



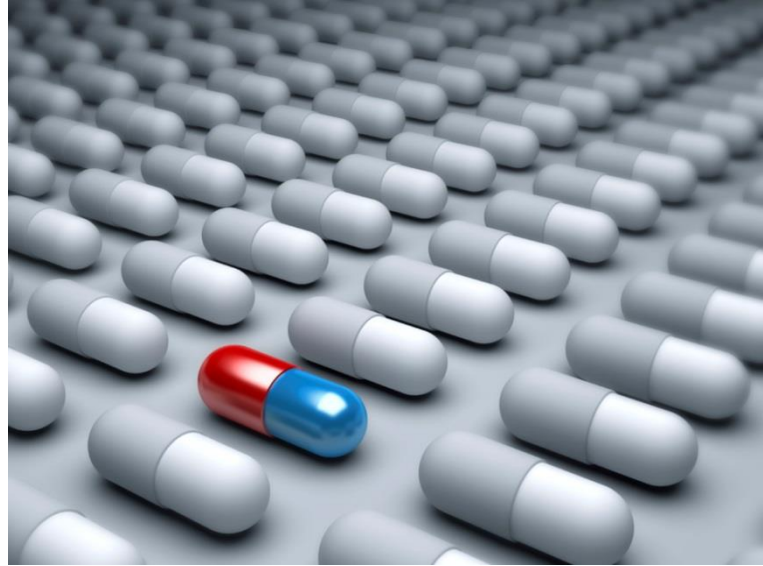
sotax

 **pharmatron**
Dr. Schleuniger®

Dissolution testing automation: Principles and benefits

Romania / Bucharest / October 2016

- The pharmaceutical market challenges
- Some drawbacks of “non-automation”
- Automation principles
- Automation benefits



We all belong to the pharmaceutical market bringing in our dreams and our fears...



...therefore the pharmaceutical market is tempting to harmonize regulation constraints

Data integrity

Biowaver

Guidelines

Inspection



21 CFR part 11



Methods
Databases

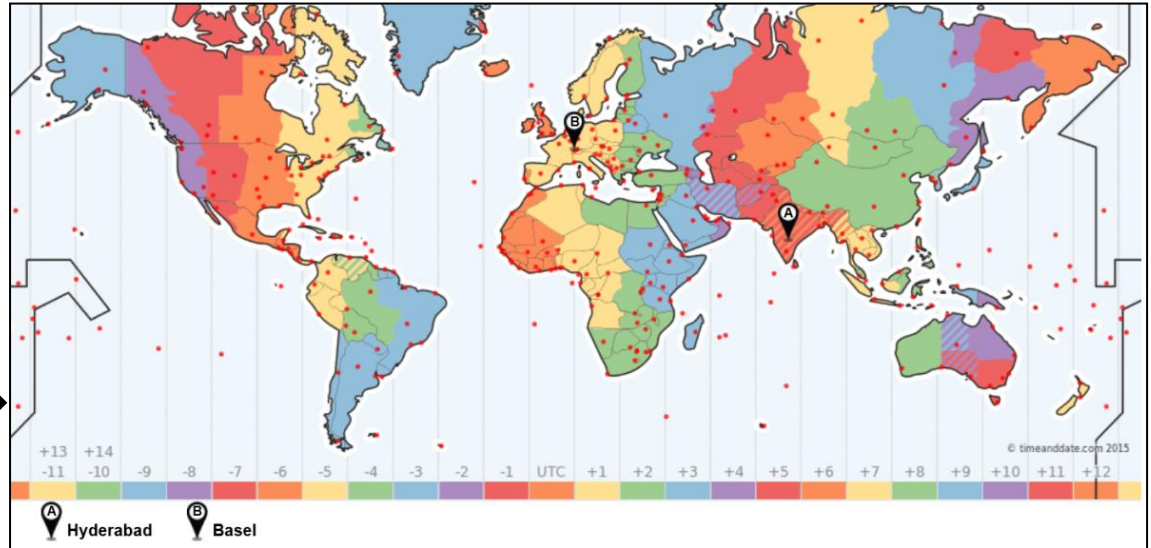
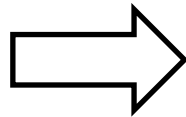


Moving geographically with markets and their associated cost pressures



R&D

QC



Keeping sustainable tools with objectivity

- The most efficient
- The most advanced
- The less risky

Dear Mr. FDA, we have
decided to go back to
manual sampling

- The easier to justify





Unemployment

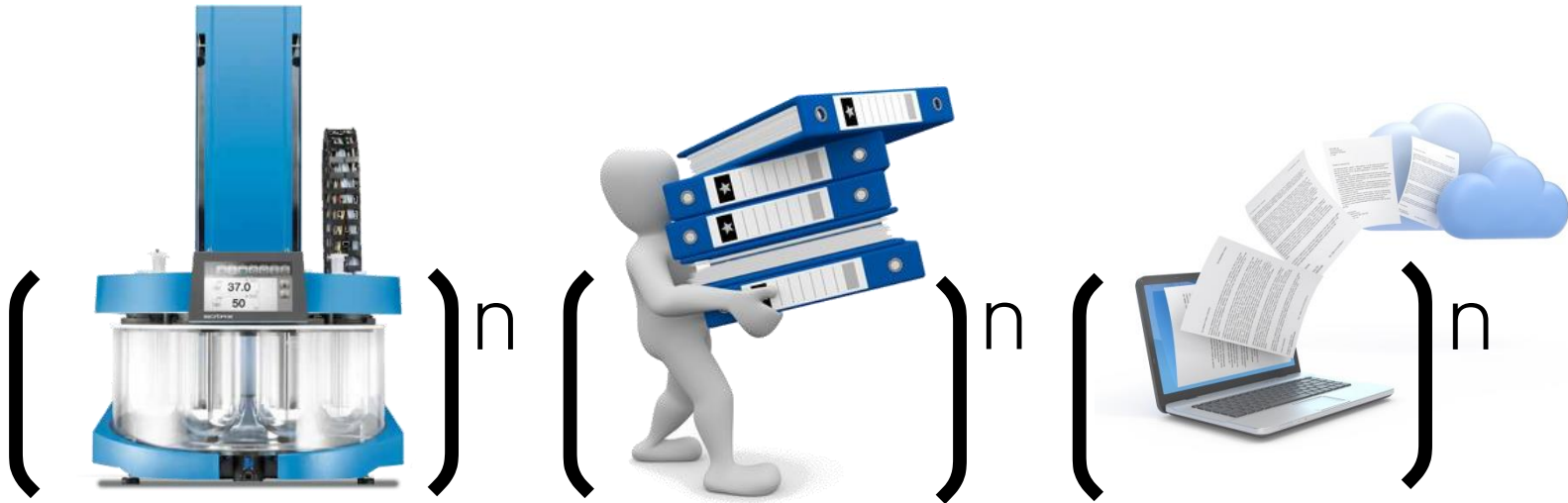


Health

- Challenges of the pharmaceutical market
- **Some drawbacks of “non-automation”**
- Automation principles
- Automation benefits



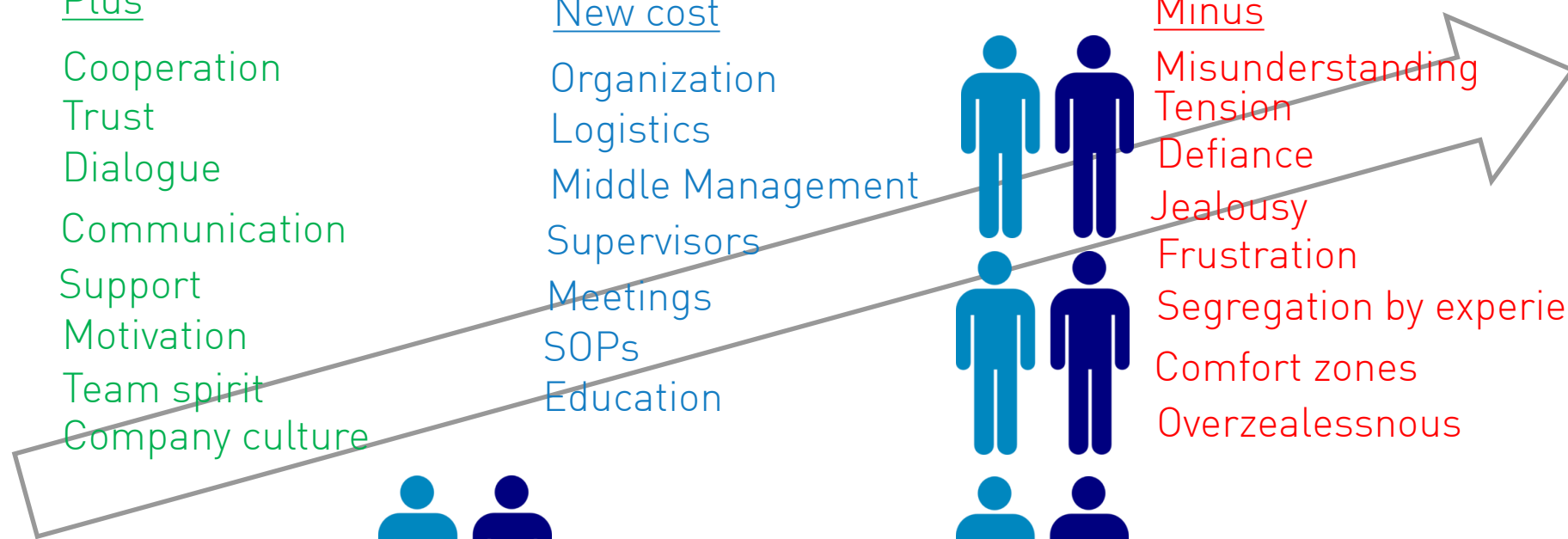
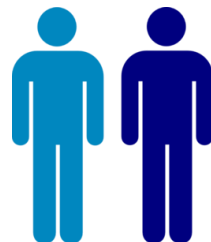
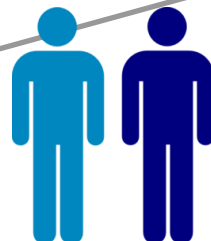
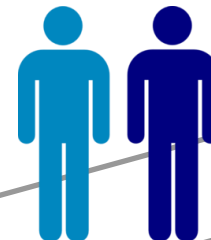
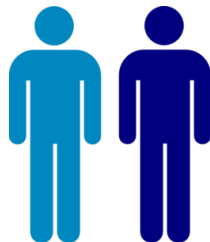
- Multiplication of instruments = multiplication of documents, certificates, procedures, qualification work.



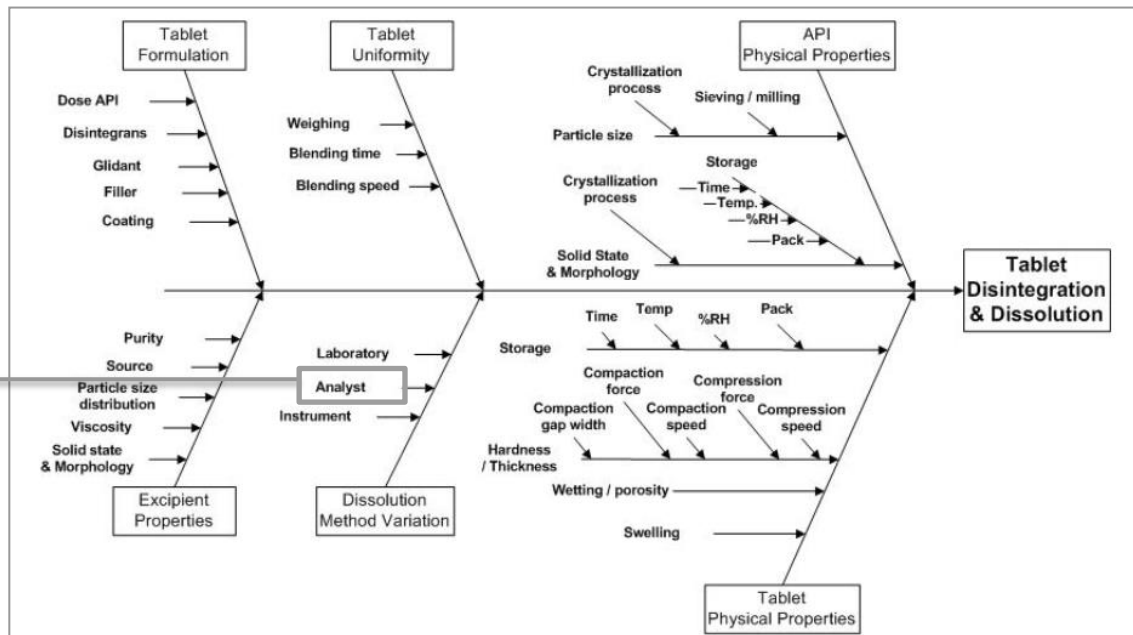
Plus
Cooperation
Trust
Dialogue
Communication
Support
Motivation
Team spirit
Company culture

New cost
Organization
Logistics
Middle Management
Supervisors
Meetings
SOPs
Education

Minus
Misunderstanding
Tension
Defiance
Jealousy
Frustration
Segregation by experience
Comfort zones
Overzealousness

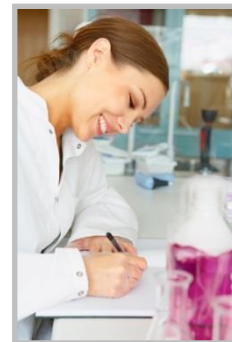


A small part of a big process



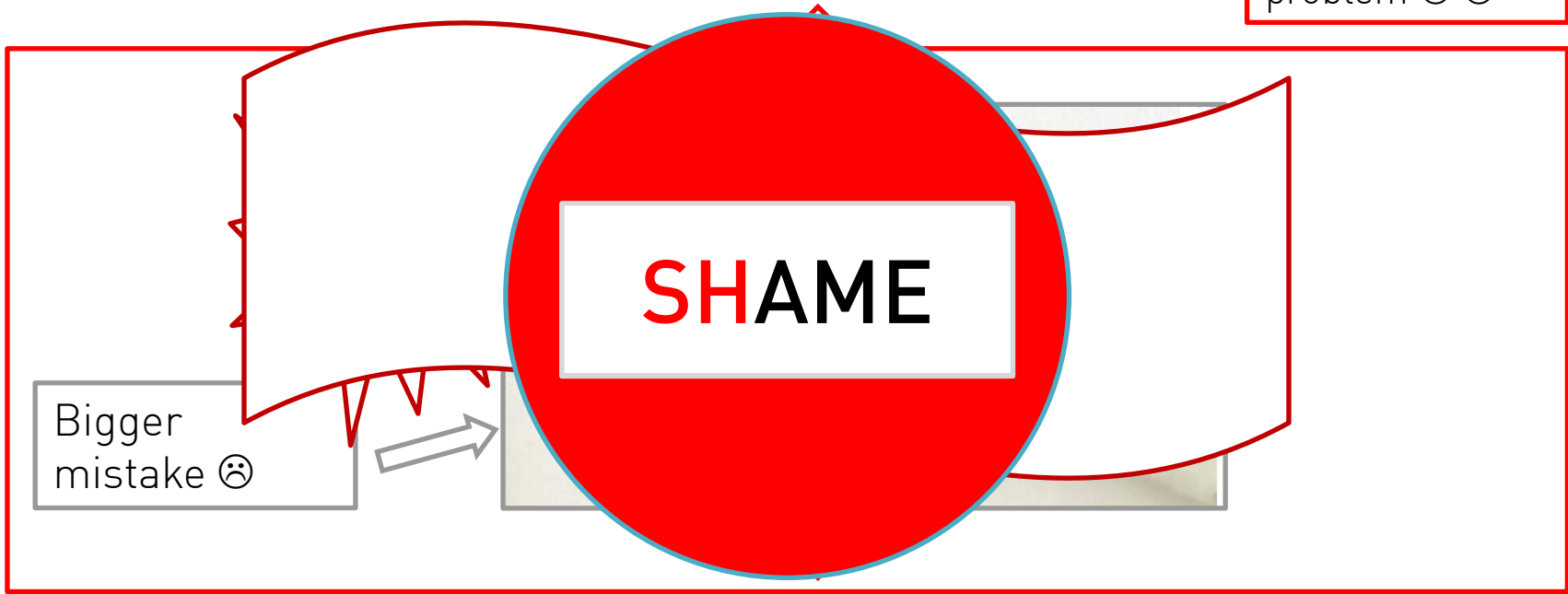
Difficulty of multi-tasking

- Can the analyst always, at every step, anticipate, act, understand AND document everything SIMULTANEOUSLY ?



- Chain of responsibilities

Management problem ☹ ☹



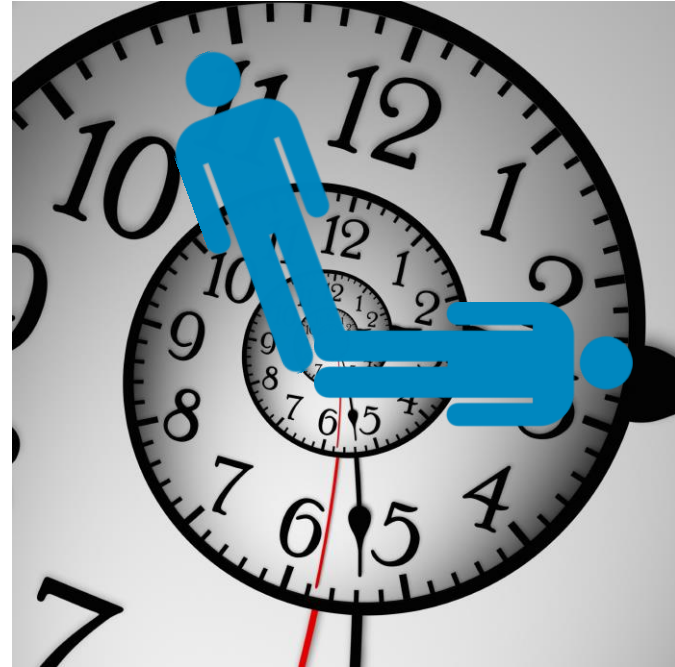
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- **Automation principles**
- Automation benefits

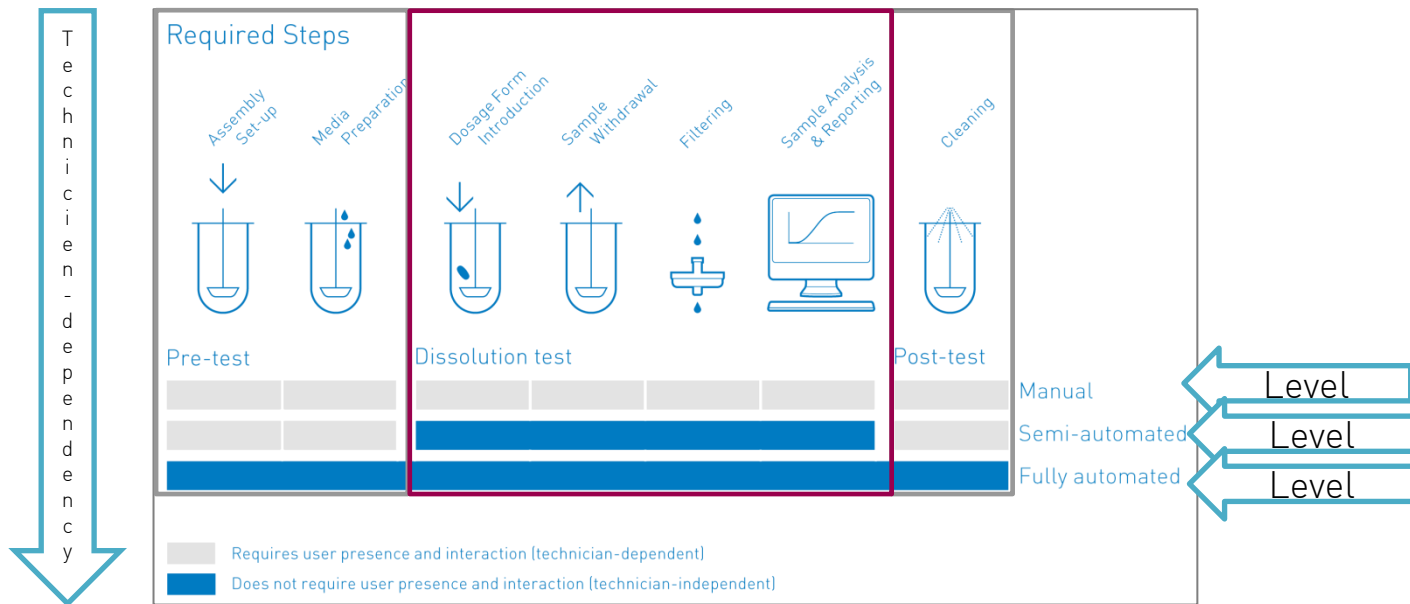


When do technicians lose time?

- Is it overall linear?
- No stress effect ?
- What remains to be done at rush hour?
- Test is the competition, rest is preparation and analysis

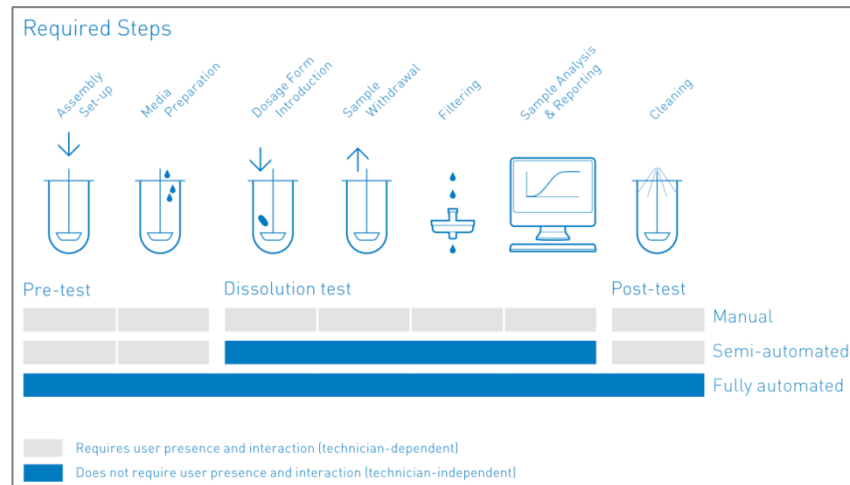
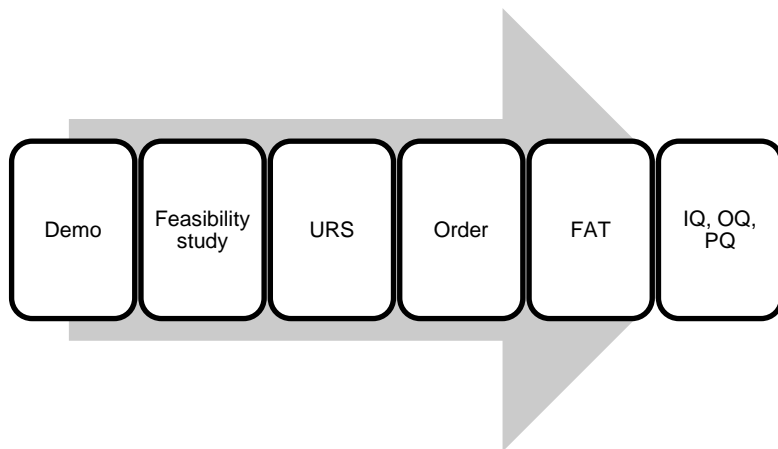
Preparing the ROI





Cutting the whole implementation process

- Risk is segregated
- Correlates with multiple signatures requirement
- Favors projection and planification



Mastering automation

- Detecting potential artefacts
- Avoiding technology per se
- Automating with priorities
- Easy methods or complicated methods first?
- Outsourcing method transfer?
- Automation should bring extra features/parameters which are MEANINGFUL



The Dissolution Procedure Development and Validation

Understanding automation

AUTOMATION

4.1 Medium Preparation

4.2 Sample Introduction and Timing

4.3 Sampling and Filtration

4.4 Cleaning

4.5 Operating Software and Computation of Results

4.6 Common Deviations from the Compendia Procedures That May Require Validation

4. AUTOMATION

Automated dissolution systems may be configured in various ways and degrees. The elements of test preparation, initiation, sampling and timing, and cleaning all can be automated. Fully automated systems are available, as are systems where individual steps, such as media preparation or sampling, are automated. This section will discuss operational steps that can be automated.

Should you have any questions or comments, please contact Will Brown, Senior Scientific Liaison, at (301-816-8380 or web@usp.org).

- How many APIs?
- Dosage
- Release speed
- Stability of dosage form
- Interface solid/liquid
- Handling
- Positioning
- Cleaning



Method development remains the key

- The method anticipates the scale-up
- It has to be discriminant, robust, informative
- Specification driven (corrective action)
- Automation shall not soften discriminancy



USP Dissolution Methods Database



Specialists in Complex Dosage Form Testing

R&D Services
Routine Analytical Services
Support Services



ROI are based on the type/duration of Methods



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 13 May 2016
2 EMA/232805/2016
3 Committee for Medicinal Products for Human use (CHMP)
4 Committee for Medicinal Products for Veterinary use (CVMP)
5 Quality Working Party (QWP)

6 Reflection paper on the dissolution specification for
7 generic oral immediate release products
8 Draft

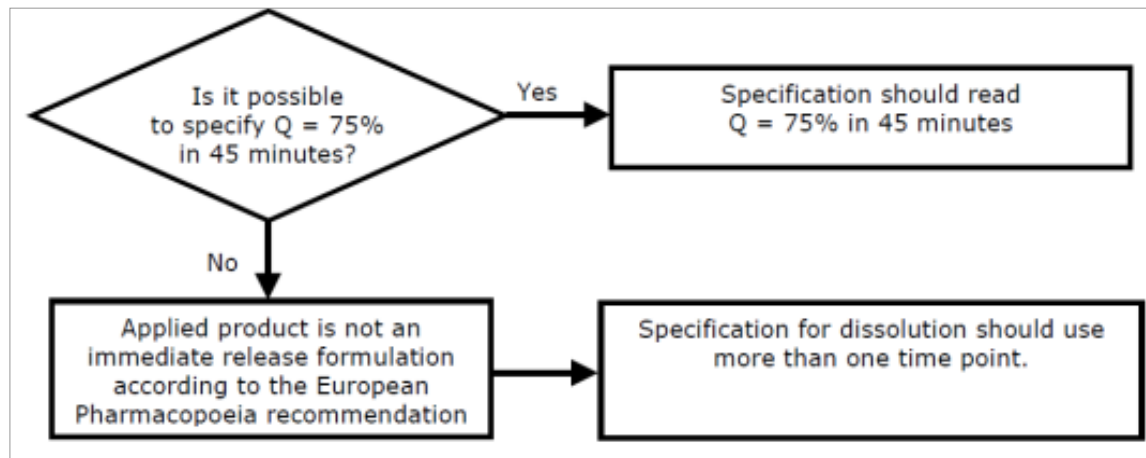
Draft agreed by the QWP	March 2016
Draft adopted by the CHMP for release for consultation	March 2016
Draft adopted by the CVMP for release for consultation	April 2016
Start of public consultation	13 May 2016
End of consultation (deadline for comments)	13 August 2016

9

Comments should be provided using this [template](#). The completed comments form should be sent to QWP@ema.europa.eu

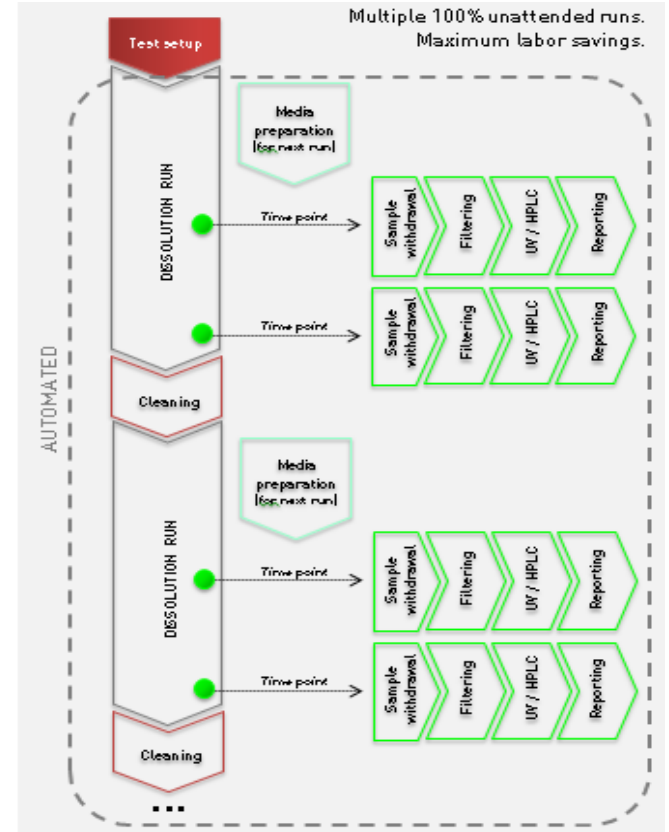
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Keywords	Dissolution specification, Generic, Oral immediate release product
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Optimize inter-test savings

- Inter test time is minimized due to multi tasking
- Tasks perceived as tedious are eliminated
- Users can move to other tasks: documentation, data analysis
- Preparation is essential, traceability starts with the test
- Handling of assembly parts is also critical



Data management reinforcement



V1_MM_061016



MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015

Introduction:

Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality. This document provides MHRA guidance on GMP data integrity expectations for the pharmaceutical industry. This guidance is intended to complement existing EU GMP relating to active substances and dosage forms, and should be read in conjunction with national medicines

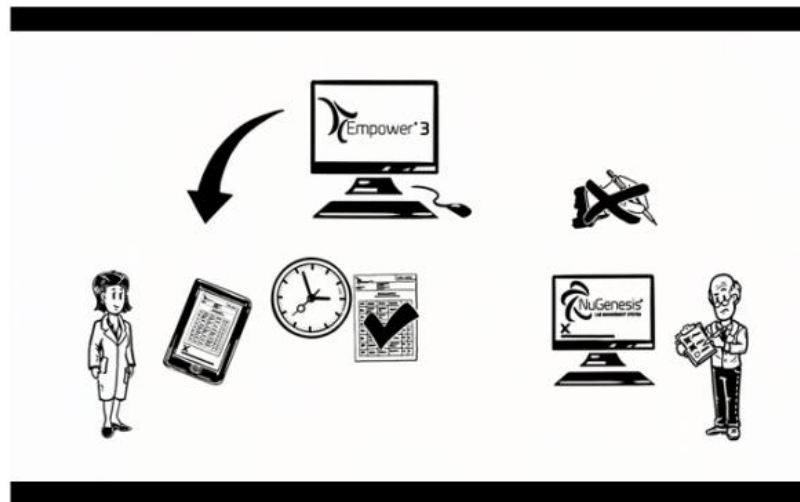
Data Integrity and Compliance With CGMP Guidance for Industry

21 CFR part 11

Attributable, Legible, Contemporaneous, Original, Accurate, complete, consistent, enduring, available

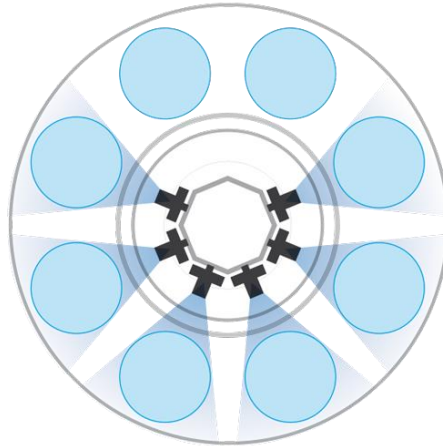
What is your department/company goal?

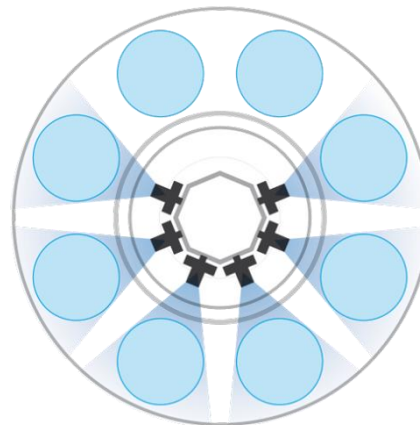
- Quality
- Clarity
- Transparency
- Library
- Support (for other locations)
- Customer or Supplier ?
- Who is the reader?
- Protection of know-how



Experience info or data integrity?

- Video monitoring
- Critical parameters...
- What do we want to know ?
- To see?
- To record?
- Scrutinized or **unattended**?





2.4.2 OBSERVATIONS

Visual observations and recordings of product dissolution and disintegration behavior are useful because dissolution and disintegration patterns can be indicative of variables in the formulation or manufacturing process. For visual observation, proper lighting (with appropriate consideration of photo-degradation) of the vessel contents and clear visibility in the bath are essential. Documenting observations by drawing sketches and taking photographs or videos can be instructive and helpful for those who are not able to observe the real-time dissolution test. Observations are especially useful during method development and formulation optimization. It is important to record observations of all six vessels to determine if the observation is seen in all six vessels, or just a few. If the test is performed to assist with formulation development, provide any unique observations to the formulator. Examples of typical observations include, but are not limited to, the following:

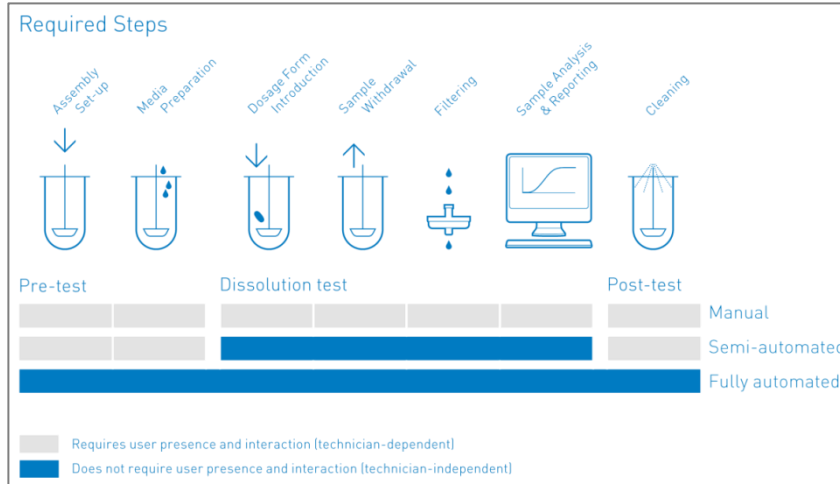
TRACEABILITY: that also includes Qualification processes !



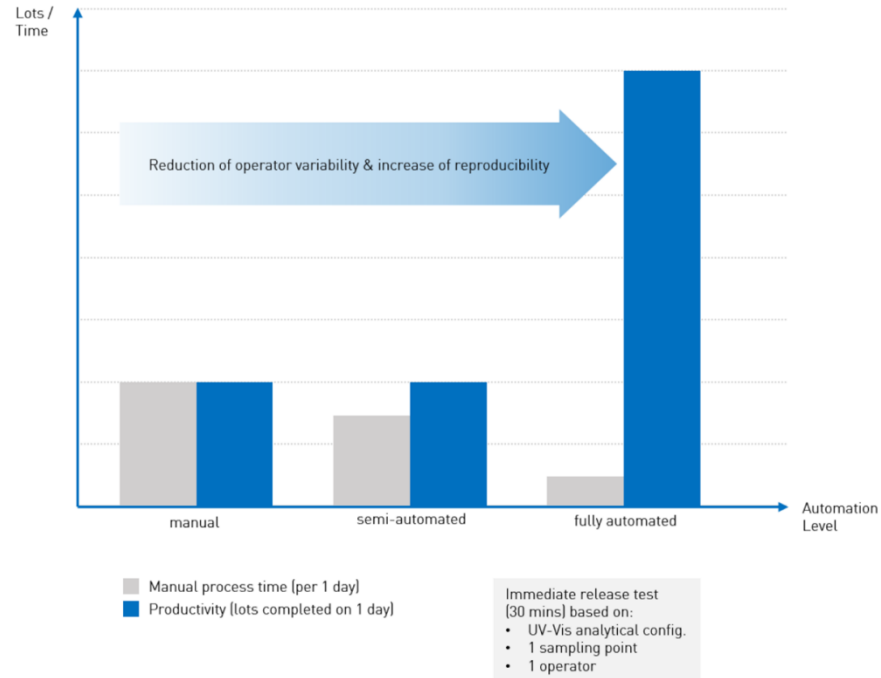
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Test after test after test...



More batches (increases with IR products)



Qualitative changes

Although difficult to quantify and therefore not usually included in traditional ROI calculations, qualitative changes can be as, if not more important in evaluating the benefit of an automated system. They can impact the achievement of organizational goals. The qualitative change factors evaluated using this method are:

- Quality: *Improved end product quality. The "product" may be data, a purified compound, a cell culture, etc.*
- Safety: *Isolating people from hazards or isolating the process from hazards or contamination.*
- Procedure Enhancement: *A resulting end product with attributes that exceed what was produced or possible to produce manually. This could include such examples as: 1) Increased density or resolution of data; 2) Evaluation of more experimental parameters; 3) Conducting a process is manually impractical, such as creating high-density microarrays.*
- Audit trail: *A permanent, computer-generated detailed record of process events and results.*
- More timely decisions: *Improved availability or interpretability of process results leading to quicker decisions.*
- Flexibility: *The retention of manipulative skills (in the automation) across staff changes and across labs. The ability to rotate through processes/procedures with no manipulative relearning.*

From Steven D.Hamilton, Hamilton Consulting group

Adding value (quality and technicity) to a job does protect it!

- Cheaper has a limit, what will be next?
- Automation business is also creating jobs
- The whole lab/factory/company is or will be connected and will therefore be pulled to automation
- Software calls for automation

Automation benefit: Adding value to users work

Btw: why spending a fortune on data integrity if we take our samples with syringes?!

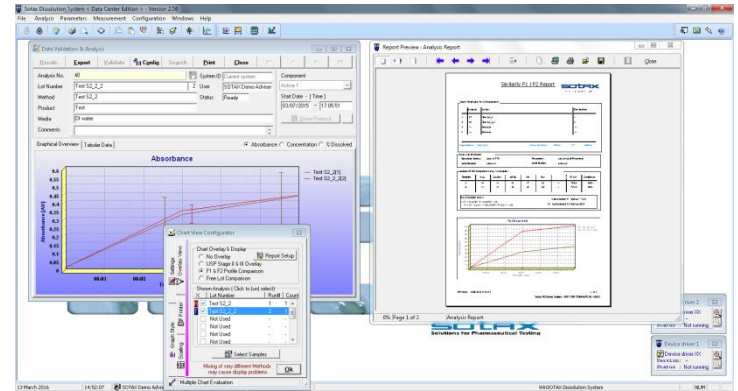


Automation benefit: integration



Double on-line

- Results on the fly!
- Double cell changer: 12 results
- F2 comparison by software



Automation benefit: Integration

Dissolution software: integrated control, calculation, report

Method Definitions

Method Name: InVIO Toplus
 Revision: 1
 Hardware: AT7 near DC/CM line
 CE Method: CE Method
 Created by: SOTAX Demo Date: 05/03/2016

Product Name: Test
 Description:

Component: Active1
Dosage [mg]: 10
Purity [%]: 100

Standard Calibration

Measurement Parameters
 Component: Active1
 Medium: DI water
 Wavelength [nm]: 242
 Pathlength [cm]: 10
 Purity [%]: 100
 Calculation mode: Linear Offset (B. Lambert)

Value Definition: Graphical Display
 Graphical Linear Regression: $Y = a \cdot X + b$ with $a = [100.00000]$, $b = [0.00000]$
 Show Curve: Avg. E11

Data Validation & Analysis

Analysis No.: 4
 Lot Number: 3
 Method: Test
 Product: Test
 Media: DI water

Dissolution % Dissolved

Time [min]	Vessel.1	Vessel.2	Vessel.3	Vessel.4	Vessel.5	Vessel.6	Blank
0	0.0	0.0	0.0	0.0	0.0	0.0	N/A
3	3.7	3.7	3.8	3.8	3.5	3.5	N/A
6	6.1	6.1	6.3	6.2	6.3	6.2	N/A
9	7.8	8.2	8.1	7.8	8.1	8.3	N/A

Time	Lambert	Vessel.1	Vessel.2	Vessel.3	Vessel.4	Vessel.5	Vessel.6	Blank
0	242	0.0275	0.0274	0.0277	0.0279	0.0274	0.0280	N/A
3	242	0.0479	0.0479	0.0475	0.0477	0.0467	0.0473	N/A
6	242	0.0816	0.0816	0.0825	0.0823	0.0823	0.0825	N/A
9	242	0.0714	0.0728	0.0725	0.0714	0.0725	0.0740	N/A

API (molecule)

Absorption spectra of API (molecule)

Calibration curve

Dissolution volume

% Dissolved

Time

Automation benefit: comparison with manufacturing

QC checks Manufacturing Reproducibility...

Give me 6 tablets, I tell you how good you are ;-)



I made 600 while you asked...:-0)



Automation benefit: comparison with manufacturing

QC checks Manufacturing Reproducibility...

I am checking your blockbuster night and day 😊

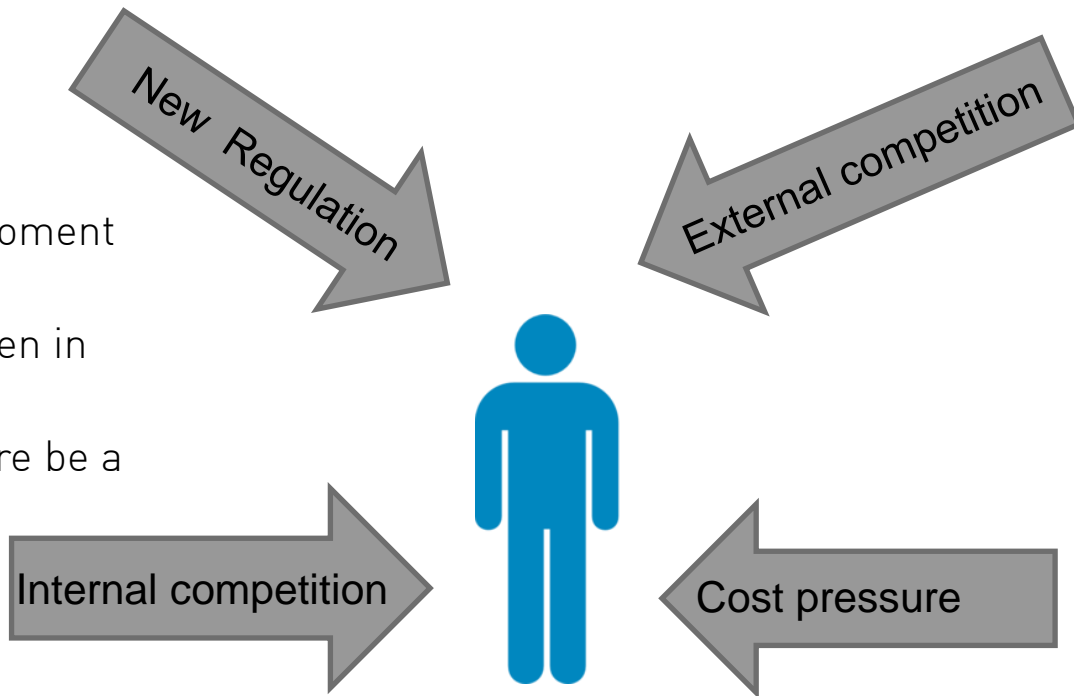


I wish I had wheels too...



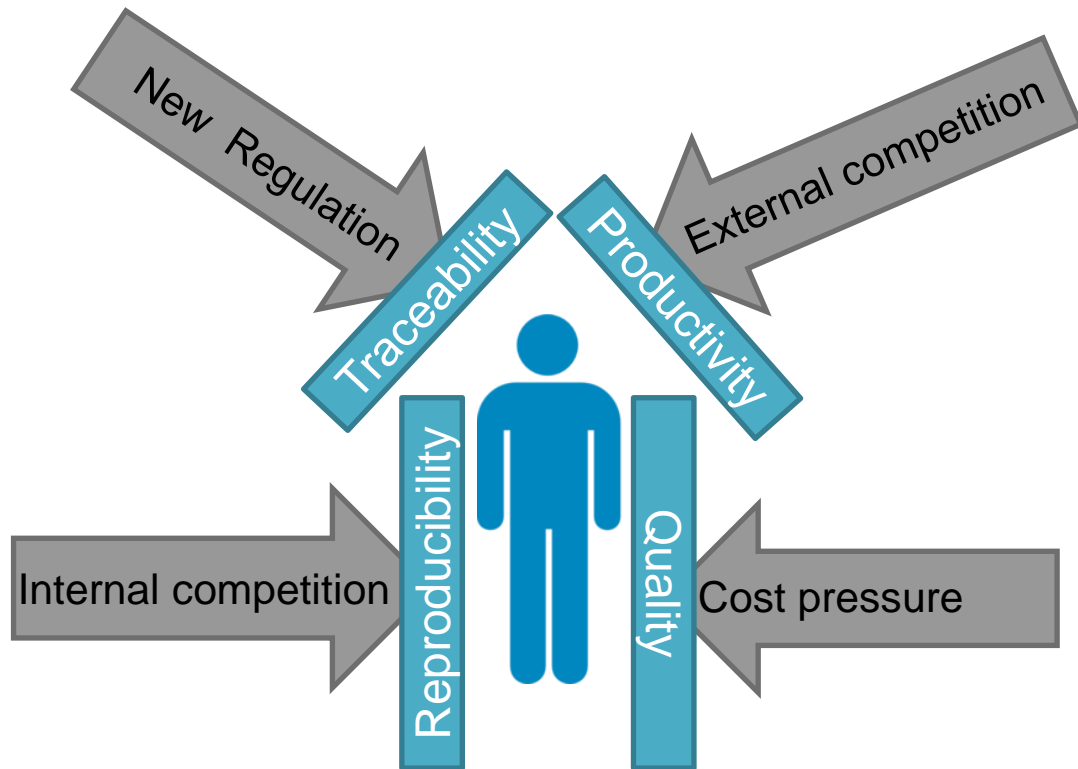
The company context

- In every process or job, there is moment of **evaluation**
- More, faster, better, cheaper is often in the conclusion
- Increasing efficiency shall therefore be a **planned** on-going process



How to increase efficiency

- Improving traceability
- Improving productivity
- Improving reproducibility
- Improving quality



- Automated systems add more value to users jobs. The big pressure on jobs is elsewhere
- Tedious manual processes can always be done elsewhere at a lower price...so what's next?
- Understanding manual / automation is required for scale-ups and method transfers
- Anticipating and leading is always better than accepting
- Quality , reproducibility and traceability are mandatory in the pharmaceutical market

