ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

9.1. Production Systems and Process Risk Assessment

1) Scenario:

The MES system is an IT platform, having several modules for serving end to end manufacturing purposes. For this example, the focus is on the production execution module, in particular the 'Synthesis' process module. Material GxP data is available and approved. Equipment is calibrated, configured under change control and in a clean status. Raw materials are available and approved. Users are trained and assigned the correct role. The recipes have lifecycle management guaranteeing change control and are in an approved status.

Sample labels are all created from a prepopulated template.

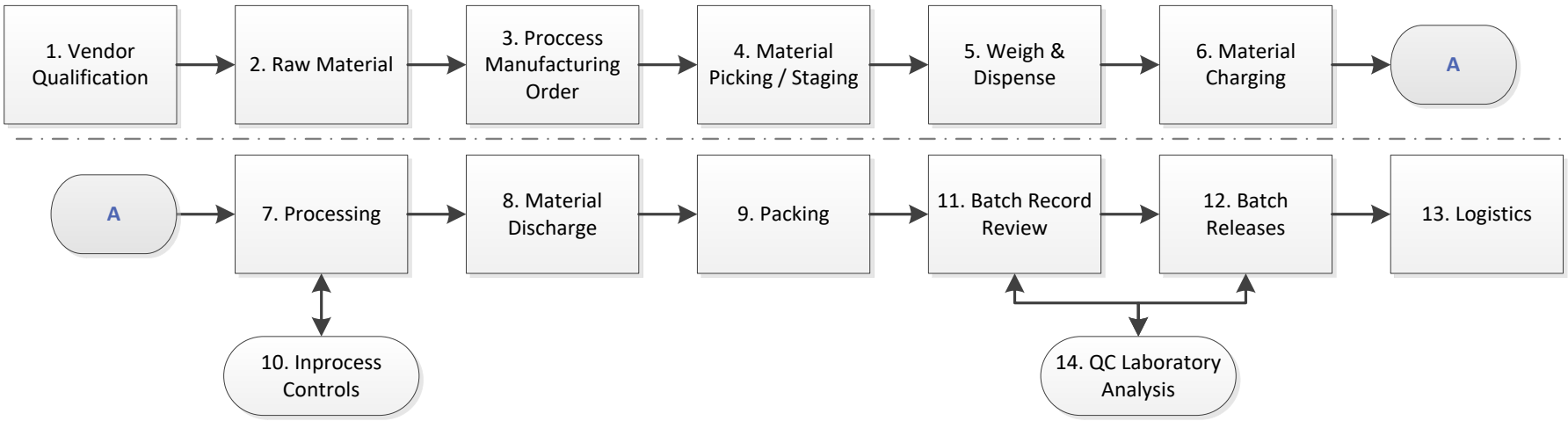
Remark:

The analytical instruments are not taking into account for this example as this is already covered under the lab system example.

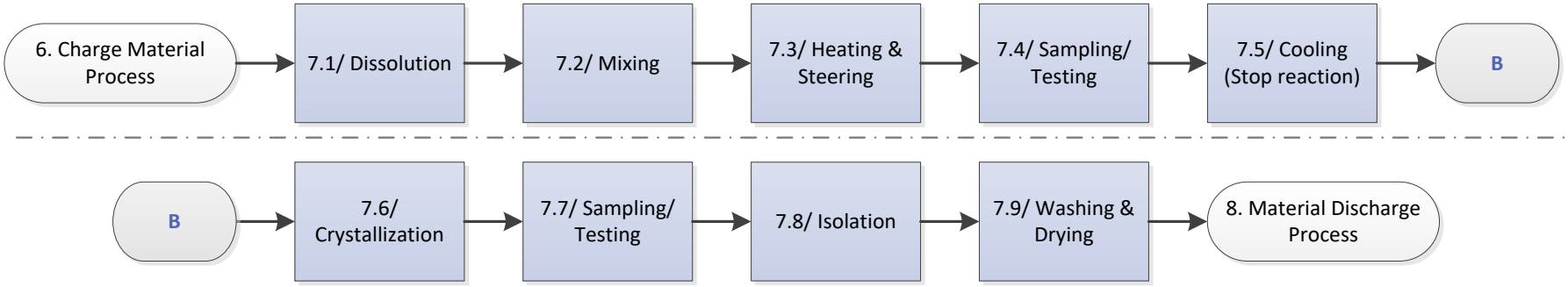
2) Business process mapping

The business process mapping utilizes the 6 FDA systems and their subsystems

➔ FDA Process: Production control system



➔ Sub Process: Processing (Synthesis)



3) Data (paper/electronic) and system identification

a. System identification: (see section 3 step A)

	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9
Start	Dissolution	Mixing	Heating & Steering	Sampling/ Testing	Cooling (Stop reaction)	Crystallization	Sampling/ Testing	Isolation	Washing & Drying
GxP Data	electronic	electronic	electronic	paper/ electronic	electronic	electronic	paper/ electronic	electronic	electronic
System	MES PCS/DCS Data Historian	MES PCS/DCS Data Historian	MES PCS/DCS Data Historian	MES Analytical Instrument[1] Sample label LIMS	MES PCS/DCS Data Historian	MES PCS/DCS Data Historian	MES Sample label LIMS	MES PCS/DCS Data Historian	MES PCS/DCS Data Historian

[1] Instrument with DI requirements is not further discussed in this example as this is already covered in the lab system example.

b. Data Identification: (see section 3 step B)

Step	7.1 Dissolution	7.2 Mixing	7.3 Heating & Steering	7.4 Sampling/ Testing	7.5 Cooling (Stop reaction)	7.6 Crystallization	7.7 Sampling/ Testing	7.8 Isolation	7.9 Washing & Drying
System 1: PCS/DCS → Transferring and controlling GxP data from the equipment towards the Data historian and MES systems									
GxP Data elements	Speed of addition Steering Speed Vessel Temp Sludge Temp Pressure	Agitation speed Steering Speed Temperature*	Temperature* Pressure Speed		Temperature* Pressure Speed	Agitation speed Temperature Quantity added		Temperature*	Temperature Pressure
System 2: Data Historian → Recording of the continuous pressure/temperature/speed (trend) data, for permanent storage									
GxP Data elements	Speed of addition Steering Speed Vessel Temp Sludge Temp Pressure	Agitation speed Steering Speed Temperature	Temperature Pressure Speed		Temperature Pressure Speed	Agitation speed Temperature Quantity added		Temperature	Temperature Pressure
System 3: MES									
GxP Data elements	User ID Start Date & Time End Date & Time Equipment ID Ph Dissolution confr. Speed of addition Steering Speed Vessel Temp Sludge Temp Pressure	User ID Start Date & Time End Date & Time Equipment ID Duration* Agitation speed Steering Speed Temperature*	User ID Start Date & Time End Date & Time Equipment ID Temperature* Pressure Speed	User ID Start Date & Time End Date & Time Equipment ID Batch Material ID Storage Condition	User ID Start Date & Time End Date & Time Equipment ID Duration	User ID Start Date & Time End Date & Time Equipment ID Ph	User ID Start Date & Time End Date & Time Equipment ID Batch Material ID Storage Condition	User ID Start Date & Time End Date & Time Equipment ID Loss on drying Visual check result Duration	User ID Start Date & Time End Date & Time Equipment ID Quantity* Duration
System 4: LIMS									
GxP Data elements				Sample ID User ID Date/Time Quantity / Batch Material ID Sample result*			Sample ID User ID Date/Time Quantity / Batch Material ID Sample result*		
System 5: Sample Label									
GxP Data elements				Sample ID User ID Date/Time Quantity / Batch Material ID Storage Condition			Sample ID User ID Date/Time Quantity / Batch Material ID Storage Condition		

c. Highlight electronic GxP data that can be modified/deleted or re-processed after creation. (as indicated by an asterix in above table) (see section 3 step C)

4) Data and System categorisation

a. Data severity assessment (see section 4.1)

This example will focus on the MES system only. The PCS/DCS, Data Historian, Sample label and LIMS should be handled in a separate assessment.

The MES is used for intermediates and APIs manufacturing.
According to the severity definitions, the API categorisation results in **very high severity data**.

b. System profiling (see section 4.2, decision tree figure 3)

System 1: PCS/DCS -> cat 6
System 2: Data Historian -> cat 5
System 3: MES -> cat 6
System 4: LIMS -> cat 6
System 5: Sample label -> cat 1

c. System assessment: (according to checklist 4.3 table 2)
Only the gaps are in below overview.

Topic	Sub topic	Question	Acceptance criteria	Does the system meet the criteria?	Description of gap
Data lifecycle management	Retention	Are all GxP data (Including meta data and audit trail data) retained in accordance with the companies Retention Schedule?	Data generated, including paper records, system records and corresponding audit trail entries, shall be retained in accordance with the companies retention schedule and any applicable legal hold notices. GxP documents shall be maintained in a secured storage location that is reasonably accessible and readily available for review to responsible personnel.	No	The units of measures are not part of the backup and archiving data set. Since these is valuable information in interpreting the time, pressure, temperature notations they become GxP meta data to be retained during the applicable schedule and for disaster recovery purposes.
Audit trail	Audit trail review	Are audit trails reviewed according to the applicable procedures?	The companies requirements on audit trail review shall be taken into account and should be supported by a risk based approach to define the process and frequency for execution.	No	For some steps, the entered duration, temperature or quantity could be modified after the data has been saved. No audit trail is available.
Security/User Access Control	Authentication	Does an inactive/unattended computer system go into a non-accessible mode after a defined period of inactivity?	An inactive/unattended computer system shall go into a non-accessible mode after a defined period of inactivity.	No	The MES user sessions are not being locked automatically after a defined period of inactivity.
Security/User Access Control	Periodic Access Review	Is a risk based approach used to define the period for access review and is a procedure in place describing how and what to review (including a check for the appropriate training expectations for each role)?	A periodic review of access shall be performed at a period based on risk.	No	Periodic access review is not being performed for the administrator roles.
Time Stamps	Access security	Can non-IT administrator roles change systems date and time settings (including time zone settings)?	Only system administrators shall have sufficient authority to change systems date and time settings. Non-administrator roles shall have read only access.	No	The client PCs are not protected for unintentional changes towards the time and date settings. Since for the sampling step the PC's time and data notations are automatically being used, this is critical to be locked for manipulation.

5) Risk Assessment (FMEA to calculate the gaps and their current individual Risk Priority Numbers (RPN)) (see section 5)

ID#	Checklist ID	Step	Function/Requirement or Data flow Step	Potential Failure Mode	Effect	Severity	Occurrence	Detectability	RPN
1	8	Retention	Are all GxP data (Including meta data and audit trail data) retained in accordance with the companies Retention Schedule?	The units of measures are not part of the backup and archiving data set. Since these is valuable information in interpreting the time, pressure, temperature notations they become GxP meta data to be retained during the applicable schedule and for disaster recovery purposes.	Data can be lost.	5	4	1	20
2	14	Audit trail review	Are audit trails reviewed according to the applicable procedures?	For some steps, the entered duration, temperature or quantity could be modified after the data has been saved. No audit trail is available.	Manipulation of data possible.	5	3	4	60
3	17	Authentication	Does an inactive/unattended computer system go into a non-accessible mode after a defined period of inactivity?	The MES user sessions are not being locked automatically after a defined period of inactivity.	Possible misabuse of someones session and cridentials.	5	3	4	60
4	23	Periodic Access Review	Is a risk based approach used to define the period for access review and is a procedure in place describing how and what to review (including a check for the appropriate training expectations for each role)?	Periodic access review is not being performed for the administrator roles.	Risk on administrators access rights being misabused while people have moved position, possibly leading to uncontrolled changes in the system.	5	3	3	45
5	34	Access security	Can non-IT administrator roles change systems date and time settings (including time zone settings)?	The client PCs are not protected for unintentional changes towards the time and date settings. Since for the sampling step the PC's time and data notations are automatically being used, this is critical to be locked for manipulation.	Possible registration of incorrect/manipulated time & date notations for some steps.	5	2	4	40

6) Risk management (see section 6)

The above table shows that 4 of the 5 gaps have a high RPN (Red). Actions have been defined to address these issues immediately. Additional actions have also been defined to mitigate the other gaps

In the next table the RPNs are recalculated after implementation of the defined actions.

ID#	Potential Failure Mode	Effect	Severity	Occurrence	Detectability	RPN	Intermediate Action	Severity	Occurrence	Detectability	RPN	Long term Recommended Action	Severity	Occurrence	Detectability	RPN
1	The units of measures are not part of the backup and archiving data set. Since these is valuable information in interpreting the time, pressure, temperature notations they become GxP meta data to be retained during the applicable schedule and for disaster recovery purposes.	Data can be lost.	5	4	1	20	Assess and include the relevant meta data in the backup and archiving data set.	5	0	1	0	N/A				0
2	For some steps, the entered duration, temperature or quantity could be modified after the data has been saved. No audit trail is available.	Manipulation of data possible.	5	3	4	60	Implement procedure to prohibit users to change regsitered paramters after saving.	5	1	4	20	Upgrade the system to enable the audit trail functionality for these paramters.	5	1	1	5
3	The MES user sessions are not being locked automatically after a defined period of inactivity.	Possible misabuse of someones session and cridentials.	5	3	4	60	Configure the system to go into a non-accessible mode after a defined period of inactivity?	5	0	4	0	N/A				0
4	Periodic access review is not being performed for the administrator roles.	Risk on administrators access rights being misabused while people have moved position, possibly leading to uncontrolled changes in the system.	5	3	3	45	Implement a process and procedure to execute the periodic review of administrator accounts.	5	1	1	5	N/A				0
5	The client PCs are not protected for unintentional changes tow ards the time and date settings. Since for the sampling step the PC's time and data notations are automatically being used, this is critical to be locked for manipulation.	Possible registration of incorrect/manipulated time & date notations for some steps.	5	2	4	40	Implement a process to prohebit for changing the date and time settings on the PC.	5	1	4	20	Lock the date and time setting on the PC.	5	0	4	0

To close out the risk in a documented and formal way, an additional column can describe the objective evidence that has been implemented to remediate the gaps.

ID#	Potential Failure Mode	Effect	RPN	Intermediate Action	Severity	Occurrence	Detectability	RPN	Long term Recommended Action	Severity	Occurrence	Detectability	RPN	References
1	The units of measures are not part of the backup and archiving data set. Since these is valuable information in interpreting the time, pressure, temperature notations they become GxP meta data to be retained during the applicable schedule and for disaster recovery purposes.	Data can be lost.	20	Assess and include the relevant meta data in the backup and archiving data set.	5	0	1	0	N/A				0	1) Inclusion of the relevant meta data in the backup and archiving data set under change control.
2	For some steps, the entered duration, temperature or quantity could be modified after the data has been saved. No audit trail is available.	Manipulation of data possible.	60	Implement procedure to prohibit users to change regsitered paramters after saving.	5	1	4	20	Upgrade the system to enable the audit trail functionality for these paramters.	5	1	1	5	1) Operational procedure 2) Change control for system upgrade including audit trail functionality 3) Audit trail review procedure adapted including the review of the related data
3	The MES user sessions are not being locked automatically after a defined period of inactivity.	Possible misabuse of someones session and cridentials.	60	Configure the system to go into a non-accessible mode after a defined period of inactivity?	5	0	4	0	N/A				0	1) Configuration of the system sessions settings under change control.
4	Periodic access review is not being performed for the administrator roles.	Risk on administrators access rights being misabused while people have moved position, possibly leading to uncontrolled changes in the system.	45	Implement a process and procedure to execute the periodic review of administrator accounts.	5	1	1	5	N/A				0	1) Procedure on periodic review of administrator accounts.
5	The client PCs are not protected for unintentional changes towards the time and date settings. Since for the sampling step the PC's time and data notations are automatically being used, this is critical to be locked for manipulation.	Possible registration of incorrect/manipulated time & date notations for some steps.	40	Implement a process to prohebit for changing the date and time settings on the PC.	5	1	4	20	Lock the date and time setting on the PC.	5	0	4	0	1) Operational procedure to prohebit for changing date and time settings. 2) Change control for locking the date and time settings on the PC's.

Checklist ID	Step	Potential Failure Mode	Effect	Long term Recommended Action	Severity	Occurrence	Detectability	RPN	References
8	Data capture/entry	It is possible that data is not saved at the end of the measurement. The system is asking if data need to be saved or not.	Data can be lost.	Update the software to go to the version which is storing automatically all of the runs.	5	1	1	5	1) Change control document upgrade UV software 2) Qualification report of UV software NameX, version xx 3)Training records analists 1, 2, x
14	Backup/restore	There is no system in place for back-up and storage of stand alone systems. (not connected to a network) There is no fixed schedule.	Data can be lost.	Install a full automated back-up system with a defined customized interval	5	1	1	5	1) Change control document connecting UV to network 2) Qualification report of back-up/restore sotware NameY, version xx
17	Backup/restore	see question 14	see question 14	NA since short term inmplementation is sufficient				0	1) Change control procedure version xx
23	Functionality	No user management audit trail available	User levels can be changed. (e.g. an analist can receive admin rights)	Even the new software doesn't have the audit trail function for user management	5	2	2	20	1) logbook reference xxx
34	Authentication	The UV systems doesn't require periodic pasword change.	Possible misabuse of someones password	Implement automatic password rules in system. (or update software)	5	0	1	0	1) Change control document upgrade UV software 2) Qualification report of UV software NameX, version xx
44	Access security	Date and time settings (including time zones) are accessable by all users.	Time of creating data can be adulterated.	Update the software to include user level access on date and time settings (including time zone)	5	0	1	0	1) Change control document upgrade UV software 2) Qualification report of UV software NameX, version xx