Quality is the most important in the Pharmaceutical Industry. (Practice in Gedeon Richter Plc.)

Sophie Pap
Senior auditor
Qualified Person
2012 November

What is quality ?

- A complex system. The key elements of quality are:
  - good design,
  - documentation,
  - application, and
  - control

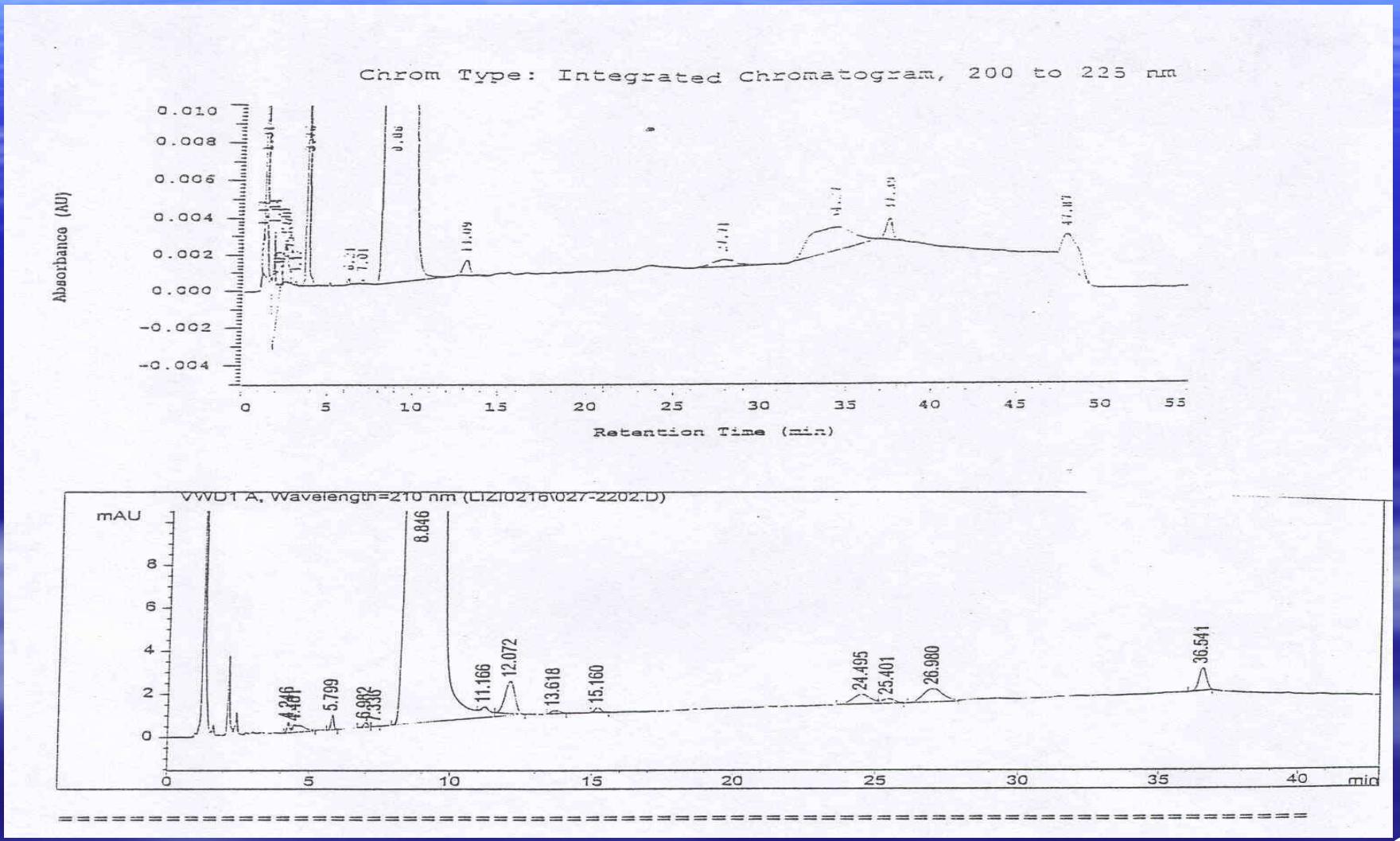
  to meet the needs and expectations of customers during the product life cycle.

- Joseph M. Juran: "Fitness for use”.

QC versus product quality

- Final quality control is not enough. The product will only pass all quality tests if it meets all customer needs – If doesn‘t, then it is sub-standard.
- The quality of the product depends on the quality of people who design and produce it - not on quality control

HPLC chromatogram



Beginning

- First step ⟶ Pharmacopoeias
- Florence 1498
- Pharmacopoeia Regni Poloniae: 1817
- Pharmacopoeia Hungarica :1871

The 20th century (Salvarsan)

- Unfortunate events have catalyzed the development of medicines regulation more than the evolution of a knowledge base.
- 1925 Therapeutic Substances Act (USA) Registration of producers and the composition of medicines.

Hungary

- Institute OKI: The establishment to control the quality of medicinal products: (model: Bureau of Chemistry later FDA) 1927
- Regulation of advertisements
- Richter Control Laboratory: Established in the 1920's

Contergan (Thalidomide)

- Marketing authorization in Europe: 1956
- The product was never approved by FDA

1962: FDA pharmacologist Frances Oldham Kelsey receives an award from President John F. Kennedy for blocking sale of thalidomide in the United State

1963 First Drug GMP,s (28 FR 6385)

Sec.

133.1 Definitions.

FINISHED PHARMACEUTICALS; MANUFACTURING PRACTICE

133.2 Current good manufacturing practice.

133.3 Buildings.

133.4 Equipment.

133.5 Personnel.

133.6 Components.

133.7 Master formula and batch-production records.

133.8 Production and control procedures.

133.9 Product containers.

133.10 Packaging and labeling.

133.11 Laboratory controls.

133.12 Distribution records.

133.13 Stability.

133.14 Complaint files.

AUTHORITY: §§ 133.1 to 133.14 issued under secs. 501, 701; 52 Stat. 1050 as amended 76 Stat. 780, 781; 1055; 21 U.S.C.A. 351, 371.

Hungary / Richter

- **1962** The National Institute of Pharmacy (NIP) is established
- The institute originated from OKI, published its own pharmacopoeia and operated its own Department of Chemistry (1968)
- Experts of Richter QC took part in the editing of the pharmacopoeia

Devonport Incident

- this scandal pointed out the problem of releasing non-sterile glucose infusion bottles onto the market.

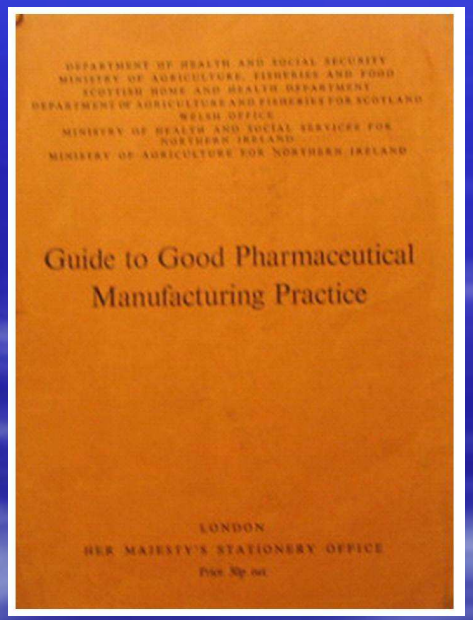
autoclave

What happened ?

- The market demand increased
- The production was non-stop
- No time for maintenance
- Sampling failure

- Who was responsible?

- the sampler
- maintenance people
- production manager
- commercial people



a fine grasp of the concept of QA
Orange Guide 1971

PIC → PIC/S

- Founded in October 1970 by the European Free Trade Association (EFTA),
- Member states :Austria, Finland, Iceland Lichtenstein, Norway, Portugal, Switzerland, Sweden and UK
- Invited states in 1976: Australia, Belgium, France, Hungary, Ireland, Italy

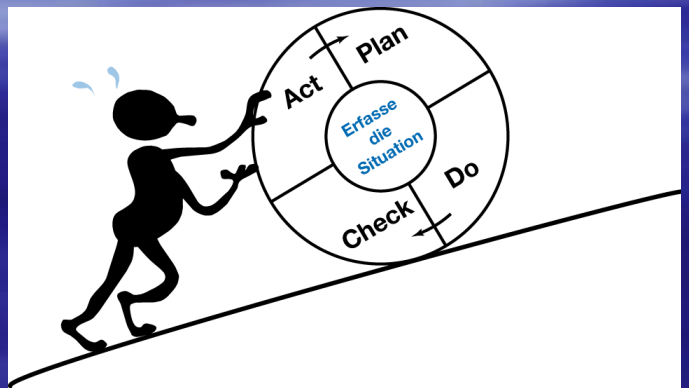
- Pharmaceutical Inspection Co-operation Scheme was formed on 2 November 1995

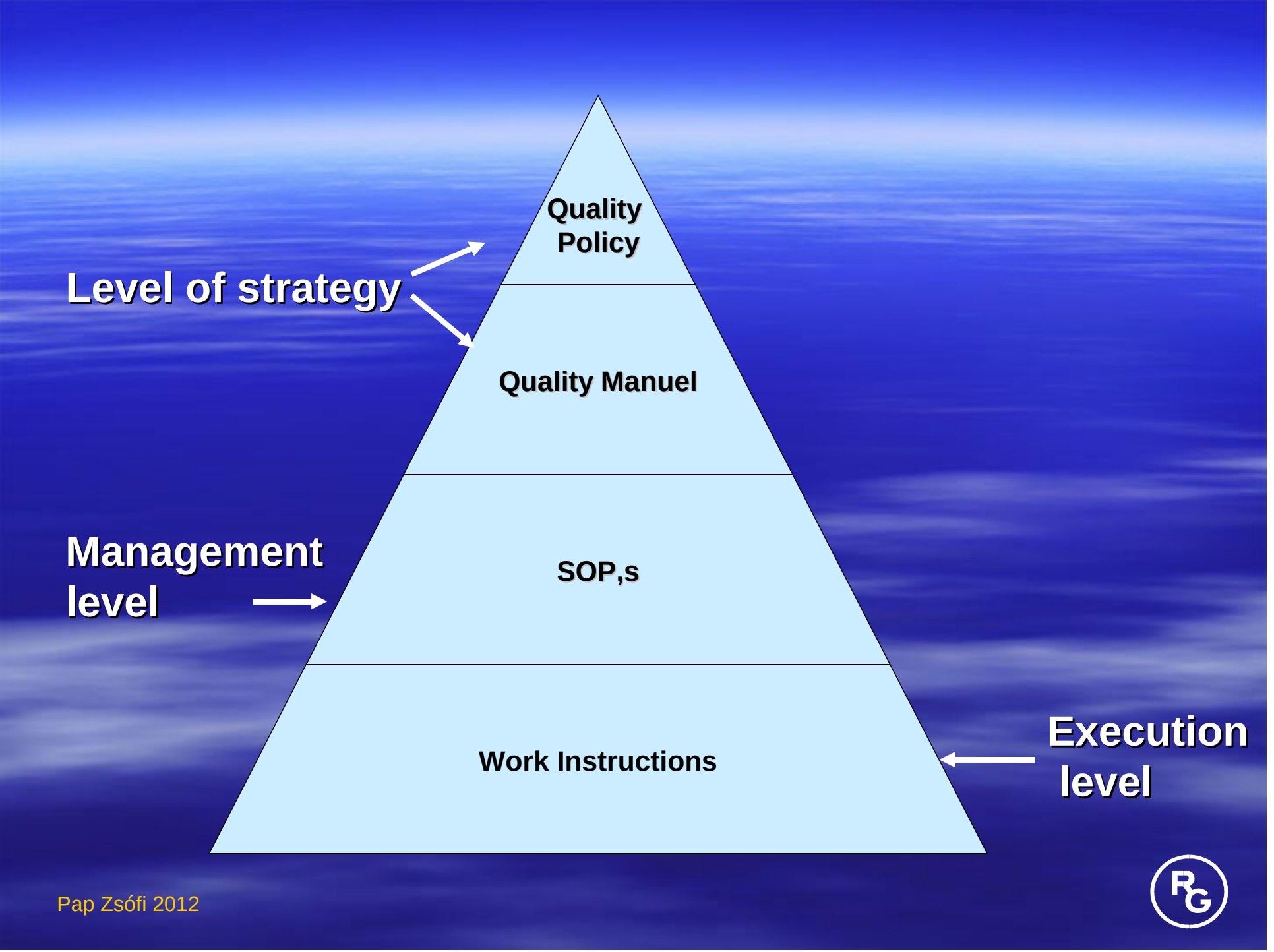
Richter: export oriented company

- **1972:** The first FDA inspection at Richter.
- **1976** Hungary is the first country to join the PIC. Inspections of manufacturing activities started based on the PIC GMP guide
- The main role : QC

Building of our QA system

- First step : Process of releasing finished products – from the end of 1970's
- Implementing of PIC GMP (in 1980's)
- QA department formation in late 1980's
- Introduction of Japanese QA approach and building of SOP system in the beginning of 1990's




Quality Policy
Level of strategy
Quality Manuel
Management level
SOP,s
Work Instructions
Execution level

GEDEON RICHTER LTD.

QUALITY POLICY

We, the senior management of the Chemical Works of Gedeon Richter Ltd. commit ourselves to the continuous improvement of quality within our company.
The objective of our quality program is to provide compliance assurance resulting in superior quality, safety and efficiency of our products.
The company rigorously follows all professional regulations and guides applicable to the needs of our global customer base (e.g. GCP, GLP, and GMP regulations guidelines).
By the involvement of its entire personnel the company provides a high degree of assurance that every person is aware of the requirements and is doing his/her part to assure that each area within the company is in regulatory compliance.

In order to promote quality oriented thinking within the company we have established the "Richter basic principles" which formulate in an easily intelligible way the tasks and expectations of our all employees:

R **egular training:** It is compulsory for each employee to acquire the knowledge and keep up with the developments in the Professional domain, and that of Quality Assurance and Safety.

I **nformation flow:** Fulfillment of demands in a timely and faultless manner requires continuous provision of information to colleagues.

C **GXP:** All activities having impact on product quality must be carried out in full compliance with the GXP principles in operation.

H **ygiene:** It is obligatory for each employee to learn and keep the instructions regarding hygiene.

T **echnological discipline:** All activities must be carried out according to the Standard Operating Procedures and the authorised Manufacturing and Control Documentation in force.

E **ffectiveness:** Satisfaction of our customers can be achieved by the consistently outstanding quality of our products. This is the way in which our activities can contribute to our continued success.

R **eliable documentation:** Traceability of the products and follow up of the occasional faults must be assured by reliable documentation practice.

Our strategy to become the most important pharmaceutical company in the Central and Eastern European region involves a broadening of the market served by the company to include the EU and USA in addition to the regional market of the CIS and Eastern Europe. We are aware that this objective can be achieved only by full compliance with the pertinent legal regulations.
We will ensure that regular training, up-to-date information and adequate working conditions are provided to facilitate working at a high level.

Budapest, October 26, 1998.

Lajos Pillich
Chairman of the Board of Directors

Erik Bogsch
Managing Director

Fundamentals of our QA philosophy (ICH Q10)

- Basis : cGMP, using ISO elements
- Quality management is everybody's job
- Continuous improvement
- Risk based approach ⟶ calculates the benefits versus cost

Examples of our practice

- 1, PQR
- 2, Statistical methods
- 3, Risk analysis

Product Quality Review

- We made the first in 1999
- Statistics used: Minitab and from 2010 Statistica soft wares
- Continuous analysis for contraceptives

TERMELÉS ÖSSZEFOGLALÓ JELENTÉS
PRODUCT QUALITY REVIEW

Feltülvizsgálati időszak/*Period:* ***2011.01.01-2011.12.31***

AZONOSÍTÓ:
ID: PQR-00525/01-12
Oldal / *Page* : **5/6**

TERMÉKNÉV: FINASTERIDE 5 MG FEHÉR FILMTABLETTA
PRODUCT NAME

ÖSSZEFOGLALÁS
SUMMARY

Fejezet *Chapter*	**TARTALOMJEGYZÉK** *TABLE OF CONTENT*	**Oldalak száma** *Number of pages*
---	**Összefoglalás értékelés** *Summary and evaluation of results of the Product Quality Review*	6
1A.FEJEZET *CHAPTER 1A*	**Vásárolt beépülő anyagok, beszállítói státusz** *Review of starting materials used in the product and status of suppliers*	1+1
1B.FEJEZET *CHAPTER 1B*	**Vásárolt hatóanyagok, beszállítói státusz** *Review of drug substance(s) used in the product and status of suppliers*	1
1C.FEJEZET *CHAPTER 1C*	**Primer csomagolóanyagok, beszállítói státusz** *Review of primary packaging used in the product and status of suppliers*	1+1

Chapter 2 and 3 : data of production

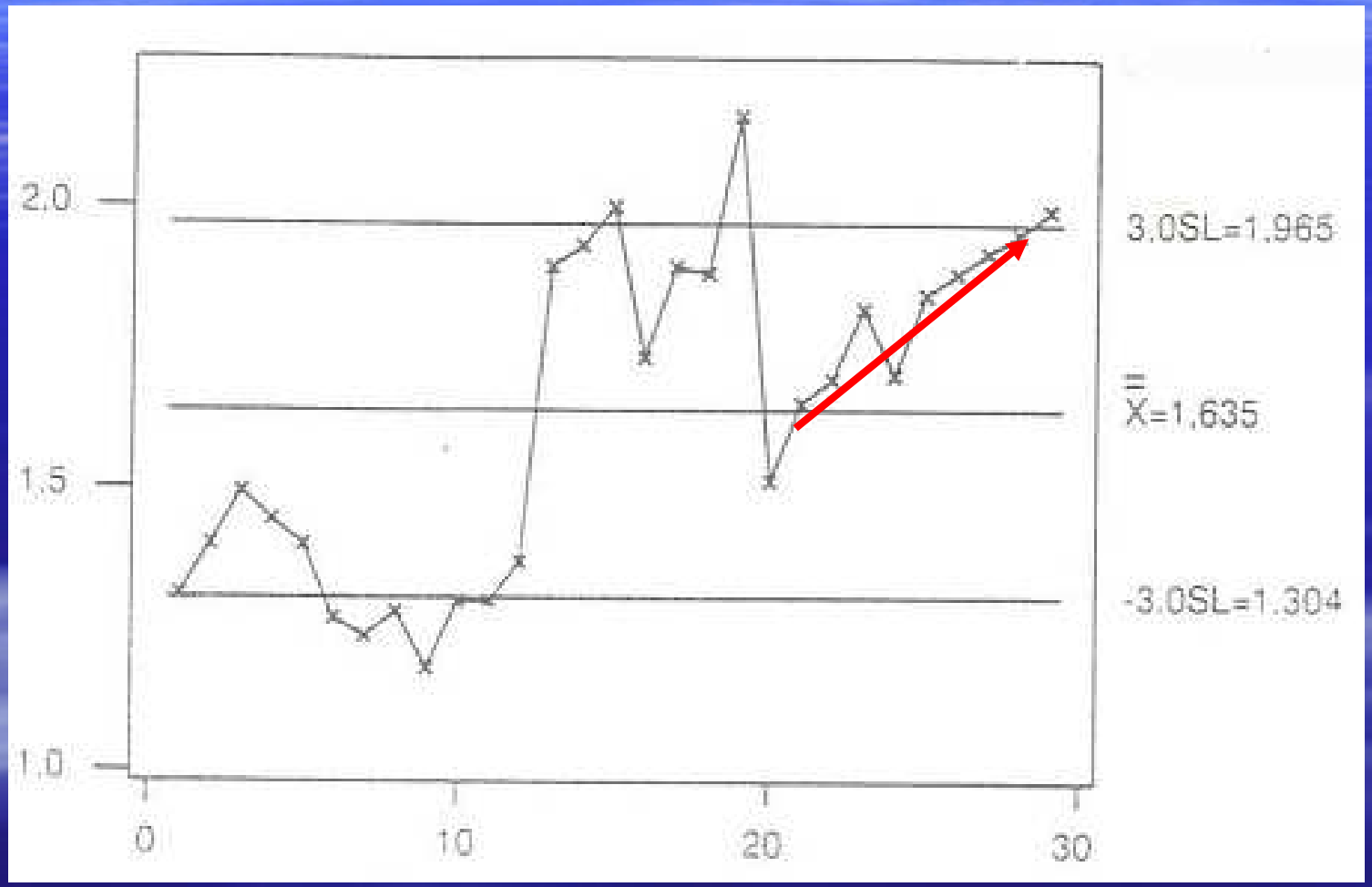
2A.FEJEZET *CHAPTER 2A*	**Gyártási lapok** *Review of Batch Manufacturing Records*	1
2B.FEJEZET *CHAPTER 2B*	**Legyártott tételek azonosítása** *Batches produced in the reviewed period*	1
2C.FEJEZET *CHAPTER 2C*	**Késztermék vizsgálati eredmények és kiértékelése** *Results of critical quality control test parameters of the finished product*	5
2D.FEJEZET *CHAPTER 2D*	**Kritikus gyártásközi eredmények és kiértékelése** *Results of critical In Process Control*	4
2E.FEJEZET *CHAPTER 2E*	**Szennyezésprofil** *Profile of impurity*	1
3.FEJEZET *CHAPTER 3*	**Letiltott tételek** *Review of all batches that failed to meet established specification and their investigation*	1

10A.FEJEZET *CHAPTER 10A*	**Folyamatvalidálás** *Status of the respective process validation reports*	2
10B.FEJEZET *CHAPTER 10B*	**Analitikai módszer validálás** *Status of the respective analytical method validation reports*	1
10C.FEJEZET *CHAPTER 10C*	**Tisztításvalidálás** *Status of the respective cleaning validation reports*	1
11.FEJEZET *CHAPTER 11*	**Törzskönyvezési adatok** *Review of new marketing authorizations*	1
12A.FEJEZET *CHAPTER 12A*	**A gyártás berendezéseinek karbantartásával, műszerek kalibrálásával kapcsolatos szerződések felülvizsgálata** *Review of written contracts on periodic maintenance of production equipment and instrument calibration*	1
12B.FEJEZET *CHAPTER 12B*	**A partnerrel kötött minőségügyi szerződések felülvizsgálata** *Review of Quality Agreements*	1
13.FEJEZET *CHAPTER 13*	**Kiegészítő adatok** *Additional data*	45

Statistical methods for quality improvement

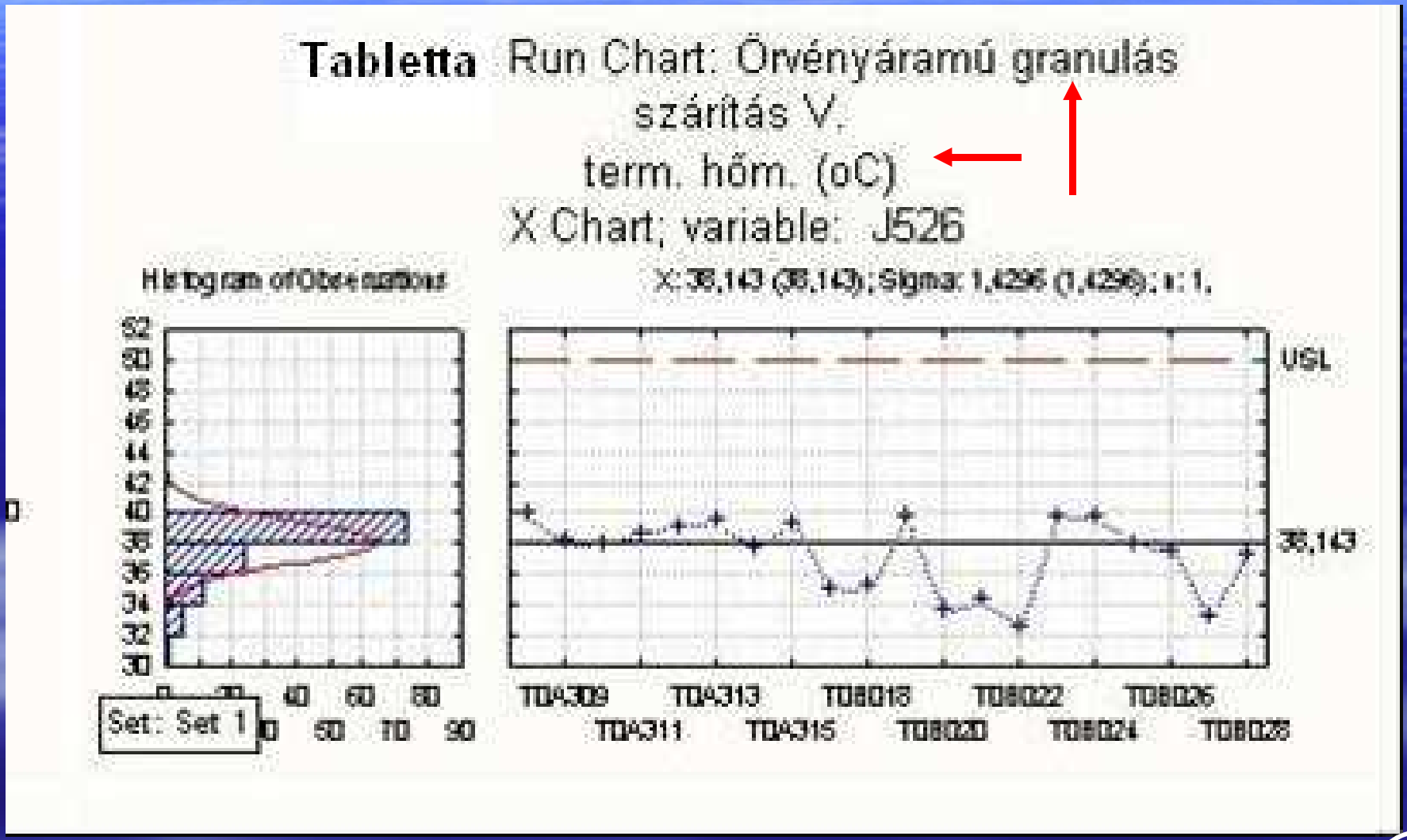
- Control charts (OOS, OOT, OOE)
- Histograms
- Stratification of data
- Pareto diagram
- Process capability index (Cpk)
- Cause and Effect (Ishikawa) diagram

Trend analysis of total impurities

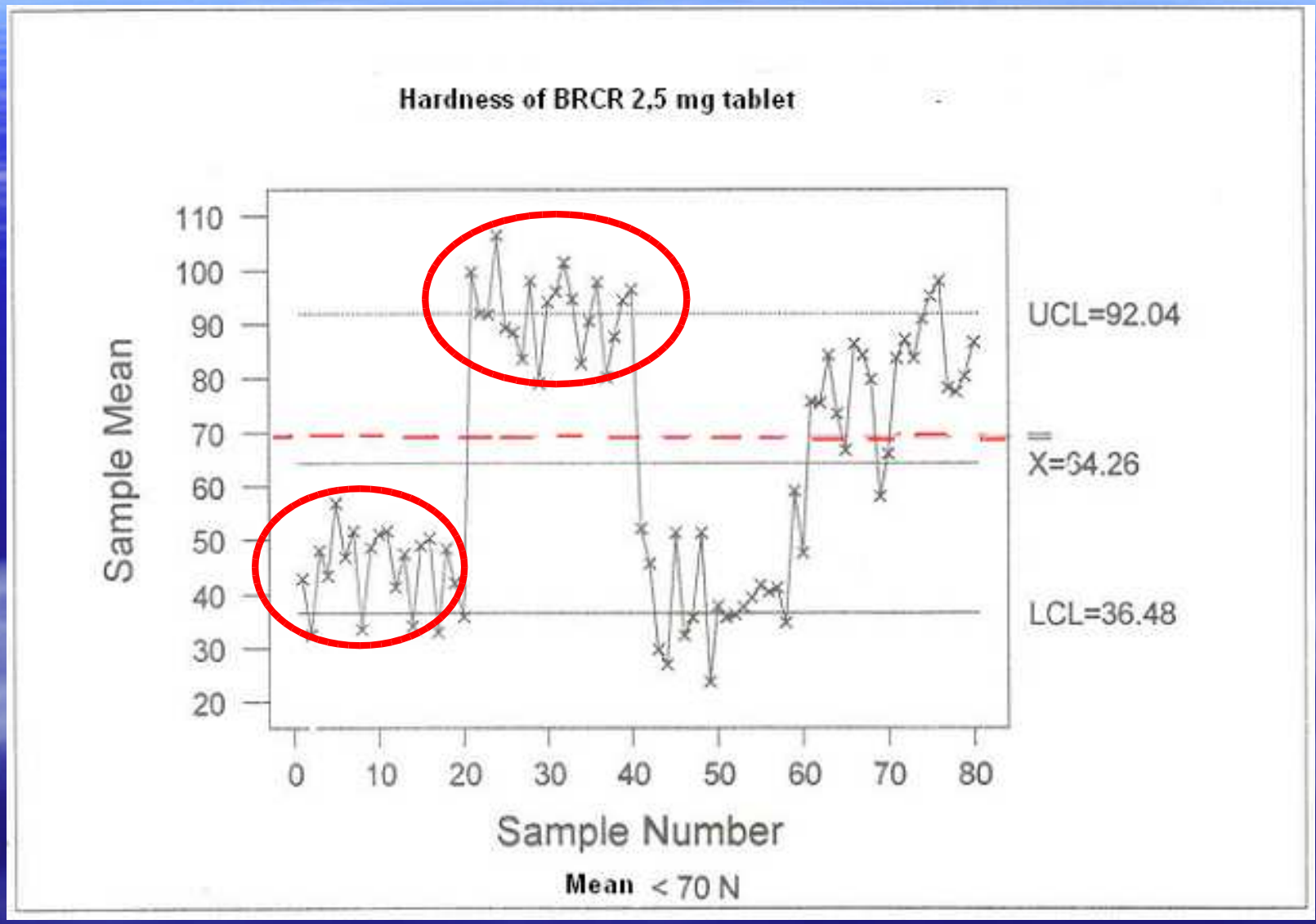


Limit
< 5 %

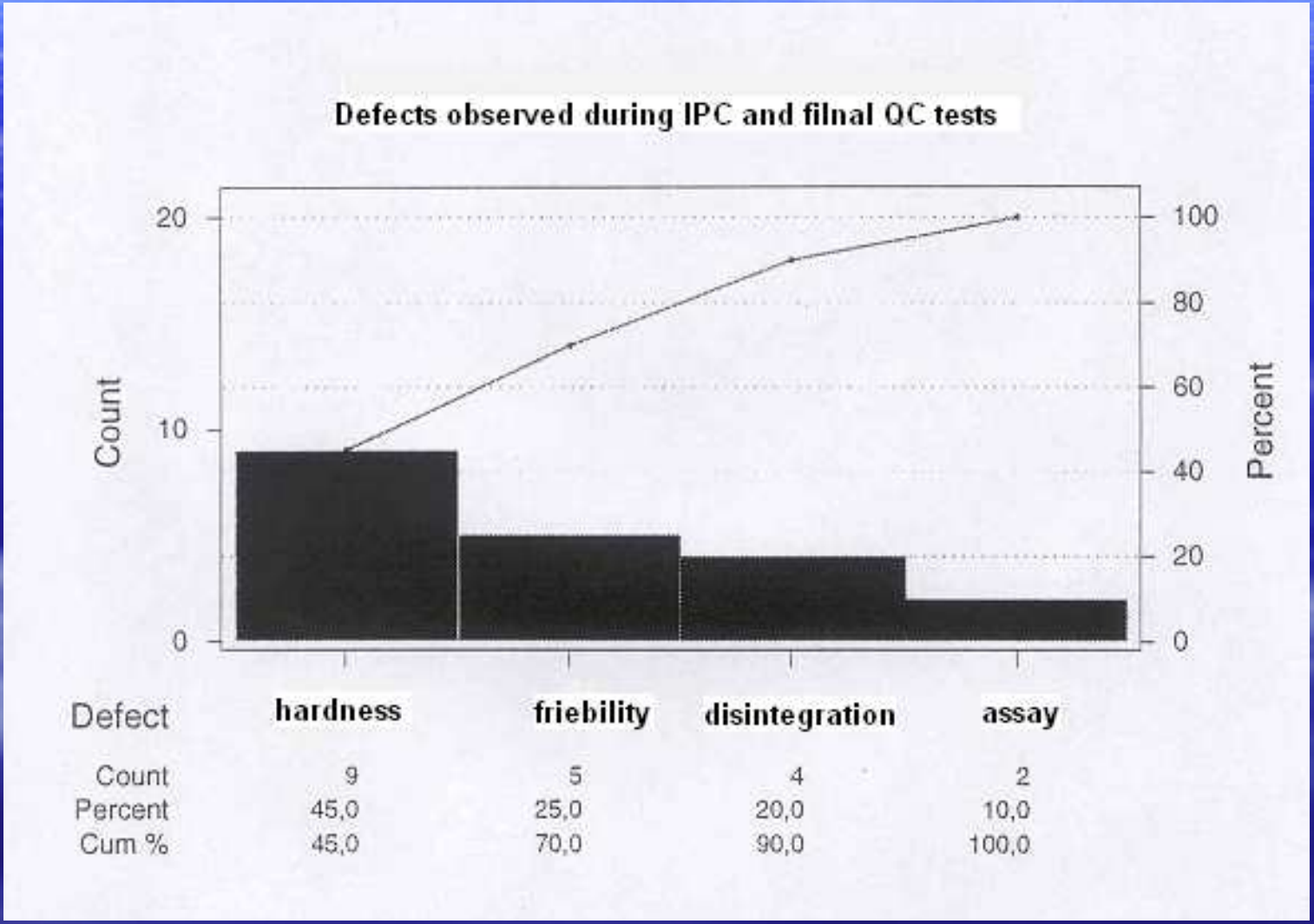
Control chart, histogram



Stratification of data



Pareto diagram



Defect	hardness	friebility	disintegration	assay
Count	9	5	4	2
Percent	45,0	25,0	20,0	10,0
Cum %	45,0	70,0	90,0	100,0

Process capability index, Cpk

$$Cpk = \frac{\text{acceptance limits}}{\text{process capability}} = \frac{\text{UCL - LCL}}{6\sigma^*}$$

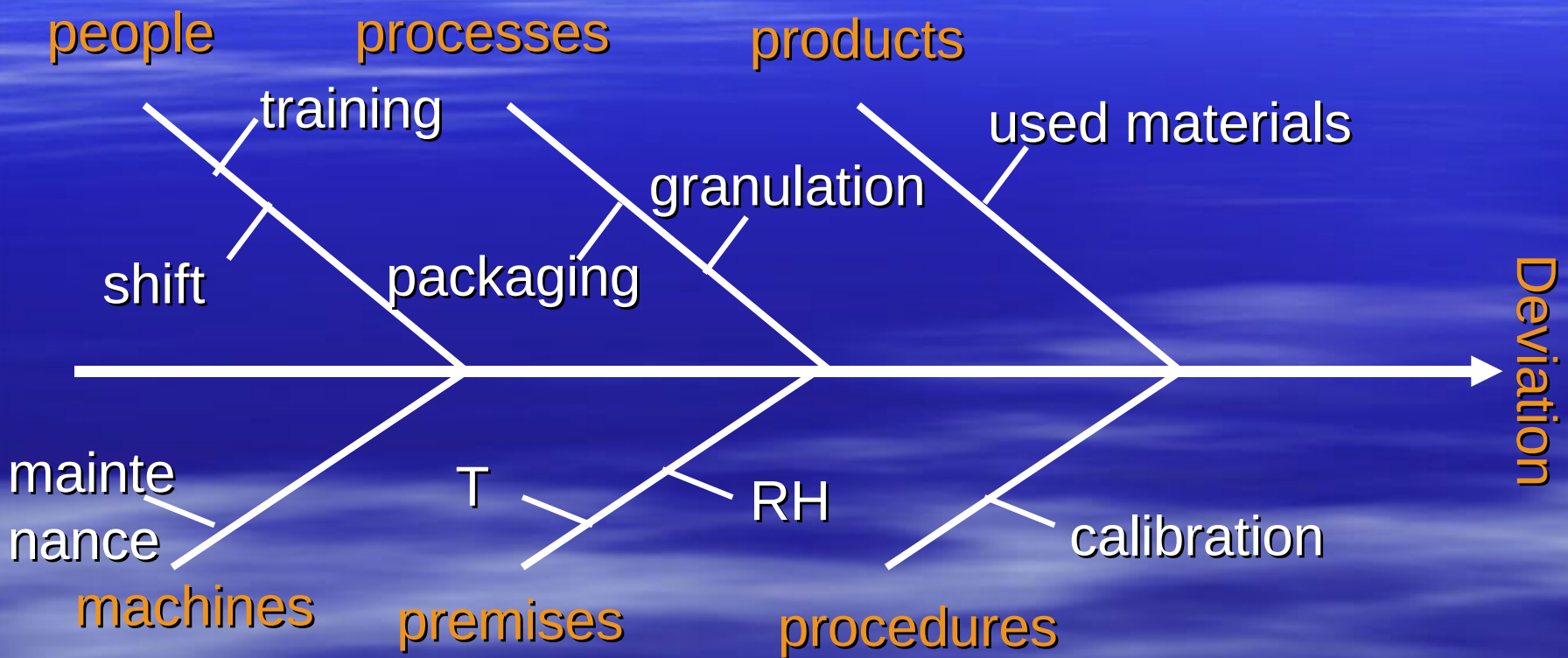
UCL ... upper control limit
LCL … lower control limit

σ* ... is the measured standard deviation of the process

Process is capable if CpK > 1,33

$$CpK = \frac{105\ \% - 95\ \%}{6 \times 1{,}25\ \%}$$

Root cause analysis / Ishikawa diagram



Practice of risk management

- Team Work !
- Examples:

Preparation of international supplier audits

Reduction of sampling point in a PW system

Equipment replacement

Why we use risk analysis for planning the audits ?

- We check the „most risky” producer = interest of the patient
- Our decision is objective because it is not possible to audit every supplier (limited capacity)
- Recommendation by ICH Q9

Common audit plan for GR Plc.

GR Budapest

GR Romania

GR Russ

GR Polska

Calculation of the risk values

- Risks concerning the patient
- Quality history of producer/supplier
- Categorization of producer/supplier

Risk calculation for a new API

risk	low		medium		high	
Route of Final product Admi-nistration	Solid dosage form	-	Semi-solid do-sage form	-	Paren-teral product	3
Status of the application	GR de-velop-ment	-	GMP pro-duction at one GR site	2	GMP pro duction at more GR sites	-

Regulatory situation in EU	No regu-latory action > 3 years	1	Regula-tory action < 3 years	-	Regula-tory action within 1 year	-
Quality system of the manufacturer	cGMP (EU/US/ WHO)	1	ISO 9001 or equivalent	-	Not exist or not known	-
Country of operation	EU	1	Develo-ped rest of the World	-	Develo-ping rest of the World	-
Number of purchased product on site	Single	-	Multiple	-	Multiple, high po-tency or sensiti-vity	3

Previous quality audit	< 3 years	-	> 3 years	-	Non or > 5 years	3
Category of the manufacturer according to the GR qualification system	Appro-ved no issue	-	Approved some minor quality issue	2	Not appro-ved or major quality issue	-
Weight factor	3 x 1=3		4 x 2=8		9 x 3=27	

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Σ = 38

Evaluation of risks

- Risk levels:
- K1 low risk < 25
- K2 medium risk 25-35
- K3 high risk > 35

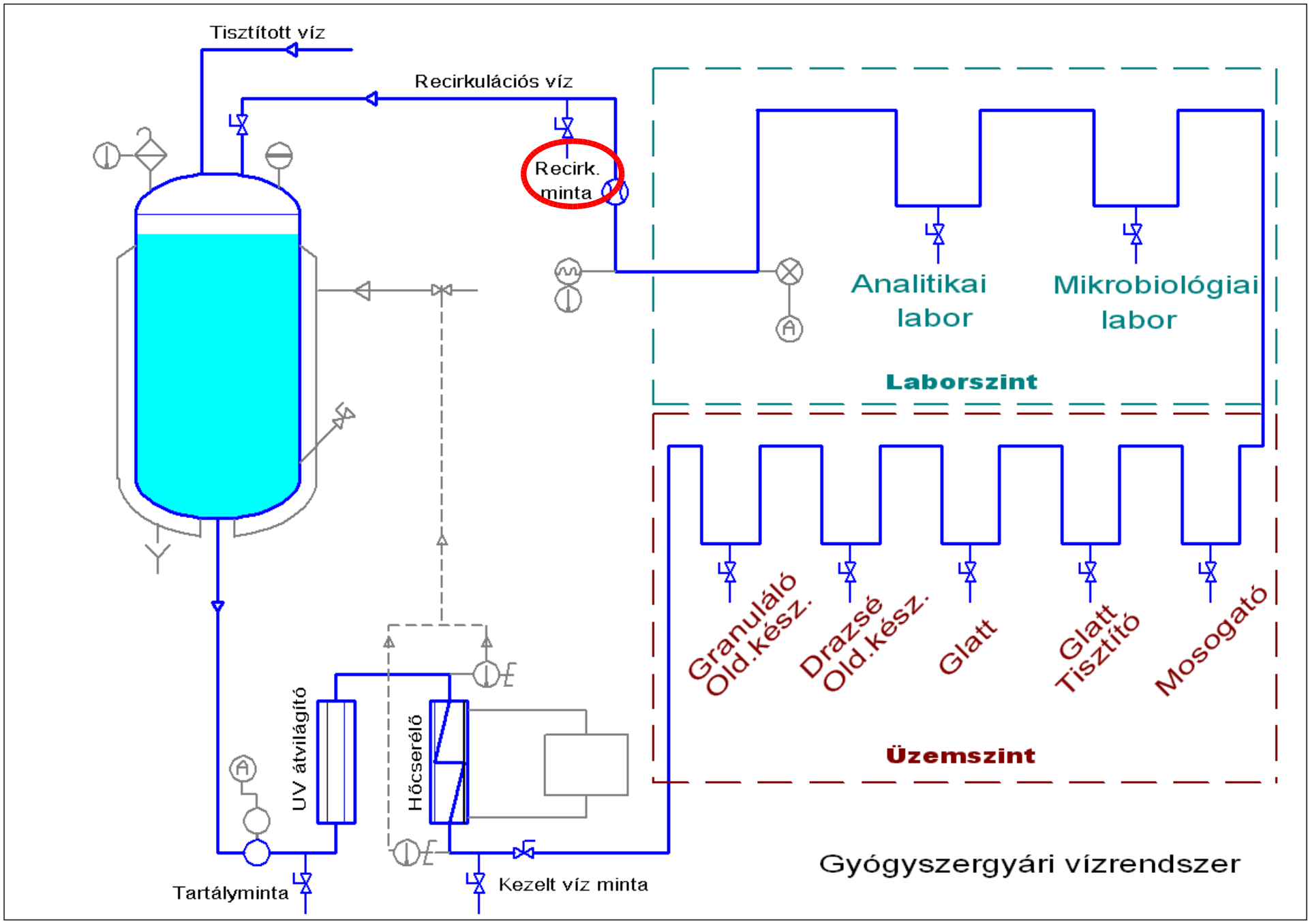
- Example : 38

Microbiological monitor of a PW system

- Target: Is it possible to reduce sampling frequency?
- Information needed:

- Knowledge of PW system (user points, application)

- Evaluation of the results from previous year


Tisztított víz
Recirkulációs víz
Recirk.
minta
Analitikai
labor
Mikrobiológiai
labor
Laborszint
Granuláló
Old.kész.
Drazsé
Old.kész.
Glatt
Glatt
Tisztító
Mosogató
Üzemszint
UV átvilágító
Hőcserélő
Tartályminta
Kezelt víz minta
Gyógyszergyári vízrendszer

Data from the previous year
PhEur limit 100 CFU/ml

Sampling points	mean CFU/ml	maxi mum
Granulation sol. preparation	0,2	2
Coating solution preparation	0,1	5
Glatt	0,3	6
Glatt CIP	0,2	1
Washing room	0,8	9
Microbiological laboratory	0,4	7
Analytical laboratory	0,3	3
Recirk water	0,4	4

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Probability, severity and X-uk

User points	P	S	QR	P	S	MR
Granulation sol.preparation	2	5	10	2	3	6
Glatt fluid granulator	1	5	5	2	3	6
Coating sol. preparation	2	5	10	2	3	6
Glatt CIP	1	4	4	2	3	6
Washing room	2	4	8	2	3	6
Microbiological laboratory	2	1	2	1	1	1
Analytical laboratory	2	1	2	1	1	1
Recirk water	1	3	3	1	3	3

QR: water quality related risk
MR: system operation risk

Risk values determination

User points	QR	MR	ΣR
Granulation sol. preparation	10	6	16
Glatt fluid granulator	5	6	11
Coating sol. preparation	10	6	16
Glatt CIP	4	6	10
Washing room	8	6	14
Microbiological laboratory	2	1	3
Analytical laboratory	2	1	3
Recirk water	3	3	6

Decision based on risk analysis

<u>Sampling frequency:</u>

weekly : > 10 risk values

every two weeks: ≤ 10 risk values

Why we use risk analysis in case of equipment changes ?

- We change the equipments in case of :

- old machine folds up
- transfer of the production to a new production line

In case of equipment change

- Is the new equipment IQ & OQ conform or not?
- If yes, the use of the new machine has no risk from technology point of view

IF NOT

Use risk analysis

Why it is impossible to always strive for IQ,OQ identity ?

- National standards replaced to EU standards
- The type of machine doesn’t exist anymore
- Example: eccentric tablet press versus double-side rotary press

Why it is not needed to strive for IQ,OQ identity ?

- We can avoid unnecessary investments
- For example : to order an old model only for IQ,OQ identity conserves the obsolete technology.

Steps of risk analysis

- Description of the change
- Evaluation of the differences
- Determine risk levels
- Summary report preparation including conclusion

Description of change

- Change of a solution preparation duplicator (no: 2-08-03) to the same function for a new one (no:2-08-14).
- The equipment is not dedicated, so the change attaches the different solution preparations and cleaning procedures. **Target:** to keep the critical process parameters within the regulatory limits,

  (heat transfer, volume, mixing speed, use of validated cleaning and sterilization procedures)

Evaluation of the differences

- The basis is the IQ,OQ documentation of equipments.
- Analysis of the process parameter data according to different products batch records.
- If these parameters are equivalent within certain limits, the product's quality will be the same, so the two machines are equal

Processes and parameters 1

IQ,OQ parameters	2-08-03 old	2-08-14 new	Equal	evaluation	RV
Heat transfer surface	2,6 m²	2,5 m²	no	< 5 %	**K1**
Nominal volume	500 liter	500 liter	yes	-	**K1**
material of Equipment	1,4541	1,4404	no	better	**K1**

Processes and parameters 2

IQ,OQ parameters	2-08-03 old	2-08-14 new	equal	evaluation	RV
Surface ruggedness	< 0,8 µm	< 0,8 µm	yes	-	**K1**
Mixing speed	780/ minute	50-480/minute	no	Geometry of mixer is better	**K2**
Way of solution completion	± 2,5 l	± 2,5 kg	yes	-	**K1**

Processes and parameters 3

IQ,OQ parameters	2-08-03 old	2-08-14 new	equal	evaluation	RV
Accuracy of solution completion	± 0,5 %	± 0,5 %	yes	-	**K1**
Time of heating up	24 min	25 min	no	< 5 %	**K1**
Time of cooling	46 min	48 min	no	< 5 %	**K1**

Two equipments are similar, risk level : K2

Summary report preparation

- Team work
- Controlled by the head of production
- Approved by QA

- Conclusion: the risk level : K2, but the differences are favourable, no need of risk reduction.

Verification of theory

- We prepare the risk analysis on the basis of our best knowledge but the result is a

HYPOTHESIS

It is suggested to conform it, so comparative studies for the products are recommended

Thank You for Your Attention

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Total Quality Management