Glatt Pharmaceutical Services Europe

Ahmad Ghoniem, Pharmacist, Business Development

Organisation und Structure

4 areas of compentence for integrated solutions

Pharmaceutical Services

Process Technology Pharma

Process Technology FFF

Process & Plant Engineering

Pharmaceutical Services

Sites

Glatt GmbH
Binzen / Germany

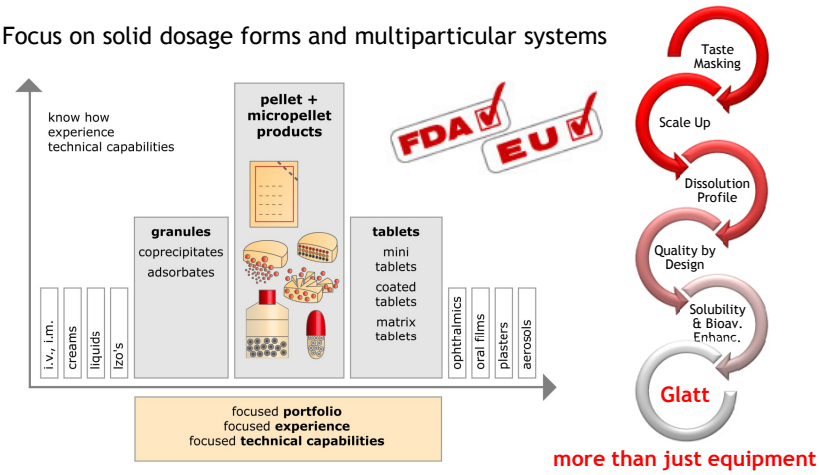
established in 1997
German / EU approval in 1998
FDA approved since 2006
approved for controlled substances

Glatt Air Techniques Ltd.
Ramsey, New Jersey / USA

established in 1973
FDA approved since 1975
approved for
controlled substances

Pharmaceutical Services

Focus on solid dosage forms and multiparticular systems

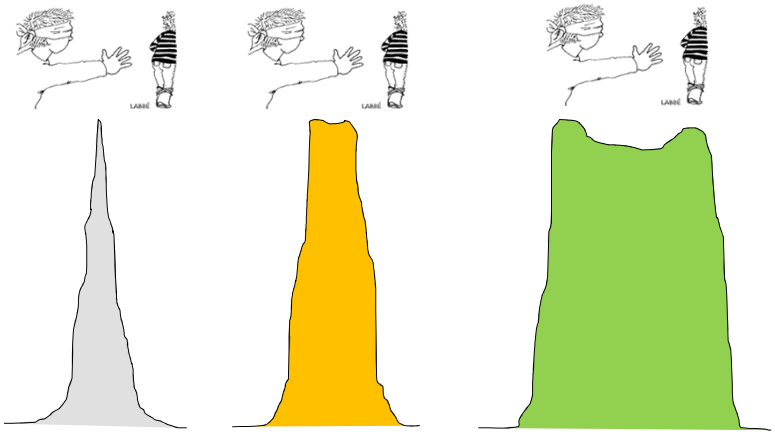


more than just equipment

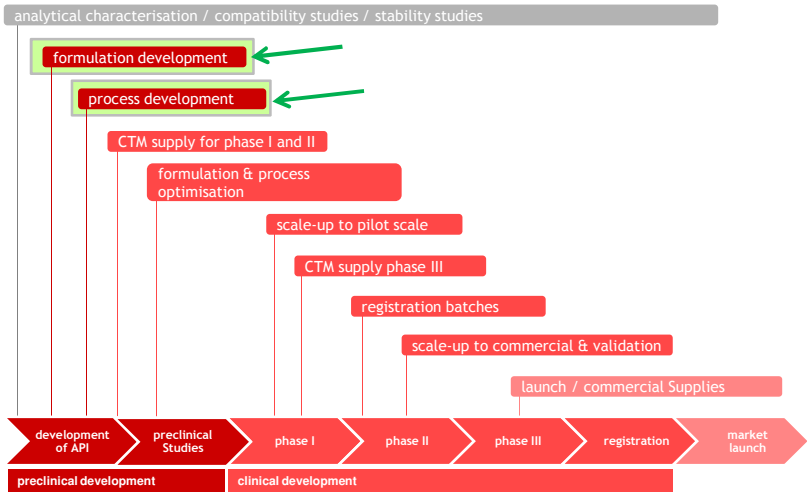
Glatt. Integrated Process Solutions.

DoE, QbD, DS, process validation … ??

Where would you play hide and seek?



From development to commercialization



Process Validation Approach

Traditional **Process Development and Validation :**

✓develop

✓scale up to pilot

✓produce CTM

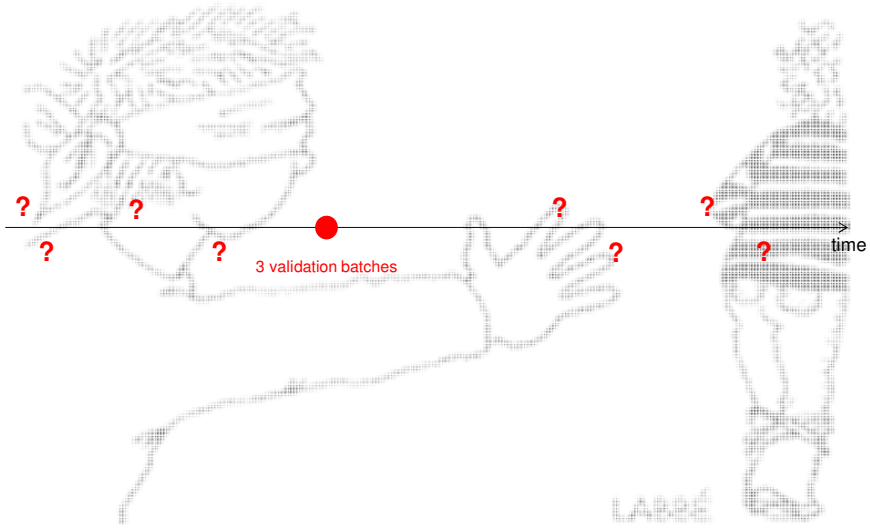
✓pass biostudy

✓produce registration batches / 3 validation batches

→ manufacture for commercial (sometimes: try to manufacture …)

→ **process robustness / ranges / limitations are rarely investigated**

Classical Approach



Development with a plan

Don‘t develop and produce based on random principle:

- **Quality must be planned**
- **Development must be planned**

Quality by Design: Planned development including risk assessment

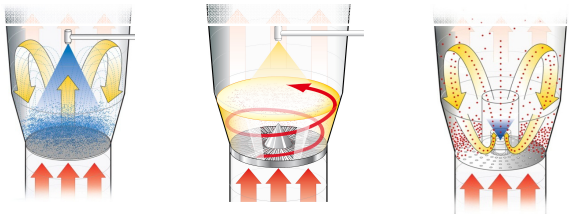
- how to select the most feasible / most acceptable formulation and technology ?
- are the excipients compatible with the API ?
- which binder quality / quantity is required in order to provide a robust granule?
- can the preferred binder be used for pediatric medicines as well?

Formulation

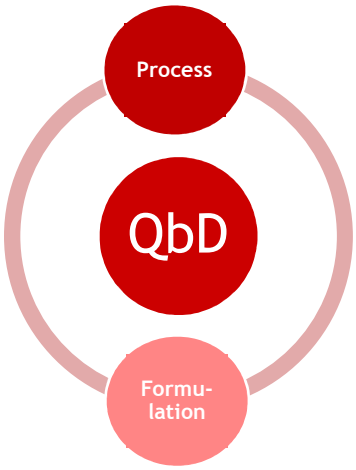
Quality by Design: Planned development including risk assessment

- Which process is most feasible for drug layering on starter beads?
- Which parameters and equipment configurations do we have to investigate in some detail?
- Which process parameters will provide a stable and reproducibole process and a reproducible product quality?

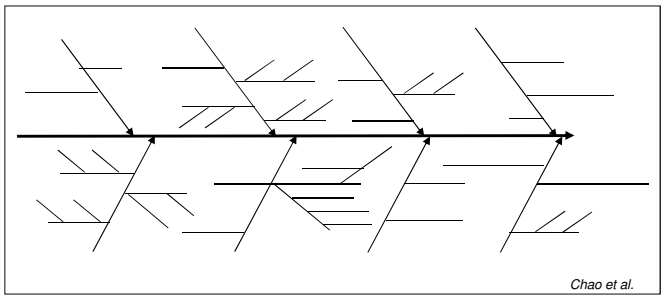
Process



QbD Approaches at Glatt Pharmaceutical Services



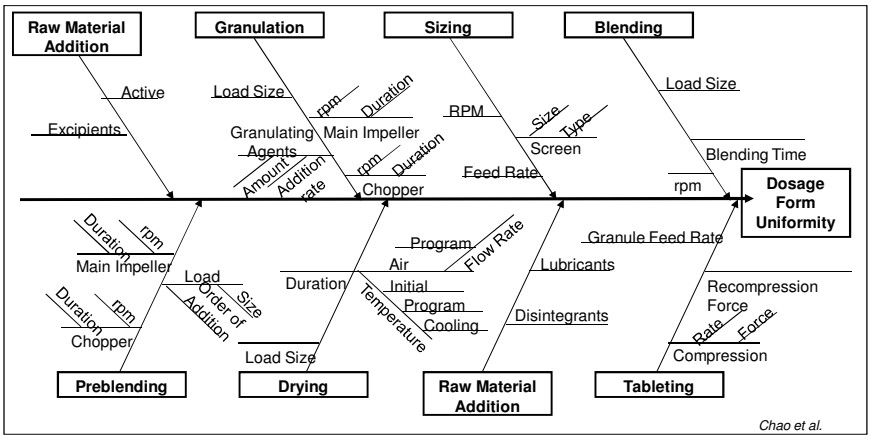
Risk assessment for a manufacturing process



- description of formulation and process
- identification / analysis / evaluation of risk for every parameter
- quantification of risk (risk priority number)
- probability / severity / detectability of risk

→ definition of parameters relevant for product quality

Risk assessment for a manufacturing process



Planned development

Quality by Design (QbD)

CONCEPT
the overall development plan

Design of Experiments (DoE)

IMPLEMENTATION
experimental plan

- plan the experiments for different processing steps
- **define the parameters to be tested**
- link the important parameters following risk assessment
- perform the experiments applying defined parameters / ranges

- do not allow the operator to **adapt parameters**

→ result: **COMPREHENSIVE!**

Planned development

Quality by Design (QbD)

Design of Experiments (DoE)

- Which parameters are important for the process and for the product quality ?
- Why are they important ?
- What happens when we chose the wrong parameter ranges ?

For that we need:
preliminary experiments in order to find out with which parameters a process works basically without a total crash?

→ only experiments which can be finalised without interruption can be evaluated in a DoE

Planned development

Design of Experiments (DoE)

We (Glatt Pharmaceutical Services) perform a DoE

- with 1 defined formulation
- with 1 defined processing step (e.g. granulation, drug layering, coating …)
- in order to optimize 1 processing step

→ We find processing parameters for

- a safe process
- a reproducible process
- a reproducible product quality

} quality

- a fast as possible process

} cost

Planned development

Quality by Design (QbD)

↓

Design of Experiments (DoE)

↓

Design Space (DS)
(when we did good development work …)

CONCEPT
the overall development plan

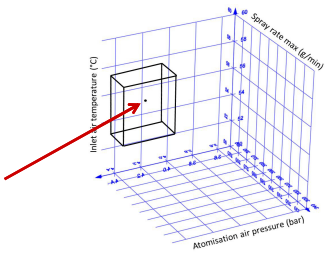
IMPLEMENTATION
experimental plan

OUTCOME
Robustness: the set and range of parameters in which a process works for sure

Design space

- robust formulations and processes for a robust production
- understand a process (QbD)
- find the „green“ robust zone of feasible process parameters

→ **reproducible product quality in small and full scale**



With and without QbD

Before:

Process Validation

Guidance for Industry
Process Validation: General Principles and Practices
(for commercial manufacturing)

FDA
January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

Widely applied process validation strategy today:

- … fast and cheap development incl scale up

- … 3 commercial batches
- … that‘s it
- … as less efforts and expenses as possible
- … hope that it will work …

Process Validation - basic considerations

Validation

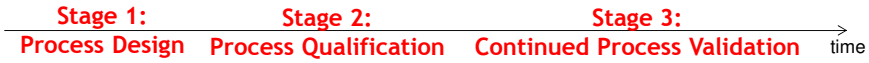
- is a typical GMP element in pharmaceutical field
- should legitimize a process / method
- is a documented proof of confidence

Traditional process validation:

- reproduction of the normal process (3 lots)
- the insufficiency of this approach has been evident due to lack of sound scientific base:
  - lack of legitimation of the selected processing parameters
  - lack of legitimation of the selected inprocess controls
  - lack of legitimation of the selected process limits
  - no discussion of process variability
  - role of risk assessment rarely appreciated

With and without QbD

Now:



Process Validation Definition/ FDA Draft Guidance to Industry 2011

Process Validation

is defined as the collection and evaluation of data from the process design stage throughout production, which establishes scientific evidence that a process is capable fo consistently delivering quality products.

Associated Terms:

- Quality by Design
- Process Design
- Design Space
- Process Analytical Technology (PAT)
- Product Life Cycle
- Process Life Cycle Validation
- Process Legitimation
- Process Parameters
- Process Ranges / Limits

Process Validation Approach

Guidance for Industry
Process Validation: General Principles and Practices
(for commercial manufacturing)

FDA
January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

- linking of **„validation“** with a **„product life cycle concept“**
- the guidance supports **process improvement and innovation** through **sound science**

Process Validation Approach (FDA Guidance for Industry 2011)

3 phases of process validation

Phase 1: **Process Design**

The commercial process is defined during this stage based on knowledge gained through development and scale up activities.

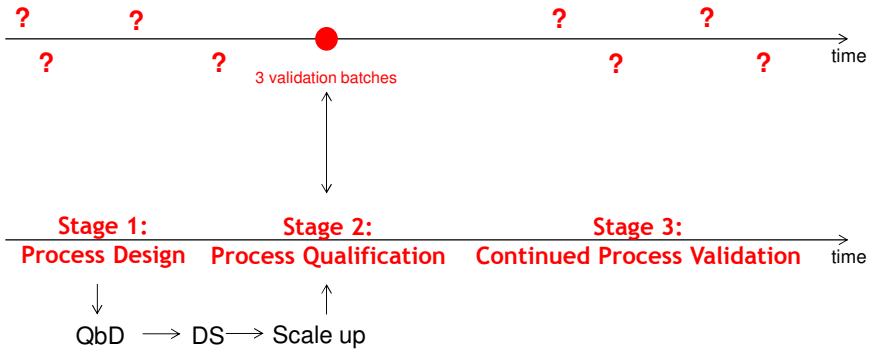
Phase 2: **Process Qualification**

During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.

Phase 3: **Continued Process Verification**

Ongoing assurance is gained during routine production that the process remains in a state of control.

Old Vs. New

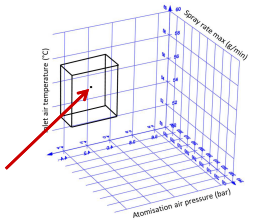


Process Validation - Design Space

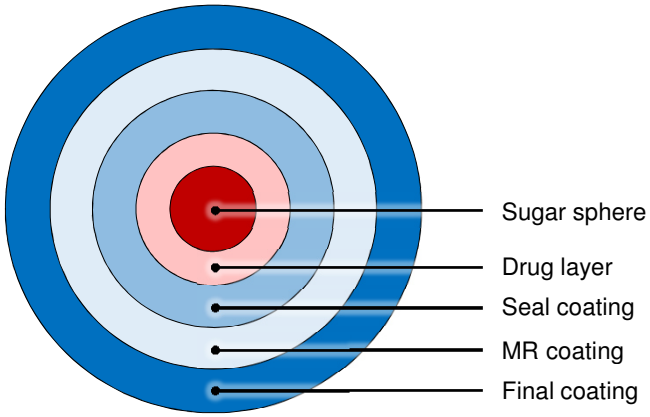
Design Space (acc. to ICH Q8)

„The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality."

- working **within** Design Space (multidimensional region) must not generally considered as a change
- movement **out of** Design Space is a change



Case Study DoE 3: Process optimisation of a Modified Release Coatings



DoE 3: modified release Coating / DoE

▪ Eudragit RL 30 D	…polymer
▪ Eudragit RS 30 D	…polymer
▪ Triethylcitrate	…plastisizer
▪ Talc (micronised)	…antitacking
▪ Water	…

DoE 3: process optimisation of a modified release coating

Configuration of Wurster fluidized bed unit

- position of Wurster column
- inlet air distribution plate
- diameter of spray nozzle insert

} defined not part of DoE

Selected parameters for process optimisation DoE:

- inlet air volume
- inlet air temperature
- spray rate / product temperature

} product humidity process velocity

- atomization air pressure

} droplet size

DoE 3: Process optimisation of a modified release coating

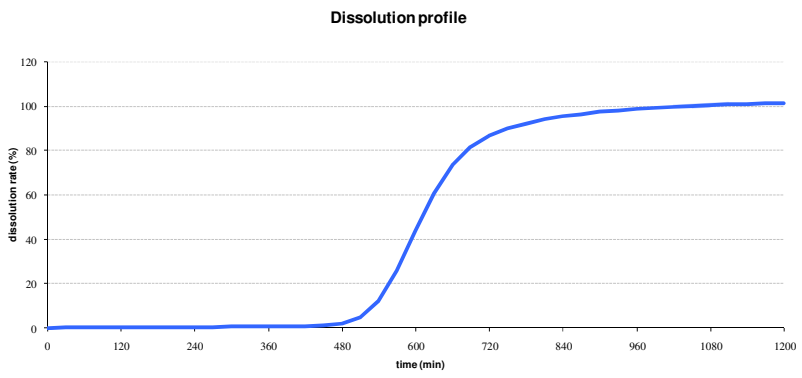
Eletriptan CR Pellets

Process Parameters of Experimental Design

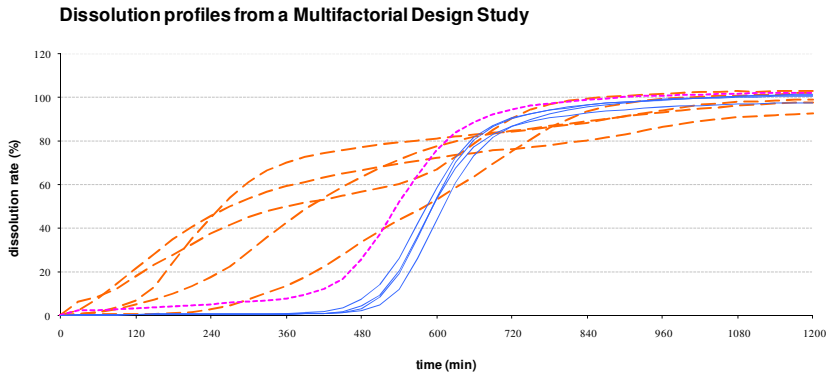
No. of Factor	Factor (Short name)	Factor	Factor	Niveaus		
				low	medium	high
1	V	inletair vol	Inlet air volume	110	130	150
2	AP	at.air press	atomisation air pressure	1,4	2	2,6
3	PT	product temp	product temperature	27	30	33
4	IT	inletairtemp	inlet air temperature	45	55	65

Process Parameters Exp. Design-1.xls
Dr. Norbert Pöllinger, 6.11.2001

DoE 3: Process optimisation of a modified release coating



DoE 3: in vitro dissolution profiles from DoE



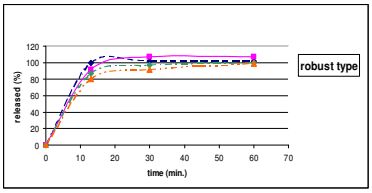
… modern cost-efficient production technologies …

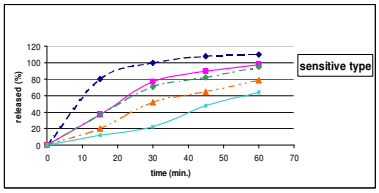
An optimized product output can be achieved with

- no failed batches
- no borderline batches / no retesting
- no reprocessing
- fast and reproducible processes
- high yields

reliable

- function of processing equipment
- maintenance and services
- cleaning concepts



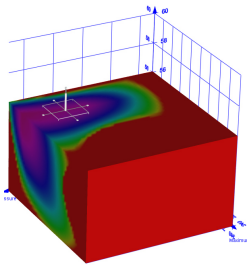


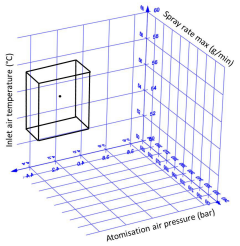
… modern cost-efficient production technologies …

Basis for cost-efficiency ?

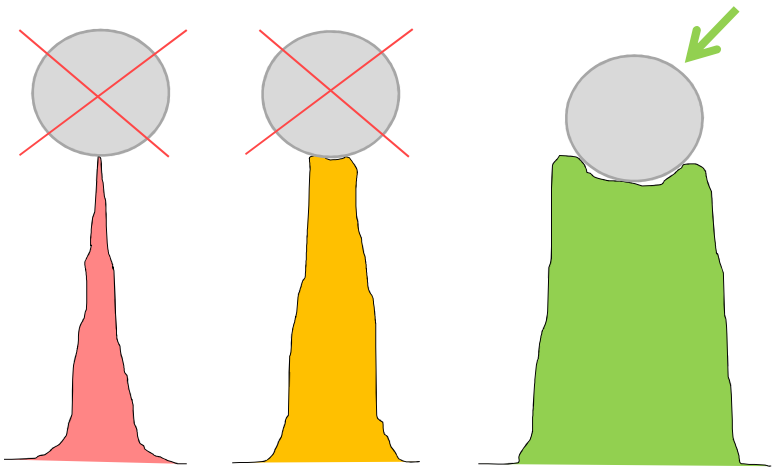
- robust formulations and processes for robust production
- understanding the processes (QbD)

→ **reproducible product quality** from small to commercial scale





Process robustness



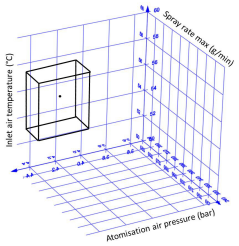
Summary

→ reproducible product quality in small and large scale applying a defined range of processing parameters = **Design Space (DS)**

→ elaborated with the **Design of Experiments (DoE)** tool

→ this is **Quality by Design (QbD)** !

→ providing a state to the art **Process Validation**



Glatt - more than equipment

from **formulation development** to
commercial processes incl **process equipment**

Glatt Pharmaceutical Services: Contacts

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