DISCLAIMER:

The information within this presentation is based on the presenter's expertise and experience and represents the views of the presenter for the purposes of stimulating discussion at this discussion camp.

Outline

I – QC Lab 管理要點

1. What is QC under GMP; PIC/S
2. COMPONENTS OF DATA QUALITY
    a. Instrument qualification
    b. Analytical method validation
    c. System suitability tests
    d. Quality control check sample
3. Chemist Qualification
4. Material managements
    a. Standard
    b. Reagents
    c. Sample

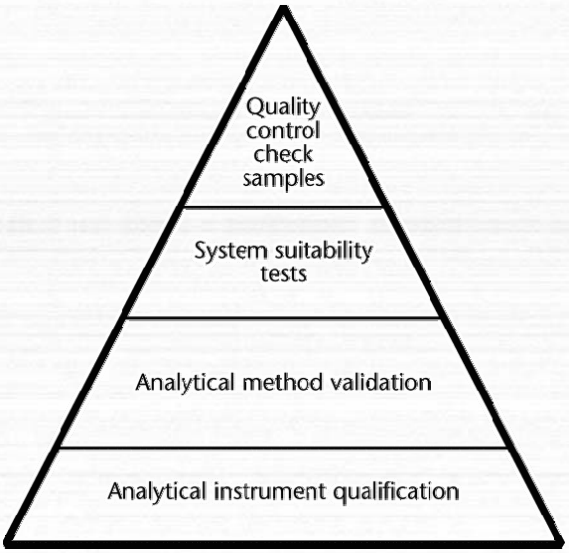
II - QC Lab 常用分析儀器之 data integrity

QC Lab 管理要點

1. What is QC under GMP; PIC/S

is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

2. COMPONENTS OF DATA QUALITY



USP General Chapters: <1058> ANALYTICAL INSTRUMENT QUALIFICATION

2-a. Instrument qualification

is the collection of documented evidence that an instrument performs suitably for its intended purpose.

Design Qualification	Installation Qualification		Operational Qualification		Performance Qualification
Timing and Applicability					
Prior to purchase of a new model of instrument	At installation of each instrument (new, old, or existing unqualified)		After installation or major repair of each instrument		Periodically at specified intervals for each instrument
Activities					
Assurance of manufacturer's DQ	Description	⇆	Fixed parameters		Preventive maintenance and repairs
Assurance of adequate support availability from manufacturer	Instrument delivery				Establish practices to address operation, calibration, maintenance, and change control
Instrument's fitness for use in laboratory	Utilities/facility	⇆	Environment		
	Assembly and installation				
	Network and data storage	⇆	Secure data storage, backup, and archive		
	Installation verification	⇆	Instrument function tests	⇆	Performance checks

2-a. Instrument qualification

Example

Oven for Loss on Drying:
Manufacturer I/O/PQ document indicates if the temperature range can be within range of ±5° of the stated temperature, the Oven is considered as qualified.

Are you sure????

USP <731> Loss On Drying:
……..The temperature specified in the monograph is to and with the capillary stopper still in place allow it to cool be regarded as being within the range of ±2° of the stated…….

2-b. Analytical method validation

USP: Analytical method validation is the collection of documented evidence that an analytical procedure is suitable for its intended use.

FDA: The Current Good Manufacturing Practice regulations [21 CFR 211.194(a)] require that test methods, which are used for assessing compliance of pharmaceutical articles with established specifications, must meet proper standards of accuracy and reliability.

There are 3 types……..

Transfer of Analytical Procedures
Validation of Analytical Procedures
Verification of Analytical Procedures

2-b. Analytical method validation

Validation of Analytical Procedures
Validation should be conducted when the analytical procedure has been developed. The parameters should include as following

Accuracy
Precision
- Repeatability
- Intermediate Precision

Specificity (should include force-degradation for stability indicating)
Detection Limit
Quantitation Limit
Linearity
Range

Reference: USP <1225>

2-b. Analytical method validation

Verification of Analytical Procedures

Generally, it is for compendia test procedure such as USP.

The verification process is the assessment of whether the procedure can be used for its intended purpose, under the actual conditions of use for a specified drug substance and/or drug product matrix. Taking into account the drug substance's synthetic route, the method of manufacture for the drug product, or both, if applicable.

Verification should include an assessment of elements such as the effect of the matrix on the recovery of impurities and drug substances from the drug product matrix, as well as the suitability of chromatographic conditions and column, the appropriateness of detector signal response, etc.

some of the analytical validation parameters may be used for the verification process.

Reference: USP <1226>

2-b. Analytical method validation

Transfer of Analytical Procedures
The transfer of analytical procedures (TAP), also referred to as method transfer, is the documented process that qualifies a laboratory (the receiving unit) to use an analytical test procedure that originated in another laboratory (the transferring unit), thus ensuring that the receiving unit has the procedural knowledge and ability to perform the transferred analytical procedure as intended.

2-b. Analytical method validation

Example
There is an impurity analytical method by HPLC will be transferred from Lab A to Lab B.
Lab A: Waters Alliance system e2695 with 2998 PDA, all reagents are ACS grade/HPLC grade and glassware are class A.
Lab B: same as Lab A.

What parameter should be evaluated during method transfer??

A comparison test with a real sample should be performed

Linearity and LOD/LOQ also……

2-c. System suitability tests

System suitability tests verify that the system will perform in accordance with the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test.

What is a suitable test for it??

Should be based on the development experience…….
Example,
Assay: %RSD, Tailing factor (symmetry factor)

Impurity: %RSD, Resolution, signal-to-noise ratio

2-d. Quality control check sample

Quality control check sample is to provide an in-process or ongoing assurance of the test's suitable performance.

What is a suitable test for it??

Should be based on the development experience…….

Follow/or similar with System Suitability tests

2. Benefit with system suitability and Quality control check

Can monitor the system and overall testing progress

Example

Inj. Vol: 100 uL
Solvent: ACN

Vial	Name	Response
1	Blank	0
2	Standard	2560123
2	Standard	2688129
2	Standard	2687367
2	Standard	2688112
2	Standard	2687789
3	Sample-1 prep	2501342
4	Sample-2 prep	2539809
2	Standard	2688223

Inj. Vol: 100 uL
Solvent: ACN

Vial	Name	Response
1	Blank	0
2	Standard	2688129
2	Standard	2701569
2	Standard	2715077
2	Standard	2728653
2	Standard	2742296
3	Sample-1 prep	2688112
4	Sample-2 prep	2687789
5	Standard	2688223

3. Chemist Qualification

Job Description

Education/Experience: Should be relative to the job description.

Training: on-board training and continual training related to JD.
(not only paper training but also practice training)

All record must be documents.

4. Material managements

4-a. Standard managements

Primary/Reference Standards:
Such as NIST Standard, compendia standard, others by well-characterized.
should be stored according to their label instructions.

Working standards:
Other than reference standard. Such as a well-qualified API by comparing reference standard.
should be periodically reevaluated to maintain their potency

4-b. Reagent managements

Standardization Reagents:
should be prepared to contain a known quantitative concentration. The concentration or factor of the reagent is used in assay calculations. Standardized reagents used in laboratory testing should be prepared according to appropriate written procedure, labeled with complete information, including reagent name, standardized concentration or standardization factor, identification of the preparer, date of preparation and the expiry date.
Non-Standardized Reagents:
should be prepared to contain a semi-quantitative or non-quantitative concentration. The concentration or factor of the reagent is not used in assay calculations. Non-standardized reagents used in laboratory testing should be prepared according to appropriate written preparers, and labeled with the name of the reagent, preparer-name, date of preparation, and the expiration date.

Resource: http://www.ivtnetwork.com/sites/default/files/Qualification%20of%20Quality%20Control%20Laboratories.pdf

4-c. Sample managements

All samples in lab. should be controlled and categorized to prevent mistaken, repeat testing, mis-use…etc.

Sample receiving -> login -> lab for analysis -> sample complete the review and enter retain room

Common tools:

appropriated label, login-book, LIMS, delicate space and environment for each type sample, retain room and container…etc

Question???

QC Lab 常用分析儀器之 data integrity (DI)

5. What is Data Integrity?

- *Data integrity* – requires that data are **complete**, **consistent,** and **accurate.**
- CGMP = minimum requirements
- Data integrity underpins CGMP
- Lapses obscure other problems

ALCOA

- **Attributable**
- **Legible**
- **Contemporaneous**
- **Original / true copy**
- **Accurate**

Resource: AAM 2017 CMC workshop - Data Integrity by Tom Cosgrove

5. What is Data Integrity?

- ***Attributable***: Establishes who performed an action and when. Traceable to an individual ~ 紀錄並可知道是**誰**、**何時**執行此動作
- ***Legible***: Data and results must be traceable, permanent, readable~ 可追尋、可讀取及永久/長期存放
- ***Contemporaneous***: Data is recorded at the time of the event/action~即時
- ***Original***: An original data record should include the first data entered and all successive data entries required to fully detail the scope of the project. Data as the file or format in which it was originally generated, preserving the accuracy, completeness, content and meaning of the record. The **paper printout of a chromatogram is no longer considered the official raw GMP data because it does not include the complete information, including but not limited to meta-data, audit trails, and system configuration** for the analysis in question.
- ***Accurate***: Data reflect true information. Where appropriate, correctness should be second-person verified. Data accuracy extends to data/information such as an equipment log, laboratory notebook, and electronic records.

Data Integrity

Is it for your electronic data only?

Is data only come form computer?

The electronic data makes data Complete? meanful?

What else in Lab could be a part of data??

It is all the data you can use as record

Data Integrity

Example 1 Mobile Phase

Accurate!!!

Weight 10g of NaH_2PO_3 ⟶ 500mL H_2O

Weight 10g of NaH2PO3 into 500 Volumetric Flask, dissolve and dilute to volume with H_2O, mix well, and then filter through 0.45um Nylon membrane

Data Integrity

Example 2 weighing

03/21: Weight 20mg of standard into 10 mL VF, dissolve and dilute to volume with MeOH, mix well.

03/22: Weight 20mg of sample into 10 mL VF, dissolve and dilute to volume with MeOH, mix well.

03/22	
Sample	
05:15	0.0000g
05:17	0.0021g

03/21	
Standard	
05:15	0.0000g
05:17	0.0019g

Data Integrity

Example 2 weighing

03/21: Weight 20mg of standard into 10 mL VF, dissolve and dilute to volume with MeOH, mix well.

03/21	
Standard	
05:15	0.0000g
05:17	0.0019g

03/22: Weight 20mg of sample into 10 mL VF, dissolve and dilute to volume with MeOH, mix well.

03/22	
Sample	
05:15	0.0000g
05:17	0.0021g

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Comtemporaneous!!!

Data Integrity

Example 3 HPLC sequence

03/21: sequence name: XXX_XXX_XXX

Vial	Inj. Vol	# of Inj.	Name	Run Time
1	100uL	2	Blank	30 min
2	100uL	5	Standard-1	30 min
3	100uL	1	Standard-2	30 min
4	100uL	1	Sample-1	30 min
5	100uL	1	Sample-2	30 min
6	100uL	1	Sample-3	30 min
7	100uL	1	Sample-4	30 min
8	100uL	1	Sample-5	30 min
9	100uL	1	Sample-6	30 min
10	100uL	1	Sample-7	30 min
11	100uL	1	Standard-1	30 min

Comtemporaneous
Legible
Original

Original: there are only 2 samples planned.
But for some reason there are additional 5 samples have been added.

Data Integrity

Example 3 HPLC sequence

03/21: sequence name: XXX_XXX_XXX

Vial	Inj. Vol	# of Inj.	Name	Run Time
1	100uL	2	Blank	30 min
2	100uL	5	Standard-1	30 min
3	100uL	1	Standard-2	30 min
4	100uL	1	Sample-1	30 min
5	100uL	1	Sample-2	30 min
11	100uL	1	Standard-1	30 min

Note, there are 5 samples will be added into sequence after sample-2 injection.
These 5 sample preparations, please refer to XXX/XXX

Data Integrity

Example 3 HPLC sequence

03/21: sequence name: XXX_XXX_XXX

Vial	Inj. Vol	# of Inj.	Name	Run Time
1	100uL	2	Blank	30 min
2	100uL	5	Standard-1	30 min
3	100uL	1	Standard-2	30 min
4	100uL	1	Sample-1	30 min
5	100uL	1	Sample-2	30 min
6	100uL	1	Sample-3	30 min
7	100uL	1	Sample-4	30 min
8	100uL	1	Sample-5	30 min
9	100uL	1	Sample-6	30 min
10	100uL	1	Sample-7	30 min
11	100uL	1	Standard-1	30 min

Data Integrity

Instrumentation

In General, analytical instruments in QC lab can be categorized into 3 groups.

1. Group A: Instrument with no measurement capability such as stir plate, hot plate, Oven….etc
2. Group B: Instrument providing measured value such as melting point, pH meter…etc
3. Group C: Instrument and computerized analytical system such as HPLC, GC, UV…etc

Data Integrity

Instrumentation

Group A: Instrument with no measurement capability such as stir plate, hot plate, Oven….etc

Relies on Chemist Notebook and instrument usage log-book/sheet

High Risk on D.I. ⟶ low Risk test item

Data Integrity

Instrumentation

Group B: Instrument providing measured value such as balance, melting point, pH meter…etc

Relies on Chemist Notebook, instrument usage log-book/sheet, and **print-out** (permanent)

Middle Risk on D.I. ⟶ Middle Risk test item

Data Integrity

Instrumentation

Group C: Instrument and computerized analytical system such as HPLC, GC, UV…etc

Relies on Chemist Notebook, instrument usage log-book/sheet, print-out, and **electronic record (audit trail)**

Low Risk on D.I. ⟶ High Risk test item

Data Integrity

Instrumentation
Group B

What element will be concerned as a risk factor??

Time! Time!! Time!!!

Data Integrity

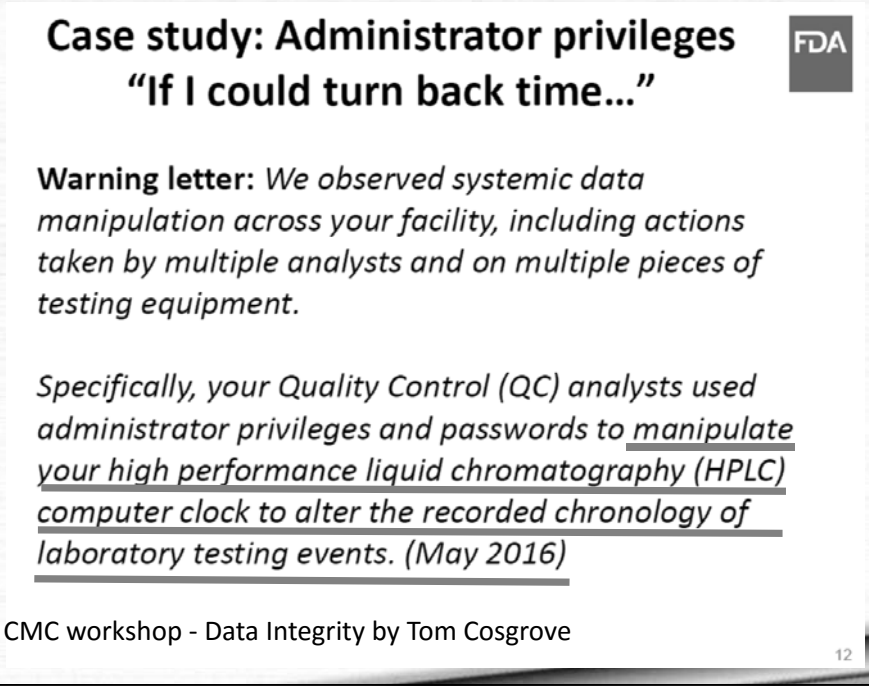
Instrumentation
Group B

How do you lower the risk???

1. Set up *privileges:* Lab. people cannot have right to adjust clock
2. All the clock of instruments in Lab should be *aligned* time to time. If there is needed, should have a record.

Data Integrity

Instrumentation
Group B



Resource: AAM 2017 CMC workshop - Data Integrity by Tom Cosgrove

Data Integrity

Instrumentation
Group C

What elements will be concerned as risk factors??

Since all the electronic data is computerized, it is easier to have more complete record but also can be modified more easily.
Therefore, the individual account/password, account privileges, audit trail should be used and controlled.

Data Integrity

Instrumentation
Group C

Account/password:
Individual user must have his/her unic ID which can link to him/herself only
The password cannot be known by any people (including boss) except self.

Screen protector and expiration time period for password

Attributable

Data Integrity

Instrumentation
Group C

Account privileges:
Admin: have all the rights about the system including create, modify, delete.
Generally, is IT person or who are independent. Cannot be Lab, QA, PD, or RD
Supervisor: have all the rights except delete function.
Supervisor, Lab manager
Chemist: only have operation right that can perform the daily testing.
Chemist
Reviewer: only have review right that can check data including audit trail .
QA

Data Integrity

Instrumentation
Group C

Audit Trail:
The disable function should be only belong to Admin level.

Audit trail should be able to see the over all activities regarding data and system.

Data Integrity

Instrumentation

What should you check for Audit Trail

Empower
Test run: any sufficient justification?

Instrument/process method: revision history and commend

Sample set vs result set: if there is multiple process? Any manual integration? reason?

System activities logsheet: any unexpected delete, modified, creation, and abnormal activity?

Data Integrity

Instrumentation

Example – test run

Case study: Stability samples

FDA

This is only a test. If it were an actual sample, it would be reported in the official data package.

- "Trial injections" of "stability samples" saved in the "test" folder.
- Official samples analyzed after "trial injection."

Warning letter?

Your response indicates that the "Test" folders were used to equilibrate the analytical columns and to determine when the system was ready for analysis. It is your responsibility to follow validated methods that include specific procedures to assess the suitability of your instruments… (March 2015)

Resource: AAM 2017 CMC workshop - Data Integrity by Tom Cosgrove

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Data Integrity

Instrument/process method: revision history and commend

Example – Processing method

version	Date	Commend	Editor
1	2015.01.01	Create	AAA
2	2015.01.30	modified	XXX
3	2017.05.05	modified	BBB

version	Date	Commend	Editor
1	2015.01.01	Create impurity method for project XXX	AAA
2	2015.01.30	Modified integration parameter and label the peak name	XXX
3	2017.05.05	Modified integration parameter based on sensitivity solution	BBB

Data Integrity

Instrument/process method: revision history and commend
Example – Sample set vs result set

There is only one ran sequence in sample set. However, same sample set has been processed several times and generated several result sets. And only one with good result has been reported.

Audit trail commend???

Data Integrity

Instrument/process method: revision history and commend
Example – System activities logsheet

There are several modified and delete data listing in system logsheet!!!!!

Audit trail commend???

Due to……..
Test method has been revised.
Computer storage space has reached to 90% capacity.

Warming Letter - Data Integrity

Apotex Research Private Limited, WL: 320-15-06, India

1. *Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b))*

Detail:

QC personnel created unauthorized folders on laboratory computerized systems without appropriate oversight. Our review of the HPLC Empower III data collected in 2013-2014 in the commercial QC laboratory found a data folder entitled "WASH." According to your management, the folder was intended for column wash injections using blank solvent prior to and following sample runs, although you have no standard operating procedure (SOP) detailing this process. One of your laboratory analysts stated that this folder does not contain any standard or sample injection results. However, our investigator found that this folder contained a total of 3,353 injection results, some of which appeared to be samples.

Warming Letter - Data Integrity

Hospira S.P.A., WL: 320-15-08, Italy

1. *Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b))*

Detail:

Specifically, your high performance liquid chromatography (HPLC) and gas chromatography (GC) data acquisition software, TotalChrom®, did not have sufficient controls to prevent the deletion or alteration of raw data files. During the inspection, the investigator observed that the server that maintains electronic raw data for HPLC and GC analyses (the J drive) contains a folder named "Test," and that chromatographic methods, sequences, and injection data saved into this folder can be deleted by analysts. The investigator also found that data files initially created and stored in the "Test" folder had been deleted, and that back-up files are overwritten (b)(4).

~TBC

Warming Letter - Data Integrity

Sri Krishna Pharmaceuticals Ltd., WL: 320-16-09, India

1. *Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).*

Detail:

Your laboratory records did not contain all raw data generated during each test for finished drug products manufactured at your firm. Your quality unit relied on incomplete records to make batch release decisions in support of regulatory submissions to the Agency.

During the inspection, your management acknowledged that employees in your QC laboratories conduct trial HPLC injections prior to the injections submitted as the reported test results. These trial injection data files were stored on separate drives from the reported test result data. In some cases original data files were deleted. The results from these trial injections and other original data were not reported.

~TBC

Warming Letter - Data Integrity

Sri Krishna Pharmaceuticals Ltd., WL: 320-16-09, India

2. *Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b))*

Detail:

During the inspection, our investigator reviewed data from your high performance liquid chromatography (HPLC) analysis for release testing, including assay and impurity testing. Your quality control analysts used administrator privileges to change the controls for the time and date settings and manipulate file names to overwrite injections and delete original HPLC test data. Analysts also routinely turned HPLC audit trails on and off. Your response acknowledges these practices.

~TBC

Warming Letter - Data Integrity

Sri Krishna Pharmaceuticals Ltd., WL: 320-16-09, India

3. *Your firm failed to follow written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and to document same at the time of performance (21 CFR 211.100(b))*

Detail:

Our investigator discovered that your firm was destroying original batch records and backdating revised replacement pages. For example, our investigator found original pages from five **(b)(4)** batch records (batches **(b)(4)** to **(b)(4)**) discarded outside your facility. Your quality control unit approved revised and backdated master batch record pages that your firm created to replace the discarded pages. The original data were subsequently transcribed and backdated to the time of production. Quality and production managers allowed this practice.

Your response indicated that your firm would not permit backdating in the future and that you would revise procedures to ensure reissued batch record pages are documented in the incident report register and a change control would be initiated for any minor editorial changes. In response to this letter, provide copies of the revised procedures and an assessment of how widespread the practice of revising and backdating batch records is.

Question???

Thank you