#sharing challenges
and solutions in practice

Ensuring Data Integrity in the daily Practice of Pharmaceutical Manufacturing

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GMP / FDA Compliance Conference

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Content

- Introduction to Vetter as a CDMO for Fill & Finish
- Data Management: Basics for Data Assessment
- Examples, Challenges, Risk Acceptance

Introduction

Vetter – Expertise for Aseptic Filling and Packaging of Injectables

Privately owned CDMO with no products of its own | Headquarters in Germany | Commercial Manufacturing in Germany | Clinical sites in the USA and Austria | Sales offices in USA, Singapore, Japan, South Korea and China

Experience with global regulatory authorities

Scalable processes to handle small batch sizes to large commercial volumes:
20 cleanrooms | 9 packaging/assembly lines | additional semi-automated packaging equipment

CLINICAL DEVELOPMENT

- Specialized clinical facilities for filling of vials (liquid and lyophilized) and syringes
- Services: Process design | Feasibility and stability studies | Technical & clinical batches | Regulatory Support | Scale-up for Phase III
- 70% of customers with clinical projects have less than 200 employees

COMMCERCIAL MANUFACTURING

- Integration of know-how, resources and technologies to deliver high quality and solve supply chain challenges
- Services: Fill and Finish | Analytical Services | Regulatory Support | Secondary Packaging | Product Lifecycle Management
- 11 product launches in 2021

> 40
years of experience

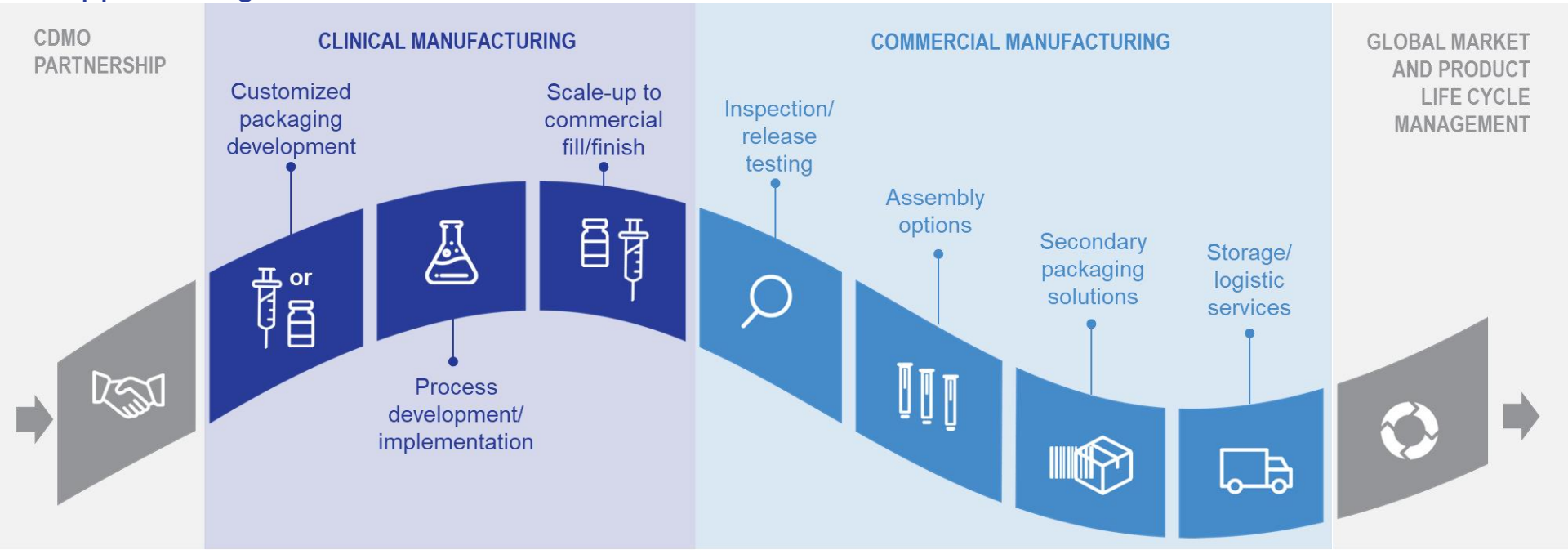
80%
of active projects are biologics

840M €
Sales 2021

5,700
Employees worldwide

Introduction

Support along the value chain



Basics for Data Assessment

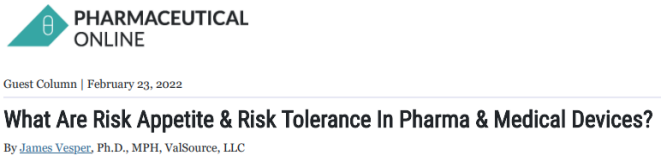
Regulatory requirements/expectations (snapshots):

- Data governance system in place, integral part of the quality system (PIC/S)
- Application of a risk based approach: „not all data or processing steps have the same importance to product quality and patient safety“ (PIC/S)
- Assessments in place: documentation/justification of applied procedure (PIC/S)
- Mitigation plans on identified gaps/risks (PIC/S)
- „Audit trail review is similar to assessing cross-outs on paper when reviewing data (…)“ (FDA Q&A)

Basics for Data Assessment

Some thoughts about risk based approach:

Reading recommendation:


PHARMACEUTICAL ONLINE

Guest Column | February 23, 2022

What Are Risk Appetite & Risk Tolerance In Pharma & Medical Devices?

By James Vesper, Ph.D., MPH, ValSource, LLC

- Is data integrity always a black/white decision?
- How much risk-benefit analysis is acceptable?
- Isn`t all of your GMP-data relevant (=critical?)? Where do you set the deviding line?
- What is the risk tolerance in your company?
- What is the risk tolerance of the agency/inspector/customer?
- How much control strategy or system/process robustness can compensate for individual DI „backlogs“

Basics for Data Assessment

Computerized system

- Configuration settings
- User administration
- User roles

System Data

- Login / Logout
- Activities (run, quit….)
- Electronic Signatures

Application Data (Input)

- Measured values (raw data)
- Calculated data and results

Generated Data (Output)

- Meta Data
- Parameters
- Master Data

- Alarms and error messages
- Audit trails
- Meta Data

Master Data

- MBR
- Recipes
- Methods
- Workflows

There is an environment/ process for each computer system…

Basics for Data Assessment

Assessment of all input and output data

Following categories can be defined:

1) System configurations (application-independent)
2) Methods, recipes, master data
3) Application data (input parameters, meta data)
4) Results (output data, processing of data)
5) Messages (alarms, error messages, system messages)

PIC/S gives helpful advice on how to evaluate your data:

1) Data criticality:
   a. influence on quality/release decision
   b. **impact** of the data to product quality or safety
2) Data risk:
   a. **vulnerability** of data to involuntary alteration, deletion, loss or recreation or deliberate falsification
   b. likelihood of **detection** of such actions
   c. factors which can increase risk of data failure include complex, inconsistent processes with open ended and subjective outcomes
   d. evaluate data flows and the methods of generating and processing data, and not just consider IT system functionality or complexity

… reads like an **FMEA**

Examples

System configuration settings

System settings are application-independent

1) They should be under control of only the system administrator (segregation of duty)
2) Changes should be justified and approved by formalized change-process

→ „control strategy“

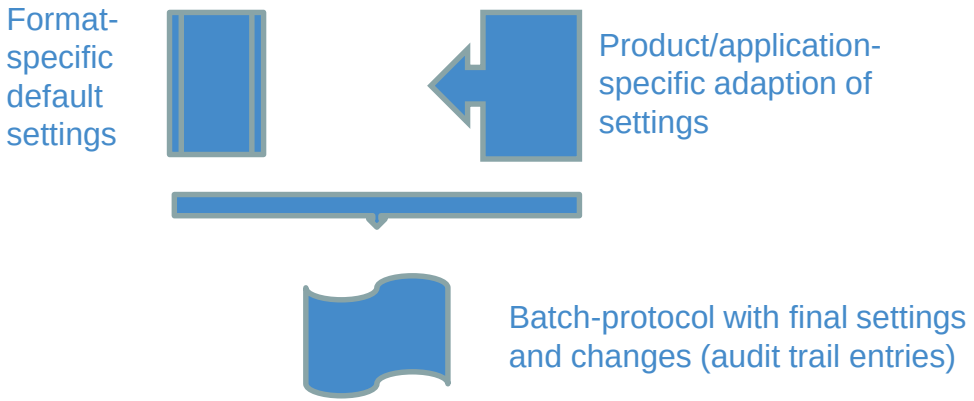
How to review?

- In case they can be changed during application, they must be handled as input parameters and reviewed during data review
- Otherwise a review on an operative level is not necessary (see control strategy)
- During periodic review of the system (or other justified frequency), the configuration should be reviewed; problem:
  - AT-functionality must be given in a way it can be reviewed in a meaningful way
  - Otherwise only a comparison of the current setting against the setting during last qualification is possible: limited effect

Examples

Methods/Recipes/Master Data

1) Not all systems do have the possibility of managing recipes
2) Some systems only have default settings that can be selected but changed before / during application (only adapted settings for e.g. specific formats / products on the filling line)

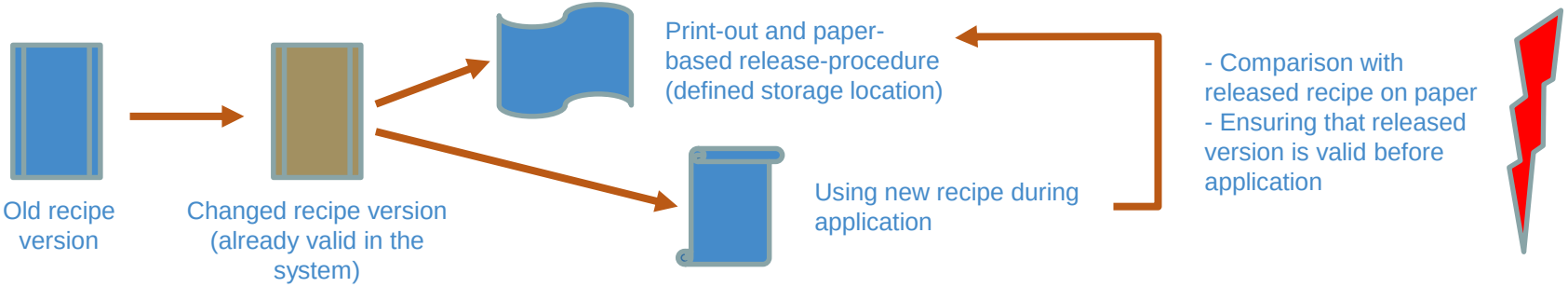


→ to be handled like input parameters

Examples

Methods/Recipes/Master Data

3) Managing recipes should be version-controlled
   - Best case: electronically signed and released, i.e. before each application, it is ensured that you only can choose approved / released recipes
   - But: some applications directly generate a new (valid) version as soon as it is changed & safed
     - No electronic signature and no electronic work flow
     - Print-out and paper-based release process of new recipe version?
     - Comparisation paper-based released version vs. chosen version? → high effort during data review and managing recipes in different systems

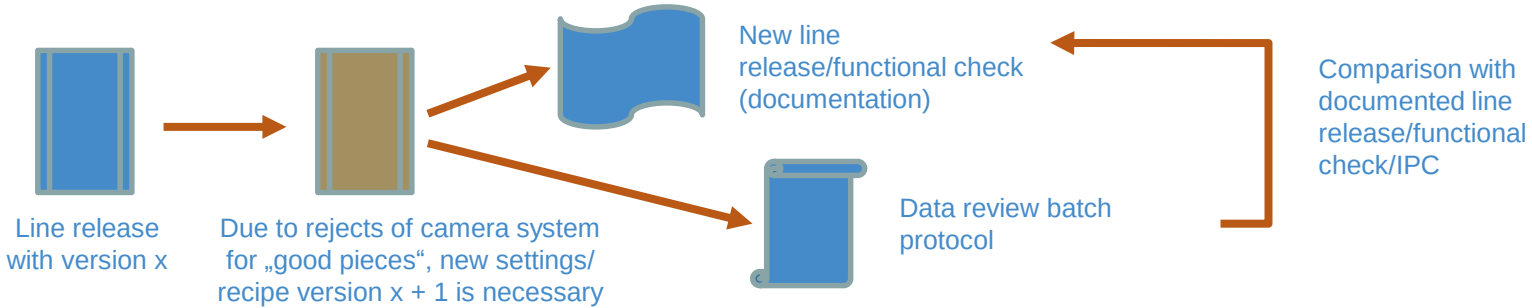


Examples

A	B	B	B	C	D	
"A"	"B"	"B"	"B"	"C"	"D"	.....
a	b		1	1	2	
"a"	"b"	.....	"1"	"1"	"2"	.....

Methods/Recipes/Master Data

3) [cont.] Managing recipes should be version-controlled
   - Camera-recipes (packaging) contain character set files (fonts) for check of imprints
     - Due to variations in packaging materials or printer settings, these files might have to be adapted („learning of character set")
     - Adaptions only allowed for privileged persons (segregation of duty) → new recipe-version without extensive approval work flow!
     - Functional check must follow prior to continuation of packaging (line release)
     - Data review must check for changed recipe versions and performed new line release/functional check



Examples

Application Data

„Audit trail review is similar to assessing cross-outs on paper when reviewing data (…)“ (FDA Q&A)

1) All data necessary to start (input parameter) (→data review)
2) All data that can be changed during application (→audit trail review/combined with data review)
   - It is important for the reviewer to know where the correct data for comparison/review is
   - Documentation of review
   - SOP description necessary, e.g.:

Data object	Check against	Check for
Batch no.	manufacturing instructions	Compliance
Start of production	Batch protocol entry	Plausibility
Set parameter	Manufacturing instructions	Compliance
Alarm message	Documentation of reaction (acknowledgement etc.)	Traceability/Justification
IPC-parameter relevant data	IPC documentation	Compliance/Traceability

Examples

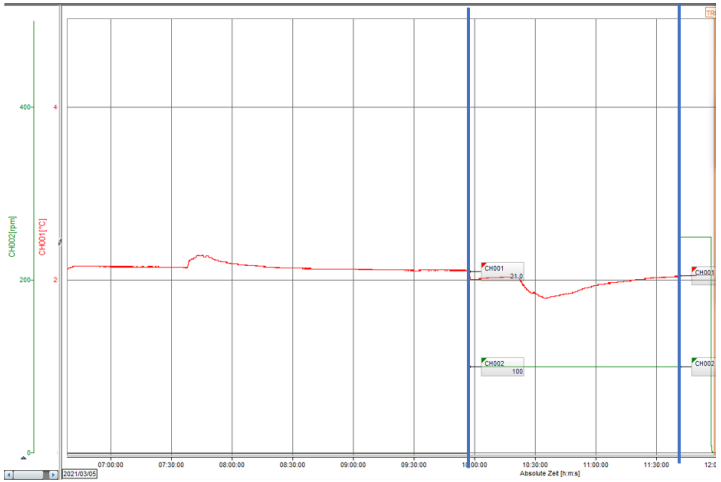
Application Data

3) Definition of quality/decision-relevant data can be very challenging:
   - Really important for quality decision and therefore part of the data review?
   - If relevant, is data on final protocol?
   - Try to fix parameters in the system configuration (no changeability during application)
   - If automated machine reaction is validated, an additional data review for this aspect should be unnecessary (e.g. rejection of units, calibration of pumping system/weighing check by inline-weighing system)
   - Some settings might have to be inactivated depending on application (e.g. no bad piece marking during media fill): audit trail entry!
   - Changing input parameters in e.g. an HMI does not require a justification (no entry of justification possible), i.e. the justification is exercising process control (and IPC documentation must be in line with changed parameter setting)
   - Change of software (functionalities) sometimes necessary

Examples

Results / Output Data

1) In case data is generated, a final protocol should contain all the defined relevant data for review
   - Protocol of an autoclave, freeze dryer etc. (electronic vs. print-out, original data vs. data used for documentation/decision)
   - Protocol of electronic recorders (data acquisition of e.g. water baths, stirring units,…)
2) Operators should have easy access to generated data of recorders
   - Access to file server
   - Easy to read/interpret
   - „Interrupted“ processes e.g. during compounding might generate different files
   - How to document the performed review?
     - ES directly in the recorder application
     - Position in the batch protocol
     - Integration in electronic batch recording



Examples

Results / Output Data

3) 4-eyes-principle in production

- For systems without electronic record capability
- Common understanding: for "critical data" a 4-eyes principle should apply
- Risk assessment necessary

Data risk:

a. **vulnerability** of data to involuntary alteration, deletion, loss or recreation or deliberate falsification

b. likelihood of **detection** of such actions

c. factors which can increase risk of data failure include complex, inconsistent processes with open ended and subjective outcomes

d. evaluate data flows and the methods of generating and processing data, and not just consider IT system functionality or complexity

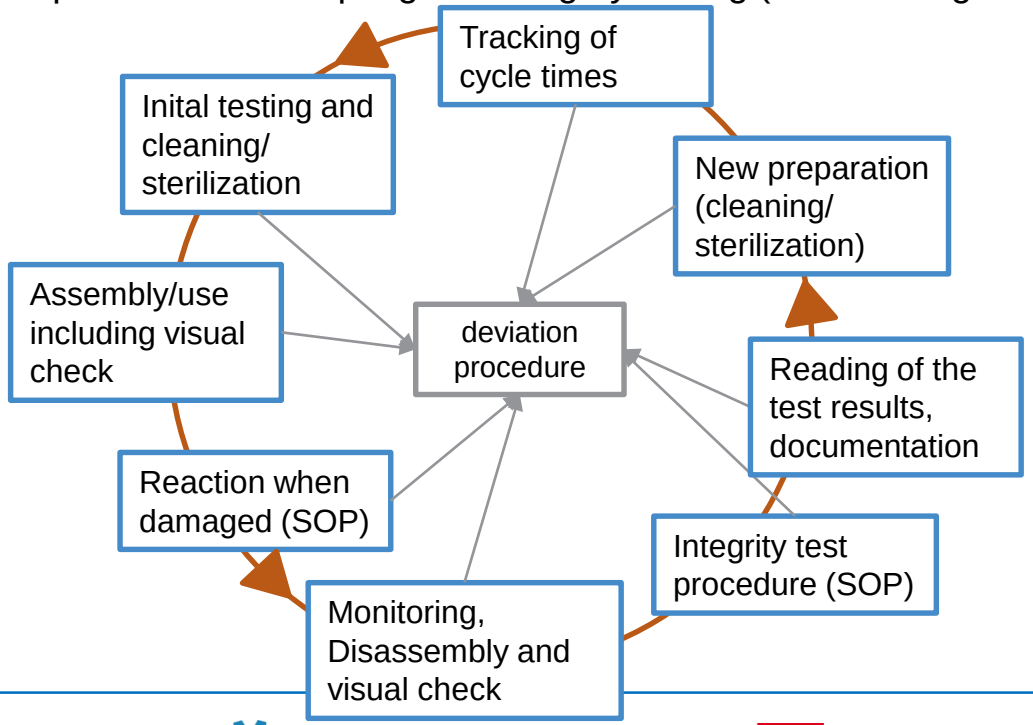
Do we dare to include these aspects in our risk assessment?

Examples

Results / Output Data

3) 4-eyes-principle in production: example glove integrity testing (with reading on the pressure gauge)

- Several check points within the cycle performed by different operators
- Deviation system in place



How critical is reading the test values in this context?

- Defined test procedure (SOP)
- Simple data generation, no calculation/ interpretation
- Easy good/bad decision
- Batch record review (SOP)

Examples

Alarm messages

1) Definition of relevant alarm messages
   - Annoyingly, there is often a multitude of alarm messages or machine messages that cannot be reviewed in a differentiated/sorted manner
   - Machine reactions are an important aspect in evaluation (control strategy „integrated“)
   - Knowledge and information of supplier are very important
   - Part of data review

   Example:

   RABS (Restricted Access Barrier System):

   Alarm message: „(RABS-) door open“ (→if opened, production must be aborted)
   - Machine must stop
   - Verification in four eyes principle
   - Documented justification if message occurred erroneously
   - Part of data review procedure

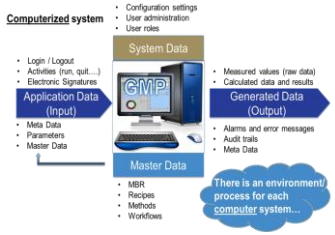
Summary

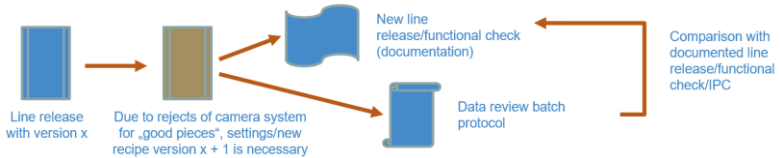
1) All kind of data have to be evaluated, apply risk management

2) Procedures around the right data review process might be complex and still pose gaps → automation and digitalization are important to prevent system breaks

3) Clear definitions for data review necessary: which data, comparison against what

4) How much risk can be accepted, especially when the process is not fully automated/digitalized





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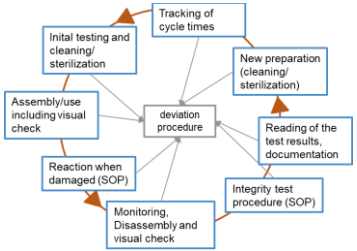

Thank you for your attention

QUESTIONS ?