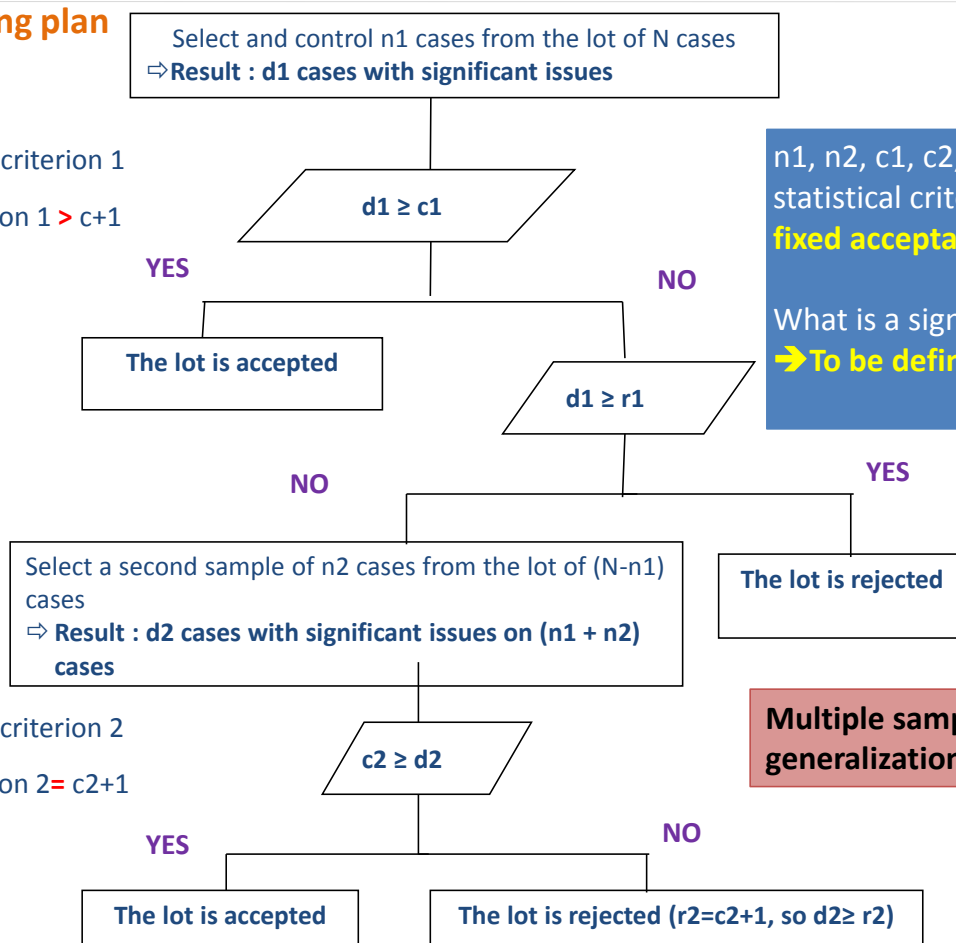
Good Statistical Practices (GSP) regarding QC of lots



Double sampling plan

c_1 = Acceptance criterion 1

r_1 = Reject criterion 1 $> c_1 + 1$



n_1, n_2, c_1, c_2, r_2 defined from statistical criteria according to **pre-fixed acceptance limit** (%)

What is a significant issue?

→ To be defined by PV responsible

c_2 = Acceptance criterion 2

r_2 = Reject criterion 2 $= c_2 + 1$

Multiple sampling plan: a generalization of the double one

Good Statistical Practices (GSP) regarding QC of lots



► How acceptance sampling works: statistics behind sampling plans

Some definitions (1/2)

- ➔ **Acceptance quality level (AQL): the poorest level of quality (nonconforming percent) that the process can tolerate**

It is the quality level corresponding to the baseline requirement of the “consumer” (the patient). The “producer” (PV assistant) would like to design sampling plan such that there is a high probability of accepting a lot that has a nonconforming percent $\leq$ AQL

- ➔ **Lot tolerance percent defective (LTPD): the quality level that is unacceptable to the “consumer”**
The “consumer” (Patient) would like the sampling plan to have a low probability of accepting a lot with nonconforming percent $\geq$ LTPD

Good Statistical Practices (GSP) regarding QC of lots



►How acceptance sampling works: statistics behind sampling plans

Some definitions (2/2)

➡Producer and Consumer risks due to mistaken sentencing

—**Type 1 error** = α = **P (reject 'good' lot)** = Producer's risk (5% is a common value for α). 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** = β = **P (accept a 'bad' lot)** = Consumer's risk (10% is a typical value for β). It is the probability for a given (n,c) sampling plan, of accepting a lot with a defect level equal to the LTPD.

Producer's Risk – The probability of rejecting a "good" lot. Consumer's Risk – The probability of accepting a "bad" lot.		Consumer's Decision	
		Accept	Reject
Producer's Activity	Lot conforms	OK	Producer's Risk
	Lot doesn't conform	Consumer's Risk	OK

Good Statistical Practices (GSP) regarding QC of lots



► How acceptance sampling works: statistics behind sampling plans

Operating Characteristic (OC) Curve (1/5)

➡ The **performance of sampling plan** is given by the operating characteristic (OC) curve.

—The OC curve shows the probability, P_a , that a submitted lot will be accepted for any given fraction defective p .

—The OC curve plots the probability of accepting the lot (Y-axis) versus the lot fraction of percent defective (X-axis)

—OC curves can be calculated using a binomial distribution, an hypergeometric distribution [$P_a = \Pr(r \text{ defectives found in a sample of } n)$], a Poisson formula [$\Pr(r \text{ defectives in } n) = P(r) = ((np)^r e^{-np}) / r!$] 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 $p_1 = \text{AQL}$ and $p_2 = \text{LTDP}$ are fixed as well as α and β , n and c can be defined (by using the Larson nomogram for example)

Good Statistical Practices (GSP) regarding QC of lots

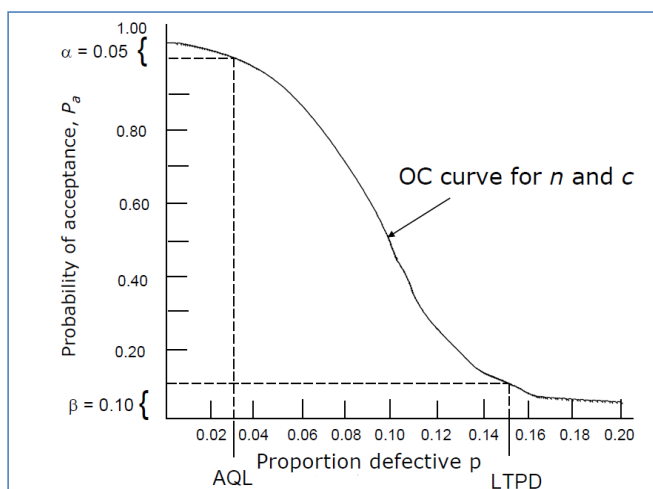


►How acceptance sampling works: statistics behind sampling plans

Operating Characteristic (OC) Curve (2/5)

To construct an OC curve, one needs to know:

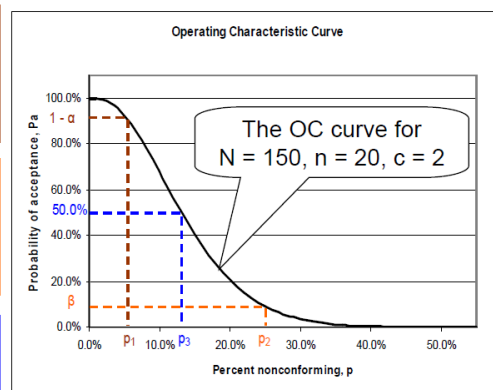
- the sample size (n)
- the number of defects (c) one is willing to accept.



The Producer's Risk has a value of α .
The point ($p_1, 1-\alpha$) shows the probability of accepting a lot with quality p_1 .

The Consumer's Risk has a value of β .
The point (p_2, β) shows the probability of accepting a lot with quality p_2 .

The point ($p_3, 0.5$) shows the probability of acceptance is 0.5.





Good Statistical Practices (GSP) regarding QC of lots

►How acceptance sampling works: statistics behind sampling plans

Operating Characteristic (OC) Curve (3/5)

➡Example for a single plan with $n=100$ and $c=2$, using the binomial distribution

— p would equal to $2/100=0.02$

—Therefore, to compute probabilities for $c \leq 2$, to bracket 0.02, P_a versus p is plotted.

—Since the sample with up to c defects is accepted, the cumulative binomial distribution is used to compute the probability of acceptance, P_a .

$$P\{d \leq c\} = \sum_{d=0}^c \frac{n!}{d!(n-d)!} p^d (1-p)^{n-d}$$

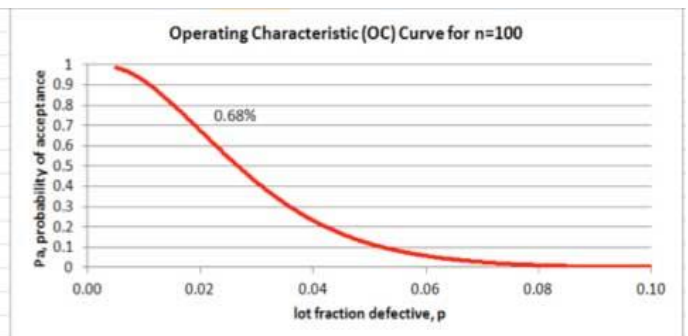
$$P(0) = \frac{100!}{0!(100-0)!} 0.02^0 (1-0.02)^{100-0} = 0.98^{100} = 0.1326$$

$$P(1) = \frac{100!}{1!(100-1)!} 0.02^1 (1-0.02)^{100-1} = 100 * 0.02 * 0.98^{99} = 0.2707$$

$$P(2) = \frac{100!}{2!(100-2)!} 0.02^2 (1-0.02)^{100-2} = \frac{100 * 99 * 98!}{2! * 98!} 0.02^2 * 0.98^{98} = 0.2734$$

$$P(0) + P(1) + P(2) = 0.1326 + 0.2707 + 0.2734 = 0.6767 \text{ or } 68\%$$

p	P _a
0.0050	0.9859
0.0100	0.9206
0.0200	0.6767
0.0300	0.4198
0.0400	0.2321
0.0500	0.1183
0.0600	0.0566
0.0700	0.0258
0.0800	0.0113
0.0900	0.0048
0.1000	0.0019



➡ OC curve for a double plan with acceptance criteria c_1 and c_2 and reject criterion $= r_1$

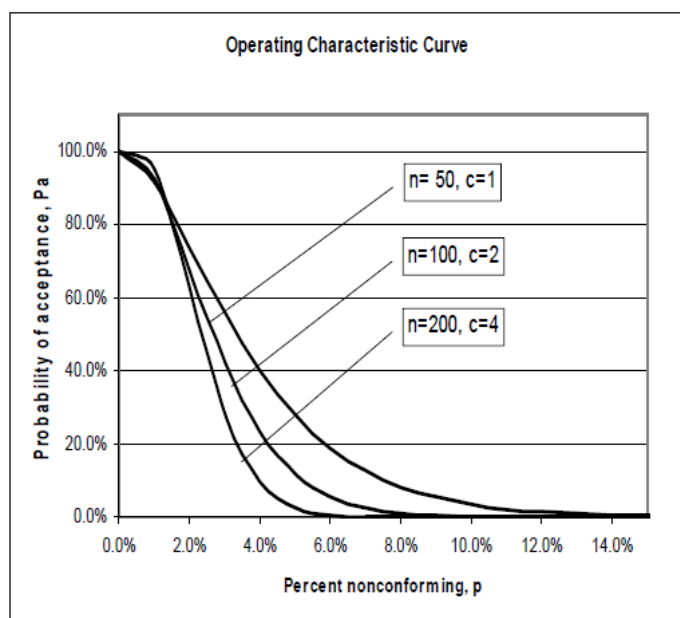
$$P_a = P(x_1 \leq c_1) + \sum_{i=c_1+1}^{r_1-1} P(x_1 = i) P(x_2 \leq c_2 - i)$$

Good Statistical Practices (GSP) regarding QC of lots

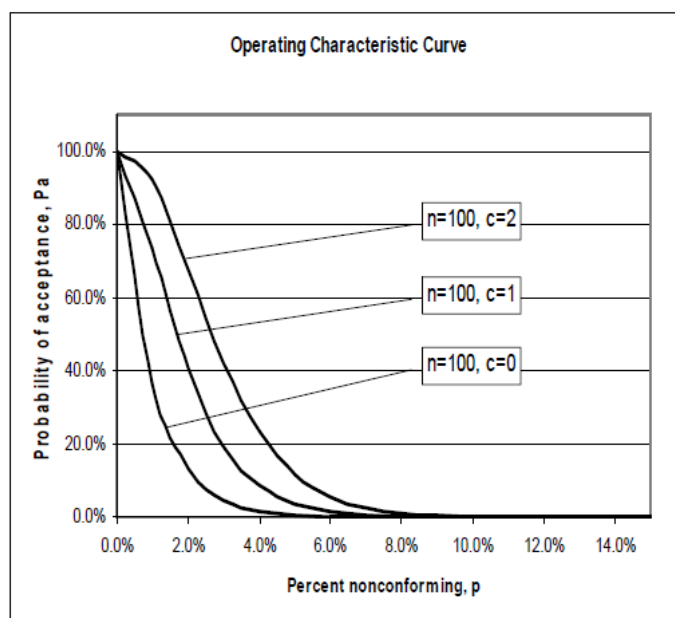


► How acceptance sampling works: statistics behind sampling plans

Operating Characteristic (OC) Curve (4/5)



if n is increased while c is constant we obtain a lower AQL and a higher LTPD



if c is increased while n is constant we obtain a higher AQL and a lower LTPD

Good Statistical Practices (GSP) regarding QC of lots



► How acceptance sampling works: statistics behind sampling plans

Operating Characteristic (OC) Curve (5/5)

⇒ What would be the “optimal plan”?

—Many plans will meet or exceed the requirements $P_A(\text{AQL}) \geq 1 - \alpha$ and $P_A(\text{LTPD}) \leq \beta$, where P_A is the probability of acceptance

—Since QC cost money, the “best” plan meets these requirements **with the smallest possible sample size**.

AGENDA



GVP AND QUALITY SYSTEM

- ▶ Overview of the PV activities within the pharmaceutical industry
- ▶ The Quality System in GVP

QUALITY LEVEL OF CURRENT PRACTICES OF SAFETY CASE PROCESSING

- ▶ How is the quality level of the safety case processing?
- ▶ Case study (current practices in terms of QC of safety case processing)

GSP IN TERMS OF QC OF LOTS APPLIED TO THE QC SYSTEM OF THE SAFETY CASE PROCESSING



- ▶ GSP regarding QC of lots ☒
- ▶ Practical implementation

CONCLUSION

Implementation of acceptance sampling for QC of safety case processing



► Application of American National Standards Institute (ANSI)/American Society for Quality (ASQ) Z1.4-2008 (*Sampling Procedures and Tables for Inspection by Attributes*)

- ➡ Based on the supporting theory summarized above (with binomial distribution)
- ➡ Provides simple instructions on how to correctly select the sampling plan based on the population size and the acceptable risk
- ➡ ANSI/ASQ Z1.4 is a common pharmaceutical industry practice for inspection of product/process defects (according to GMP). It provides tightened, normal, and reduced plans to be applied for attributes inspection for percent nonconforming or nonconformities per 100 units.
- ➡ ANSI/ASQ Z1.4 is the classic plan, evolved from MIL-STD-105 (developed by Harold F. Dodge during WW II ; standard cancelled in 1995 but content adopted by ANSI/ASQ Z1.4)
- ➡ The FDA recognizes ANSI/ASQ Z1.4 as a General consensus standard
[Extent of Recognition: All applicable single, double, and multiple sampling plans]

Implementation of acceptance sampling to QC of safety case processing



► How does the ANSI/ASQ Z1.4 work?

- ➡ It provides **acceptance sampling tables** based on the acceptable quality level (AQL) designation that is generally **specified in the company standard operating procedure (SOP)**.

Remark: Different AQLs may be designated for different types of « findings » (critical, major, and minor).

- ➡ To correctly use ANSI/ASQ Z1.4, we need to know
 - Lot Size
 - Inspection Level
 - Single, Double, or Multiple Sampling
 - Lot acceptance history
 - AQL

Implementation of acceptance sampling to QC of safety case processing



► How does the ANSI/ASQ Z1.4 work?

- ➡ It provides **acceptance sampling tables** based on the acceptable quality level (AQL)

Inspection level

- determines how the lot size and the sample size are related
- The standard divides inspection levels into two main categories: special inspection levels (S-1, S-2, S-3, and S-4) and general inspection levels (I, II, III).
- According to the standard, **inspection Level II should be used**

- ➡ To correctly use ANSI/ASQ Z1.4, we need to know

- Lot Size
- Inspection Level
- Single, Double, or Multiple Sampling
- Lot acceptance history

Lot acceptance history

- Z1.4 uses a system of switching rules
- Based on the lot history, we inspect the same (normal), less (reduced), or more (tightened)

Implementation of acceptance sampling to QC of safety case processing

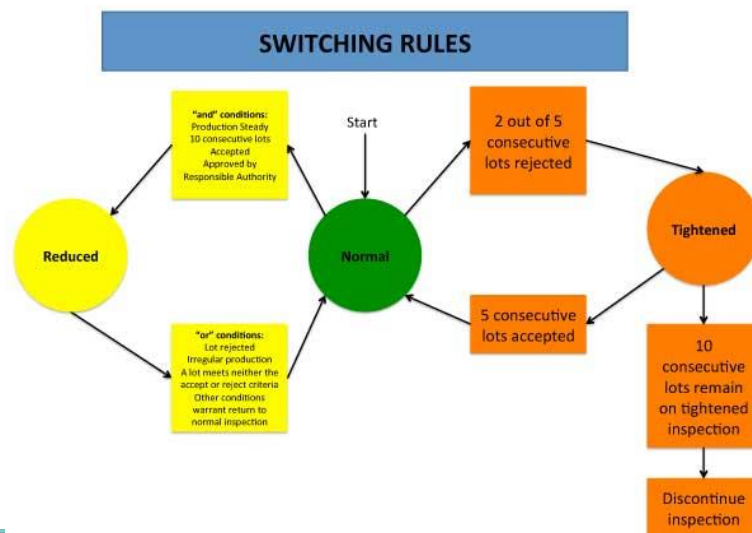


► How does the ANSI/ASQ Z1.4 work?

➡ Switching rules :

- Normal inspection should always be conducted at the start of inspection
- When normal inspection is applied, tightened inspection can be implemented when two out of five or fewer consecutive lots failed normal inspection
- When tightened inspection is applied, normal inspection can be implemented when five consecutive lots pass the tightened inspection
- The reduced inspection can be used conditionally when the normal inspection passes for more than two consecutive lots
- Inspection can be discontinued when 10 consecutive lots remain on tightened inspection.

➡ Switching rules diagram

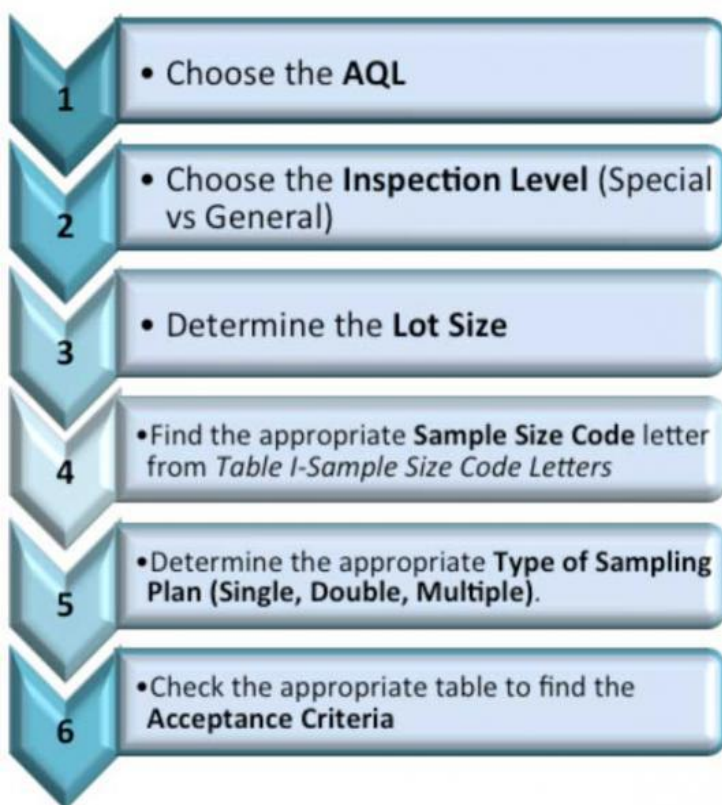


Implementation of acceptance sampling to QC of safety case processing



► How does the ANSI/ASQ Z1.4 work?

➡ Designing the sampling plan:



SOP

Level II as recommended

Known ➔ between 26 to 50

Read in Table I ➔ Letter « D »

Double is recommended

can reduce the sample size, and thereby reduce cost
(Each double sample $\approx 62.5\%$ of the single sample)

Read in Table II –A, II-B, II-C or III-A, III-B, III-C
For AQL=6,5%, $n_1=5$, $n_2=5$, $a_1=0$, $r_1=2$, $a_2=1$
(Table III-A)

Implementation of acceptance sampling to QC of safety case processing



► How does the ANSI/ASQ Z1.4 work?

➡ Designing the sampling plan:

CODE
LETTERS

Table I—Sample size code letters

(See 9.2 and 9.3)

Lot or batch size			Special inspection levels				General inspection levels		
			S-1	S-2	S-3	S-4	I	II	III
2	to	8	A	A	A	A	A	A	B
9	to	15	A	A	A	A	A	B	C
16	to	25	A	A	B	B	B	C	D
26	to	50	A	B	B	C	C	D	E
51	to	90	B	B	C	C	C	E	F
91	to	150	B	B	C	D	D	F	G
151	to	280	B	C	D	E	E	G	H
281	to	500	B	C	D	E	F	H	J
501	to	1200	C	C	E	F	G	J	K
1201	to	3200	C	D	E	G	H	K	L
3201	to	10000	C	D	F	G	J	L	M
10001	to	35000	C	D	F	H	K	M	N
35001	to	150000	D	E	G	J	L	N	P
150001	to	500000	D	E	G	J	M	P	Q
500001	and over		D	E	H	K	N	Q	R

Implementation of acceptance sampling to QC of safety case processing



► How does the ANSI/ASQ Z1.4 work?

➡ Designing the sampling plan:

Table II-A—Single sampling plans for normal inspection (Master table)

(See 9.4 and 9.5)

Sample size code letter	Sample size	Acceptance Quality Limits, AQLs, in Percent Nonconforming Items and Nonconformities per 100 Items (Normal Inspection)																											
		0.010	0.015	0.025	0.040	0.065	0.10	0.15	0.25	0.40	0.65	1.0	1.5	2.5	4.0	6.5	10	15	25	40	65	100	150	250	400	650	1000		
		Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re
A	2																												
B	3																												
C	5																												
D	8																												
E	13																												
F	20																												
G	32																												
H	50																												
J	80																												
K	125																												
L	200																												
M	315																												
N	500																												
P	800																												
Q	1250																												
R	2000																												

↓ = Use the first sampling plan below the arrow. If sample size equals, or exceeds, lot size, carry out 100 percent inspection.

↑ = Use the first sampling plan above the arrow.

Ac = Acceptance number.

Re = Rejection number.

SINGLE
NORMAL
PLANS

Implementation of acceptance sampling to QC of safety case processing



► How does the ANSI/ASQ Z1.4 work?

➡ Designing the sampling plan:

DOUBLE
NORMAL
PLANS

Table III-A—Double sampling plans for normal inspection (Master table)

(See 9.4 and 9.5)

Sample size code letter	Sample	Sample size	Cumulative sample size	Acceptance Quality Limits (reduced inspection)																									
				0.010	0.015	0.025	0.040	0.065	0.10	0.15	0.25	0.40	0.65	1.0	1.5	2.5	4.0	6.5	10	15	25	40	65	100	150	250	400	650	1000
				Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re
A																		*											
B	First	2	2																										
B	Second	3	4																										
C	First	3	3																										
C	Second	3	6																										
D	First	5	5																										
D	Second	5	10																										
E	First	8	8																										
E	Second	8	16																										
F	First	13	13																										
F	Second	13	26																										
G	First	20	20																										
G	Second	20	40																										
H	First	32	32																										
H	Second	32	64																										
J	First	50	50																										
J	Second	50	100																										
K	First	80	80																										
K	Second	80	160																										
L	First	125	125																										
L	Second	125	250																										
M	First	200	200																										
M	Second	200	400																										
N	First	315	315																										
N	Second	315	630																										
P	First	500	500																										
P	Second	500	1000																										
Q	First	800	800																										
Q	Second	800	1600																										
R	First	1250	1250																										
R	Second	1250	2500																										

↓ = Use first sampling plan below arrow. If sample size equals or exceeds lot or batch size, do 100 percent inspection.

↑ = Use first sampling plan above arrow.

Ac = Acceptance number.

Re = Rejection number.

* = Use corresponding single sampling plan.

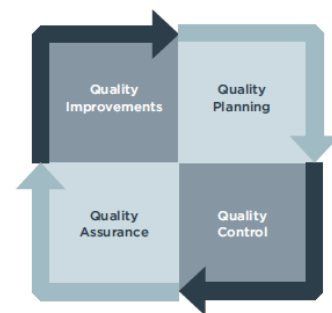
+ = Use corresponding single sampling plan or double sampling plan for code letter B below.

Implementation of acceptance sampling to QC of safety case processing



- ▶ Control levels can be reduced or strengthened depending on preceeding controls and RISKS levels

➔ According to GVP « Quality Improvement »



➔ In PV, the interpretation of QCs allow classification of « PV Assistant » with respect to Lots of cases produced by this Assistant:

- "doubtful" ➔ Strenghtned controls can be applied for this PV Assistant
- If results of QC are good and stable over the time for the PV Assistant, a reduced plan can be applied for this PV officer

➔ ANSI/ASQ Z1.4 allows this mitigation of risks (use the switching rules diagram)

AGENDA



GVP AND QUALITY SYSTEM

- ▶ Overview of the PV activities within the pharmaceutical industry
- ▶ The Quality System in GVP

QUALITY LEVEL OF CURRENT PRACTICES OF SAFETY CASE PROCESSING

- ▶ How is the quality level of the safety case processing?
- ▶ Case study (current practices in terms of QC of safety case processing)

GSP IN TERMS OF QC OF LOTS APPLIED TO THE QC SYSTEM OF THE SAFETY CASE PROCESSING

- ▶ GSP regarding QC of lots
- ▶ Practical implementation

CONCLUSION



CONCLUSION



- GVP insist on the need for better planning and completing quality controls of all PV activities
- Safety case processing = critical step of PV since PV is backed up with the cases data capture and data management
- Current QC practices regarding Safety case processing are very often not adapted



To be in line with GVP, acceptance sampling by attributes methods **based on ANSI/ASQ Z1.4** standard can be easily implemented for the QC of safety case management

The use of sampling tables provides **a quick way** of selecting the sampling plan instead of developing a sampling plan using complex statistics

How implementing sampling plan for the QC of case management



- ▶ Define a lot as being the whole case processed within 1 month by a given PV Assistant
- ▶ Use the ANSI/ASQ Z1.4-2008 (*Sampling Procedures and Tables for Inspection by Attributes*) that is commonly used in manufacturing and recognized by Health Authorities
- ▶ OPT for a double (or multiple) sampling plan
- ▶ DEFINE what a « significant issue » is
- ▶ DEFINE AQL depending on the acceptable error rate you accept (several % errors rate depending on the Risks can be defined)
- ▶ DETERMINE the size of the samples to be controlled based on AQL from published tables in the ANSI/ASQ Z1.4-2008
- ▶ Use the switching rules defined in the standard to DEFINE strengthened or reduced control plans or use other rules

➡ Update the SOP and verify the effectiveness of the new process