Construction, Commission, Qualification, and Validation implementation against FDA
与FDA相符合的施工、调试、确认及验证的实施

by Flemming Holm

1. QA Intent and Framework
   QA目的及构架

2. QA Tools
   QA工具

3. Quality Issue Examples
   质量问题案例

4. Actual Implementation of cFDA, EMEA, US FDA, and PIC
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5. Future
   未来

Verification/Qualification/Validation of Methods FDA Perspective
核实/确认/方法验证 FDA观点

Intent/目的:

Ensure that quality concepts and practices are utilized from construction phase of a capital project in such a manner to assure that facilities are delivered per client's requirements in terms of time, quality and expectation.
确保一个项目从施工阶段就开始应用质量概念和实践，以保证设施在时间、质量和预期方面按照客户的要求交付。

Construction Quality Assurance is an act to assure that the defined specifications and standards **have been followed** and sound construction techniques and suppliers have been utilized in the construction and fabrication of facilities, processes and systems for minimizing risk of product contamination in all forms.
施工质量保证是确保已遵循规定的规范和标准，并在设施、工艺和系统的施工和制造中使用良好的施工技术和供应商，以最大限度地降低所有形式的产品污染风险的行为

Validation (highest level of testing) under actual conditions of use/应用的实际条件下的验证（测试的最高级）

Qualification (medium level of testing) under actual conditions of use/应用的实际条件下的确认（测试的中间级）

Verification (minimum level of testing) under actual conditions of use/应用的实际条件下的合适（测试的中间级）

Verification/Qualification/Validation of Methods FDA Perspective
核实/确认/方法验证 FDA观点

Intent/目的

What does it mean/涵义是什么

- 21 CFR Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
- 21 CFR, Part 210: 现行良好生产实践在药品生产、工艺、 包装及储存过程中的运用；总则

- 21 CFR Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
- 21 CFR Part 211: 现行良好成产实践在成品中的应用

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1. QA Intent and Frame/QA 目的及框架

Remember: 2 dept./切记：两个部门

1. Production manager/生产经理
2. QA Manager/QA 经理

Independent person

完全独立的两个人

A Few Examples of GMP Regulations/GMP规范新案例

1. Process/工艺
2. They are found in 21 CFR 211.3 (15)/可在21 CFR 211.3（15）中找到
3. 21 CFR 210.3 (09) deals with the definition of components, drug product etc. in General;/21 CFR 210.3一般设计成分、药品的定义

- Pharmaceutical companies, indicates procedures are considered part of Current Good Manufacturing Practice (CGMP) outlined in 21 CFR Part 210. Any changes in production and processes must be controlled, recorded, reviewed and approved by the quality control unit for production of medicines.
- 制药公司，程序被视为当前良好生产规范（cGMP）的一部分，如21 CFR第210部分所述。生产和工艺的任何变更必须由药品生产质量控制单位进行控制、记录、审查和批准。
- Quality control unit means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.
- 质量控制单位是指由公司指定负责与质量控制有关的职责的任何人员或组织机构。
- In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.
- 在制品是指通过化学反应制造、复合、混合或衍生的用于制备药品的任何材料。

A Few Examples of GMP Regulations/GMP规范新案例

1. Process/工艺
2. They are found in 21 CFR 211.84/可在21 CFR 211.84中找到
3. 21 CFR 211.84 deals with the testing of components, drug product, containers, and closures:/ 21 CFR 211.84涉及成分、药品容器和瓶盖的测试

- Sub-Section 21 CFR 211.84(a) indicates that each lot of components, drug product containers, and closures should be sampled and tested appropriately then released
- 第21分节 CFR 211.84（a）指出，每批成分、药品容器和瓶盖应进行适当取样和测试，然后放行。
- Sub-Section 21 CFR 211.84(d)(2) indicates that each component should be tested for conformity with all appropriate written specifications for quality & purity and strength
- 第21分节CFR 211.84（d）（2）指出，应测试每个部件是否符合质量、纯度和强度的所有适当书面规范。
- Sub-Section 21 CFR 211.84(d)(3) indicates that containers and closures also should be tested for conformity with all appropriate written specifications
- 第21分节CFR 211.84（d）（3）指出，集装箱和瓶盖也应进行测试，以确保符合所有适当的书面规范

Framework/构架

Implementation of Quality Assurance

质量保证的实施

Remember: 2 dept./切记：两个部门

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Best Practice

GXP Regulation

Framework/构架

- The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) in their Q9 Quality Risk Management document [1] state: *"The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk."*
- 国际协调人用药品技术要求理事会（ICH）在其Q9质量风险管理文件[1]中指出："药品（包括其成分）的制造和使用必然会带来一定程度的风险。"
- The FDA also has acknowledged this fact in the Report to the FDA Commissioner from the Task Force on Risk Management, May 1999 [2]: *"Although medicinal products are required to be safe, safety does not mean zero risk. A safe product is one that has reasonable risks, given the magnitude of the benefits expected and the alternative available."*
- FDA在1999年5月向FDA专员提交的风险管理工作组报告中也承认了这一事实[2]："尽管要求药品安全，但安全并不意味着零风险。安全产品是一种具有合理风险的产品，考虑到预期收益的大小和可用的替代方案。
- In addition, the EMEA (now known as European Medicines Agency (EMA)) acknowledged this fact in their Action Plan to Further Progress the European Risk Management Strategy, 4 May 2005 [3]: *"However, in view of the increasing and justified demands from patients and the general public for an adequate protection of public health, resulting in*
- 此外，欧洲、中东和非洲（现在称为欧洲药品管理局（EMA））在其《进一步推进2005年5月4日欧洲风险管理战略的行动计划》[3]中承认这一事实："然而，鉴于患者和公众越来越合理地要求充分保护公共卫生，因此
- *the availability of safe and effective medicines, it is important to re-emphasise that the concept of "zero risk" does not apply to medicinal products. The licensing of medicinal products needs to be assessed in the context of the benefit/ risk balance concept, whereby demonstrated benefits must outweigh known risks, leading to a favorable benefit/risk ratio and the resulting marketing authorization."*
- 安全有效的药品的供应，重要的是要重新强调"零风险"的概念不适用于药品。药品的许可需要在利益/风险平衡概念的背景下进行评估，由此证明的利益必须大于已知的风险，从而产生有利的利益/风险比和由此产生的营销授权。"

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2. QA Tools/ QA工具

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FDA Basis Documentation/FDA的基本文件:

SIA,FMEA, CA, TS, URS, (CPP CIA)

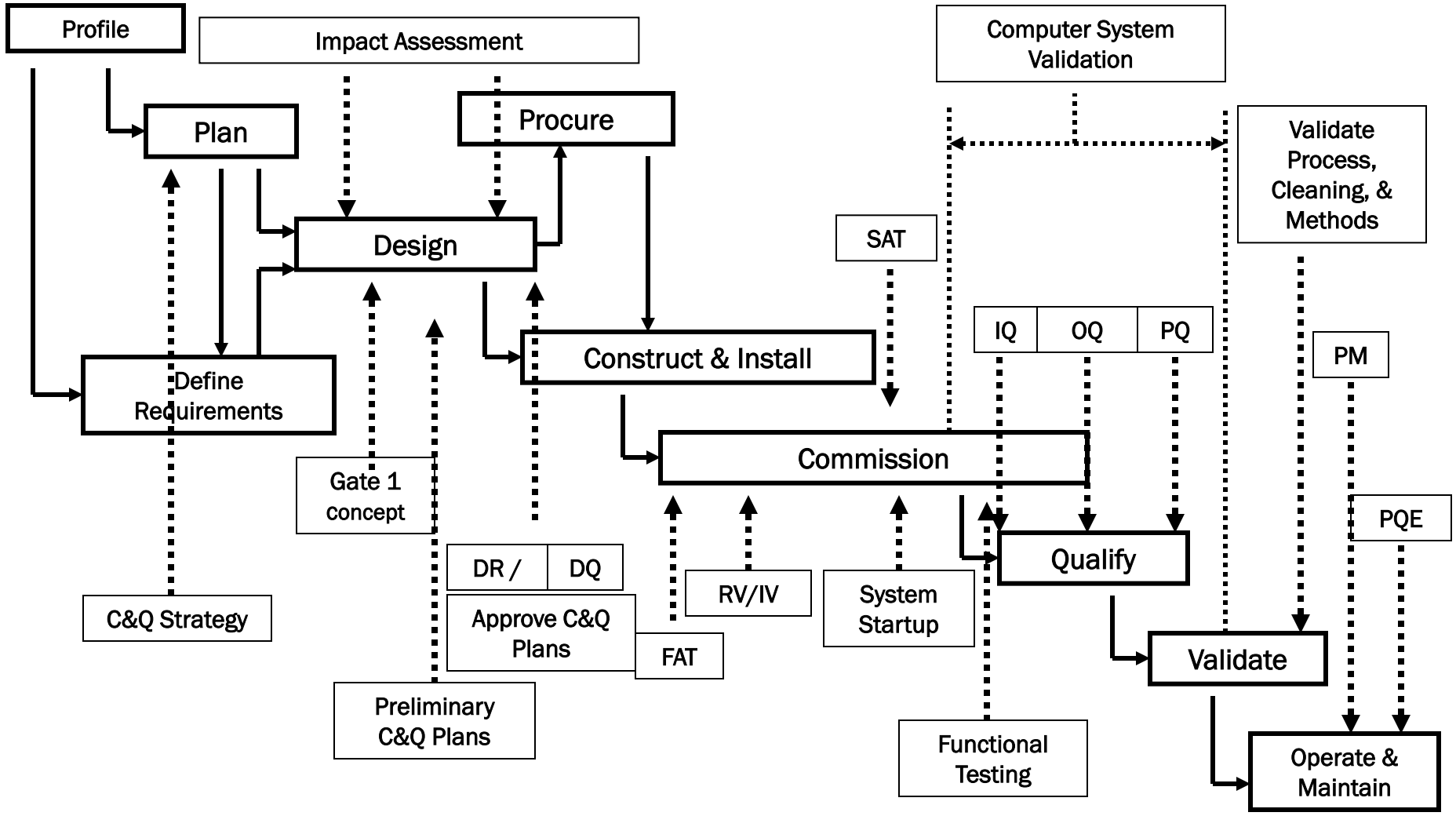
Facilities Delivery/设施交付:

Vendor Assessment/供应商评估, DQ, IQ, OQ, PQ, and PV.

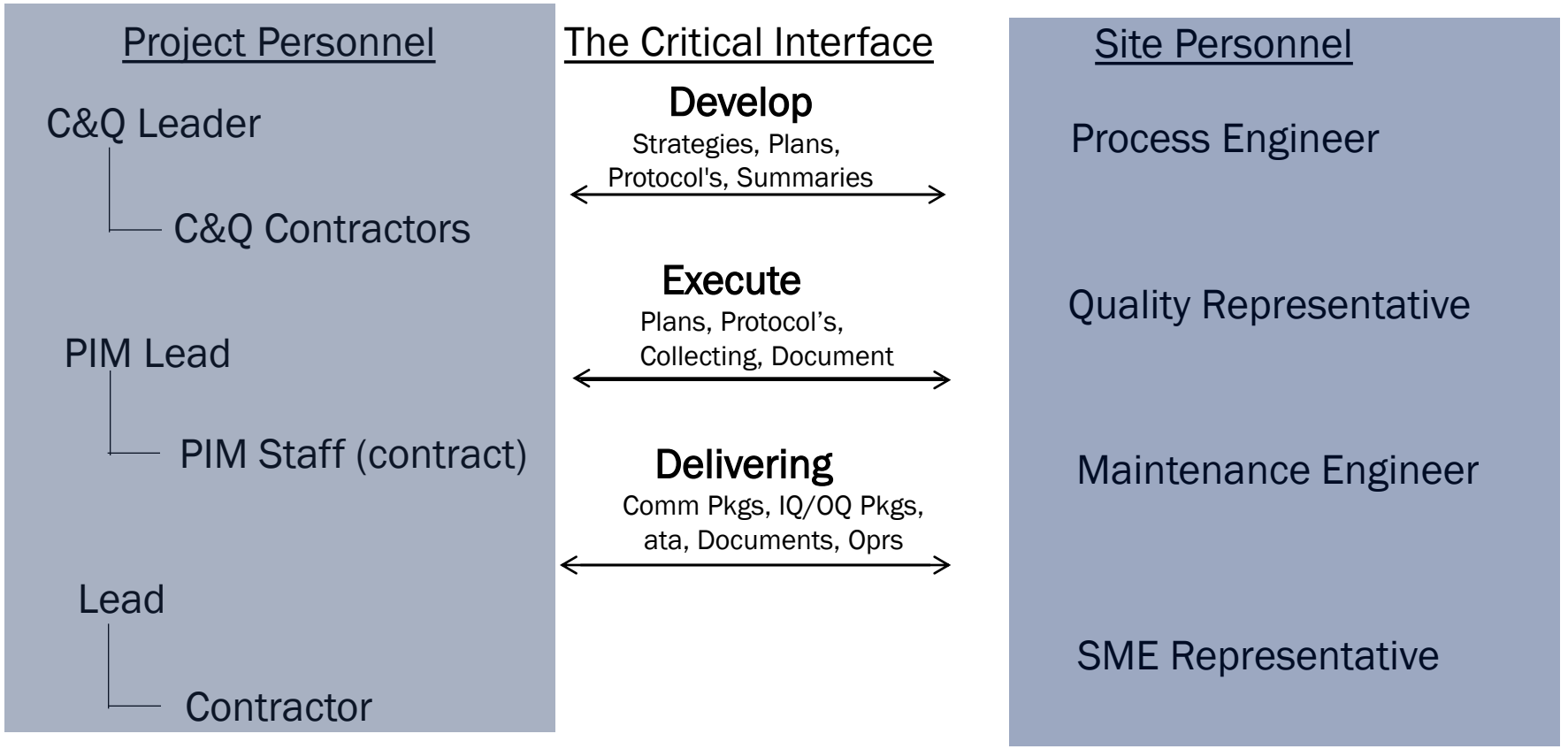
Could be done in one Plan or Program.

可在一个方案或程序中执行

Facility Delivery Process/设施交付流程



Project Team/项目团队



System progress/系统进度

STATUS DATE		5-Jun-2014		System Activities (Document development and execution)															
SYSTEM		SCHEDULE PRIORITY	RV	TRX	TOP/MC	IV	IV SUM	SSP	RV SUM	FT	FT SUM	SAT	SAT SUM	IQ	IQ SUM	OQ	OQ SUM	PQ	COM PACK	TCCC
PW		1	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
BMS		2	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
UMS		2	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
CA		3	E	E	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
CHW		3	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
HHW		4	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
HVACCUP		5	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
EMS		5	E	E	E	E	/	E	E	E	E	/	/	E	E	E	E	E	E	E
HVACPAC		5	E	E	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
PTSM		5	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
HVACCRT		6	E	E	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
HVACCHS		7	E	E	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
PACK		5	/	/	/	E	E	/	/	/	/	/	/	/	/	/	/	/	E	E
NCI		3	E	E	E	E	E	/	E	E	E	/	/	E	E	E	E	/	E	E
ICP		4	E	E	E	E	E	/	E	/	/	E	E	E	E	E	E	E	E	E
HVACGEN	AHU-01	5	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
	AHU-06	5	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
	AHU-07	5	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
	AHU-08	5	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
	AHU-09	5	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E
	AHU-10	5	E	/	E	E	E	E	E	E	E	/	/	/	/	/	/	/	E	E

System ITP template/系统ITP模板

Project Name:_____ Project Number : _____

CONTRACTOR INSPECTION AND TEST PLAN DETAILS

RESPONSIBILITIES LEGEND

W = WITNESS; I = INSPECT; R = REVIEW; A = APPROVE / ACCEPT; H=HOLD; M = MONITOR; X = EXECUTE; NA = NOT APPLICABLE

Contractor Name :

Revision/Date: Rev 0 / 04-Jun 2014

Contract No.

ITP Scope: Bonding and grounding in Concrete slab and soil

ITP-000

Activity No.	Activity Description	Verifying Document	Procedure and/or Specification Reference	Frequency and / or Timing of activity	Contractor Person(s) Responsible	RESPONSIBILITIES			
						Contractor	Contractor 3rd Party	Client CMT	Client Inspector
1	Design verification	Design calculation and layout drawing summery statement	GB_50217-2007 § 5	end of design before construction	XX	X	NA	R	NA
2	Material of construction	Receiving inspection	Section 16060 § 2	Upon delivery of equipment	XX/ sub contractor	X	NA	R	W
3	Installation execution test	16080A17	Section 16060 § 3	Prior to concrete placement	XX/ sub contractor	X	NA	R	W
4	Dimension of grounding connection and rod	Layout drawing and cable plan	GB 50196-2006 § 3.2	Before covering of grounding rod and cables with soil (prior to backfilling)	XX/ sub contractor	X	NA	R	W
5	Laying of grounding connection and rod	Layout drawing	GB 50196-2006 § 3.3	Before covering of grounding rod and cables with soil (prior to backfilling)	XX/ sub contractor	X	NA	R	W
6	Connection of grounding connector	Layout drawing and check secmatic	GB 50196-2006 § 3.4	Before covering of grounding rod and cables with soil (prior to backfilling)	XX/ sub contractor	X	NA	R	W
7	Distends of Lightning rod to Grounding rod	Layout drawing	GB 50196-2006 § 3.5	Before covering of grounding rod and Lightning rod with soil (prior to backfilling)	XX/ sub contractor	X	NA	R	W
8	Resistance test	16080A20,	GB 50057-1994/2010	Prior to concrete placement	XX/ sub contractor	X	NA	M	W
9	Resistance test	16080A18,	GB 50057-1994/2010	Before TOP or energizing	XX/ sub contractor	X	NA	M	W
				prior to backfilling					

MC check list: Civil/Structural/Architectural/ MC 检查清单：土建/结构/建筑

Construction completion/施工完成

- Visual inspection for complete and correct installation/完整及正确安装的目视检查.
- Welding/焊接.
- Thickness checks, Adhesion checks/厚度检查、附着力检查
- Preservation/维护.
- Insulation/保温.
- Painting/刷漆.
- Fire proofing/防火.
- Doors/门.

Example/案例:

MC check list
CSA

MC check list: Electrical/MC检查清单：电气

Construction Completion/施工完成

- Visual inspection for complete and correct installation/完整及正确安装的目检.
- Insulation and continuity testing of cables/电缆绝缘和持续性试验.
- Insulation testing of generator, transformers and motors, Panels, distribution board etc/发电机、变压器和电机、面板、配电板等的绝缘测试等
- Grounding checks/接地检查.
- Static check of switches and control devices/开关和控制装置的静态检查.
- Battery preparations/电池准备.
- Lighting and socket outlet checks/照明和插座检查.
- Area completion/区域完成.
- Heat tracing/伴热.
- Preservation/保存.

Example/案例

MC check list
Electrical

MC check list: Equipment/MC检查清单：设备

FAT/工厂验收测试

- Visual inspection for complete and correct installation/完整及正确安装的目检.
- Internal inspection of tanks and vessels/罐体和容器的内部检查.
- Alignment/一致性.
- Load testing of lifting equipment/起重设备的负荷试验.
- Bolt tensioning/螺栓张紧.
- Dimension control/尺寸控制.
- Preservation/保存.
- Interface/boundary/界面/边界

Example/案例

MC check list Equipment

MC check list: HVAC/MC 检查清单 HVAC

Construction completion/施工完成

- All components installed (AHU, ductwork, filters, fan, heating/cooling coil, damper, humidifier)/所有部件都已安装（AHU，管道系统、过滤器、风扇、加热/冷却线圈、阻尼器、加湿器）
- Integrity test/完整性测试
- Leakage test/泄漏测试
- PID walk down/PID巡查
- Insulation, labeling, tag number/绝缘、贴标、贴签

Example/案例

MC check list HVAC

MC check list: Instrumentation/MC 检查清单：仪表

- Certification /证书
- Datasheet/数据表
- Calibration/校准
- Installation, wire connection, pneumatic connection, power connection/安装、接线、气动连接、电源连接

Example/案例

MC check list
Instrument

MC check list: Piping/MC 检查清单：管道

- Welding procedure/quality report/焊接程序/质量报告
- Receiving inspection/接受检查
- Isolation of black pipe and clean pipe/非洁净管道和洁净管道的分离
- Protection of clean pipe and instruments/洁净管道和仪表的保护
- Component list check/部件清单检查
- Pipe support/rack check/管道支持/货架检查
- Flushing/blowing/冲洗/吹气
- Pressure test/压力测试
- Material/材质
- Pipe class flowchart/管道等级流程图

Example/案例

MC check list
Piping

MC check and C&Q test/MC 检查和C&Q 测试

According to the specifications, to achieve the user requirements we need to start some commission/qualification test along with mechanical completion even together with construction.
The C&Q activities take place throughout the project just like the MC completion does.
根据规范，为了达到用户的要求，我们需要在机械竣工时，甚至在施工时，进行调试/确认测试。C&Q活动在整个项目中进行，就像MC完成一样。

- Equipment → FAT?
- Material → material class?
  visual check?
  receiving inspection?
  certificate?

Test method/测试方法

- Walk down/巡查
- Receiving inspection/接收检查
- ITP/检查测试计划
- Document check (mill report, certificate)/文件检查（工厂报告、证书）
- Deliverable index/交付索引

3. Quality Issue Examples/质量问题案例

Picture to be shown in the Conference

Test example will be shown in the speech is confidential material.