Engineering Pharma

Huai Nyin (Grace) Yow and colleagues discuss the engineering challenges specific to pharmaceutical projects

IS engineering a pharmaceutical project more challenging than for other industries? An engineering project, generally, has a defined development path: conception; design (P&IDs, design calculations, equipment selection, 3D-model and software writing); procurement; build; installation; commissioning; operational testing; and lastly but not least, client handover.

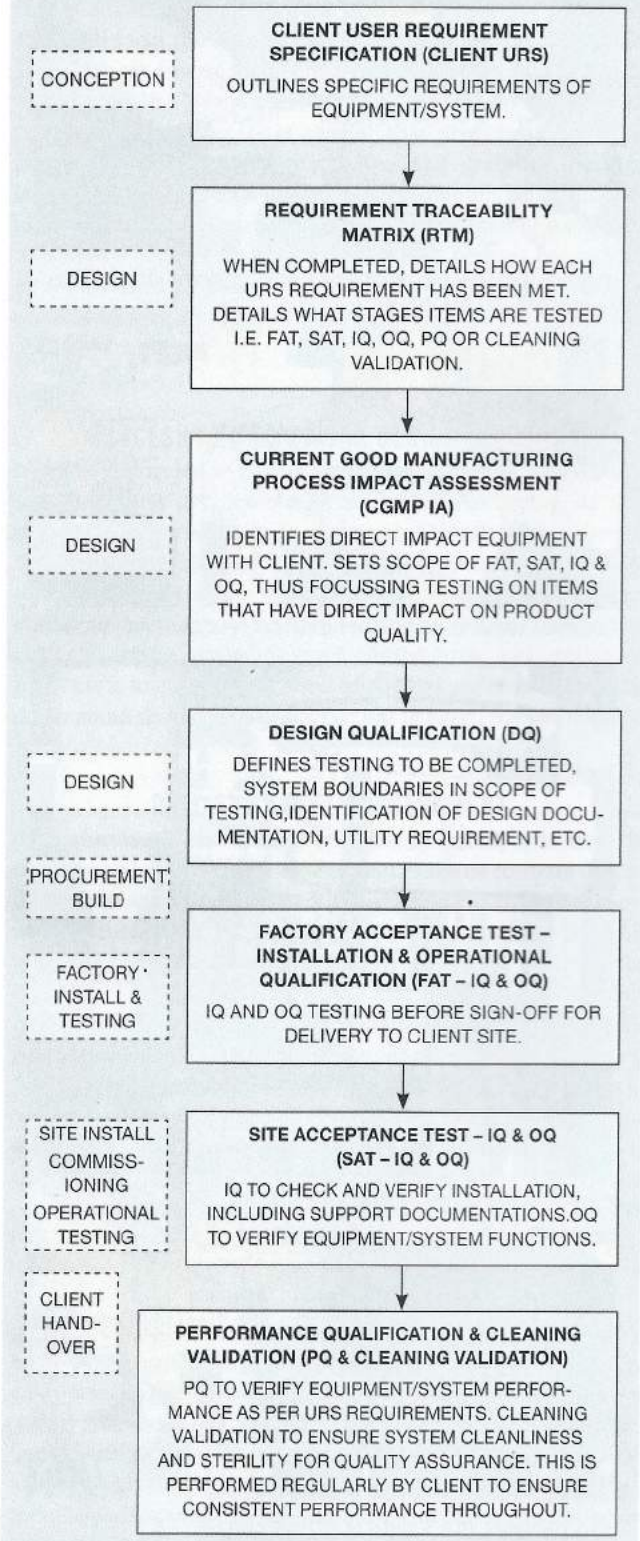
Engineering of a pharmaceutical project is very similar, with added detail of validation activities and compliance for regulatory approval. This is because ultimately the drug, and its production process, must be given the regulatory approval stamp before the drug can help its intended users. And by definition, a regulatory-approved drug has successfully passed all testing and clinical trials, with the results independently assessed to confirm that the drug is safe and effective for its intended users.

In this article, we will present a selection of key engineering practices to consider when designing or engineering a pharmaceutical project. We will provide a brief overview of how these engineering topics relate to the qualification process, which is required for regulatory approval.

QUALIFICATION OVERVIEW

Figure 1 presents the typical qualification process for a pharmaceutical project: user requirement specification (URS); requirement traceability matrix (RTM); impact assessment (IA); design qualification (DQ); factory acceptance test (FAT); site acceptance test (SAT); installation qualification (IQ); operational qualification (OQ); performance qualification (PQ); and cleaning validation. *Figure 1* contains a brief explanation of each step, alongside its relationship with the development of

FIGURE 1: QUALIFICATION/VALIDATION PROCESS FOR A PHARMACEUTICAL ENGINEERING PROJECT



an engineering project. Once the conception process and client URS are completed, we can begin our design by considering the following topics.

DESIGN – STANDARDS AND GUIDELINES

The first thing to consider is the site or company standards, and the market in which the drug will be sold. Each country will have its own regulatory process. Therefore, it is important to understand which standards to follow in our design. A few common standards and guidelines typically applied in pharmaceutical projects to ensure quality acceptance and assurance of the manufactured drug are:

- American Society of Mechanical Engineers: Bioprocessing Equipment (ASME BPE) Standards.
- International Society for Pharmaceutical Engineering (ISPE) Guides.
- Good Manufacturing Practice (GMP) Standards.
- Good Automated Manufacturing Practice (GAMP) Standards.
- Food and Drug Administration (FDA) Code of Federal Regulations (CFR).
- EudraLex – European Drug Regulatory Legislation.
- Medicines & Healthcare products Regulatory Agency (MHRA) Guidance.
- International Pharmacopoeia.
- European Pharmacopoeia.
- US Pharmacopoeia.
- Japanese Pharmacopoeia.

Note that compliance to more general standards and regulations (eg CE marking, ATEX Directive 94/9/EC, Health & Safety at Work Act 1974, etc) is still compulsory, where applicable.

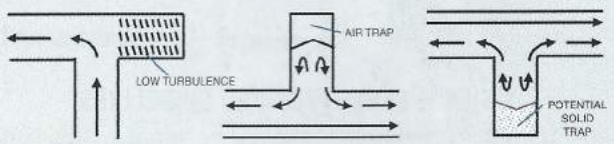
PROCESS AND PIPEWORK DESIGN – PRODUCT AND SERVICES

Here, the process design begins. Read and dissect the URS. Talk to the client and its development partner(s). Capture everything in written format, so that discussions and decisions are clear. This information will feed into the RTM and CGMP IA. Most of the time, the client already has a design vision in mind. It will be helpful to understand that vision.

Make sure the properties of all chemicals, process, and utilities requirements (including pipework specifications and flow paths) are fully understood. A few examples include vapour pressure effect on net positive suction head (NPSH) of pumps, water/steam quality determining single or double tubesheet heat exchanger, product sedimenting/creaming effects governing pipework size and vessel design, etc.

Do consider any sampling and testing requirements at this stage, which will typically be required for the clean utilities (eg clean/pure steam, sterile gases, purified water,

FIGURE 2: DEAD LEG ISSUES IN PIPEWORK



water-for-injection (WFI)), filters, etc. Also, do consider any sterilisation requirements for microbe reduction. For final product sterilisation, this should be performed as close to packaging as possible. Obtaining this knowledge and understanding will benefit the project in the long run.

PROCESS AND PIPEWORK DESIGN – CLEANING

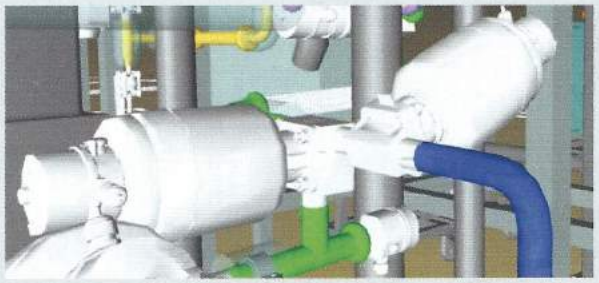
Now, as the process design (including calculations) is being understood and realised from URS into piping and instrumentation diagrams (P&IDs), it is important to give the cleaning process as much attention as the production process. Often the cleaning, sanitising and drying regimes become an afterthought and this will subsequently result in failure of the OQ, as microbes and biofilms thrive in the new production system.

Cleaning-in-place (CIP) velocity (in process pipework) should be at least 1.5 m/s to ensure turbulent flow with minimal boundary layer on the internal pipe wall. It is essential to ensure sufficient CIP contact time is provided to the entire process line. Therefore, where practicable, minimise the use of tees, avoid dead legs and avoid splitting routes. *Figure 2* presents the issues with dead legs in pipework. Where these are unavoidable, direct the flow into the dead leg and ensure minimal dead leg length (L), with a recommendation of L/D of 2 or less (according to ASME BPE standards). D is defined as the internal diameter (ID) of the leg or nominal dimension of a valve or instrument. For valve design, consider a valve block, whilst for instrument installation, consider use of instrument tee. *Figure 3* presents examples of equipment suitable for pharmaceutical projects.

PROCESS AND PIPEWORK DESIGN – SANITISATION

Generally, following successful CIP, the pharmaceutical system will be sanitised. This can take place in-situ, also known as sanitise-in-place (SIP), or the critical components can be taken away for sanitisation in a designated CIP/SIP station or autoclave. The purpose of sanitisation is to reduce the microbe counts, thus ensuring production of a safe drug, as well as to provide hot surfaces to assist with the subsequent drying process. Clean saturated steam is recommended for sanitisation and this normally occurs at 121°C for 30 mins. Note, sanitisation temperature vs time is an exponential relationship, with the time required for sanitisation increasing

FIGURE 3: EQUIPMENT EXAMPLES FOR PHARMACEUTICAL PROJECTS



'T' DIAPHRAGM VALVE (ALSO KNOWN AS ZERO DEAD LEG) AND 2-WAY DIAPHRAGM VALVE

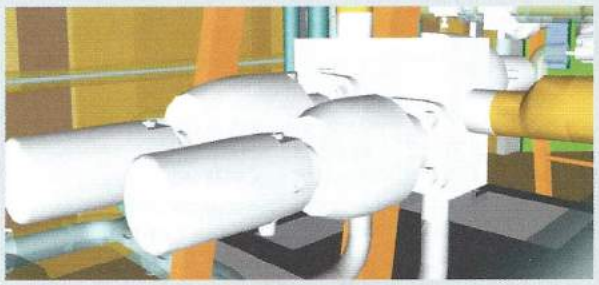
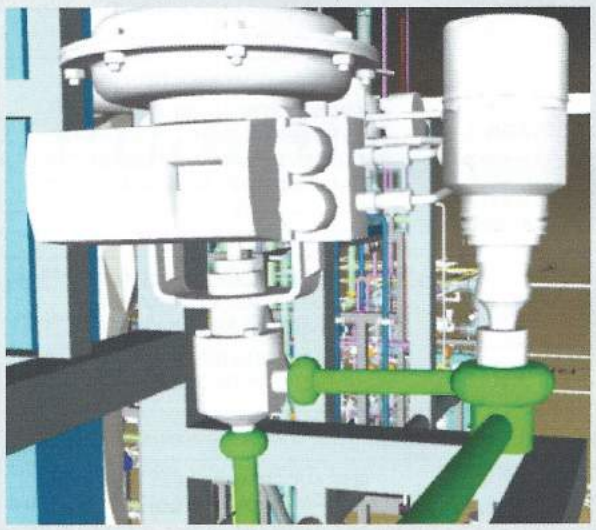
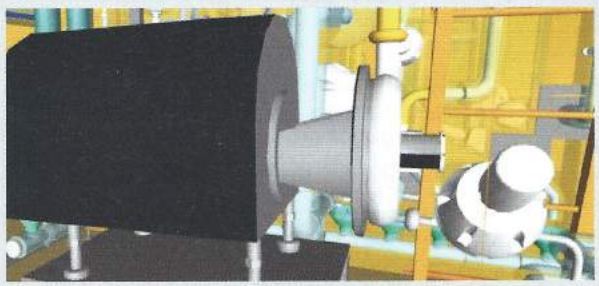


DIAGRAM VALVE BLOCK WITH WELDED-ON ECCENTRIC REDUCER



ANGLE CONTROL VALVE AND INSTRUMENT TEE



CENTRIFUGAL PUMP WITH LOW POINT DRAIN

dramatically at lower temperatures.

For effective SIP, air must be removed from the system. This can be achieved either by pulling a vacuum or introducing steam at the highest point within the system. The steam flow will push the air out through the steam trap(s). A steam trap with automatic air venting function should be used and installed at the lowest points within the system to help with condensate draining. It is crucial that process pipework is sloped to encourage gravity-driven self-draining. According to ASME BPE standards, the recommended minimum slope for gravity-drained process contact lines is 0.57° (ie a 1 in 100 fall). Consider using special pipe fittings (eg 88°/92° bend, eccentric reducer – see example in *Figure 3*, tangential tee etc) that encourages 2° pipework slope for more effective gravity-draining.

PROCESS AND PIPEWORK DESIGN – DRYING

If SIP is performed as part of the cleaning regime, it is recommended to use dry, hot sterile air for system drying, as this will minimise condensate formation and reduce drying time. If SIP is not required, consider flushing the system with ethanol to help with water removal. Following ethanol rinsing, dry, sterile nitrogen should be used to dry the system. If there are multiple drying routes involved, consider the route sequencing. This is to ensure any collected puddles are removed via the drain point(s), rather than purged out through the vent line.

RISK AND SAFETY ASSESSMENT

Once the P&IDs and design have been agreed, it is time to perform a risk and safety assessment. Various formats can be used, such as company-based risk analysis, hazard and operability study (HAZOP), failure mode effect analysis (FMEA), layer of protection analysis (LOPA) etc. It is essential to involve all key parties during the assessment, including but not limited to the development partner(s), health and safety representative, microbiology team, operator(s), maintenance team, process/project/electrical designer(s), software developer(s) and qualification representative. The risk and safety assessment will feed into the testing that forms part of the IQ, OQ, PQ and cleaning validation processes. All of the above-mentioned design and safety considerations and assessments will feed into RTM, CGMP IA and DQ as well.

EQUIPMENT SELECTION & PROCUREMENT

For a pharmaceutical project, sanitary, hygienic or specialty equipment (eg diaphragm valve, valve block, angle control valve, split butterfly valve, targeted spray ball, centrifugal pump with inbuilt casing drain etc) may be required. A few examples are illustrated in *Figure 3*. Consult with the equipment supplier for the recommended orientation or installation angle for effective gravity draining of the equipment. Sanitary and hygienic equipment can be purchased with European Hygienic Equipment Design Group (EHEDG) or 3-A Sanitary Standards Inc (3-A SSI) certification. Both organisations aim to contribute to hygienic engineering and design to ensure production safety.

TABLE 1: PHARMACEUTICAL EQUIPMENT/PIPEWORK SELECTION CRITERIA

CRITERIA	TYPICAL OPTIONS
Product-contact OR non product-contact	• If product-contact, is it direct or indirect and what are the corresponding requirements? • If non product-contact, what are the requirements?
Stainless steel grade *– Check chemical compatibility with all media (including water quality)*	• 316/316L – Dual certified • 316Ti • Low ferrite content <1%
Gasket/seal material *– Check chemical and temperature compatibility with all media (including CIP/SIP/hot air drying)* *– Use the correct gasket and torque settings during assembly*	• Polymeric based (eg EPDM, PTFE, FFKM, etc) • Modified polymer based (eg PTFE-filled with graphite, etc) • Stainless steel based (eg Tuf-steel, etc) • Carbon graphite based
Connection type *– Consider maintenance requirements vs number of leakage points vs validated software/operation*	• Tri-clamp fitting • DIN11864 aseptic coupling • Welded end
Internal surface finish *– Consider transfer media within pipework (eg WFI, sterile air, etc)*	• SF1 0.51 µm Ra Max – Mechanical polish • SF3 0.76 µm Ra Max – Mechanical polish • SF4 0.38 µm Ra Max – Electropolish
External surface finish *– Consider clean room status and cleaning regime (eg alcohol wipe down, etc)*	• 2B • 1.2 µm Ra Max • 0.9 µm Ra Max
Surface treatment *– Specify at the beginning of the project, as it is easier to consider as part of routing design and equipment selection*	• Passivation • Mechanical polish • Electropolish

During equipment and pipework selection, consider these key factors, as presented in *Table 1*. *Table 1* also provides a few typical options for a pharmaceutical project. Remember the development partner or scientist is a good information source for material requirements and suitability, as they would have produced numerous drug batches. The final equipment selection relies on the judgement of the engineers on the project, who understand the URS, as well as process and project requirements.

CERTIFICATIONS

As part of equipment and pipework selection, it is important to understand the certification requirements. Typical

pharmaceutical certifications required for product-contact items for IQ compliance are:

- Mill test report (MTR) or material certification – 3.1.
- FDA elastomer compliance certification.
- USP elastomer compliance certification (if applicable).
- Animal derived ingredient (ADI) free certification.
- Surface finish report.
- Certificate of conformity.
- 3-point or 5-point calibration certificate (if applicable).
- Pressure test report (if applicable).
- ATEX compliance certification (if applicable).
- CE certification (if applicable).
- Weld mapping (if applicable).
  - Including manual/automatic welding agreement, weld logs, welder certificates and welding procedures.
  - Optional – daily weld samples, weld printout, welding rod certificates, argon bulk gas certification.
- Non-destructive testing (NDT) (if applicable).
  - Can include borescope, X-ray, dye penetration, etc.

Most of the time, the certificates cannot be specified subsequently. This is due to the requirements for material traceability back to its origins. In addition, it is easier to measure the properties (eg internal surface finish) of the individual components (eg the plug within a control valve) before the final item (in this example, the control valve) is assembled. It may be an option to send the equipment back to the manufacturer for measurements or calibrations, but this will be a costly (financial and time) option.

Also, remember to ask the supplier or manufacturer to cross-reference the equipment serial number with the P&ID tags, especially on the certificates, as this will ensure a smoother build and IQ process. Certificates should be checked upon equipment delivery and, more importantly, before they are installed. This will ensure the correct equipment has been supplied (both physically and in terms of paperwork) to minimise any correction work required later.

3D MODELLING

3D modelling is a great asset for engineering of a pharmaceutical project. The designers, engineers and client can visualise their plant and identify any issues (eg gravity draining, access, manual handling, space restrictions, ergonomics, maintenance requirements) before build. This will also facilitate discussions on access for instrumentation periodic calibration, services sampling and filter integrity testing requirements. These activities are critical for ensuring process validity for drug production and should be considered during design, as they may be performed in-situ or offline. The 3D model also assists in discussions with suppliers, especially for purchase of bespoke equipment (eg vessel, valve block/manifold). The use of a 3D model provides an optimum, agreed final design that allows isometric drawings to be developed for fabrication work. This will save fabrication time as well as on-site build time. These isometric drawings will also be used during IQ.

Another advantage of 3D modelling is the option for a skid-based system. 3D modelling allows the visualisation of the build, support, and disassembly, which enables skids to be easily transported to site and moved into final location. This

FIGURE 4A: (LEFT TO RIGHT) 3D MODEL VS BUILD FOR REACTION VESSELS WITH ASSOCIATED PIPEWORK AND INLINE EQUIPMENT

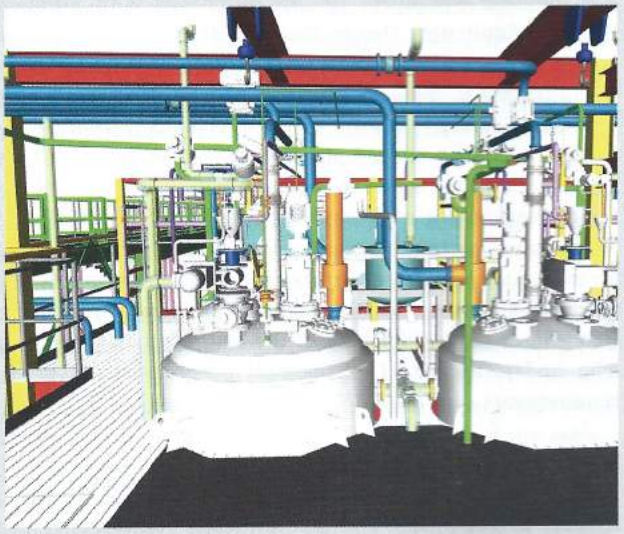
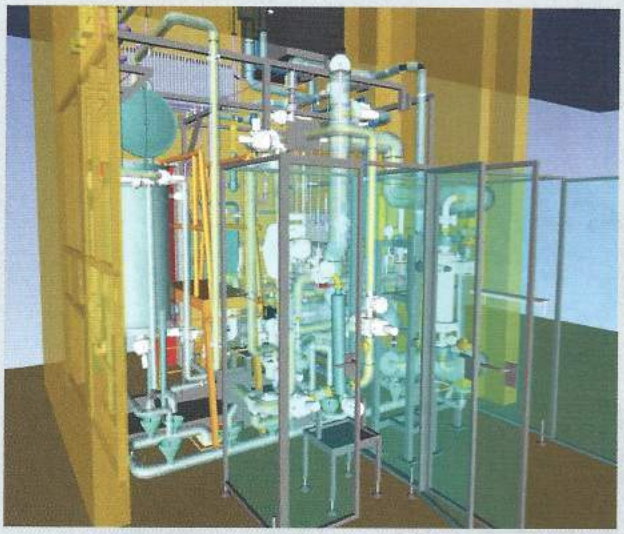


FIGURE 4B: (LEFT TO RIGHT) 3D MODEL VS BUILD FOR BEADS CLEANING AND DRYING SKID-BASED SYSTEM



is a better and cleaner fabrication option, especially when installing in clean rooms (where cutting or welding is more restrictive). However, 3D modelling can only be successful following a detailed site survey (including ingress route). This should be performed at the beginning of the project. Communicate any site changes throughout the project clearly to the design team. It may be funny later, but it will not be funny during ingress if the skid is marginally too big to fit through double doors or an airlock. *Figure 4* presents examples of using 3D modelling as a visualisation and design tool, which eventually translates into the final build.

SOFTWARE

To produce a regulatory-approved drug, it is key that the production and cleaning processes for each drug batch are identical. This is achieved by having validated recipe(s), software, and cleaning procedures. Software will be tested and validated during OQ. Recipe(s) will be validated during PQ. Cleaning procedures will be validated as part of the cleaning validation regime.

TO PRODUCE A REGULATORY APPROVED DRUG, IT IS KEY THAT THE PRODUCTION AND CLEANING PROCESSES FOR EACH DRUG BATCH ARE IDENTICAL. THIS IS ACHIEVED BY HAVING VALIDATED RECIPE(S), SOFTWARE, AND CLEANING PROCEDURES

As a minimum, key instrumentation, as identified during CGMP IA, will be trended, and logged. Operator(s) will have to acknowledge any alarms that appear, and typically if alarm(s) occur, this will question the integrity of the batch. Where process parameters are critical, some may install additional protections, for example a barcode scanner (to ensure the correct parts – eg filter cartridges, gaskets – are installed) or dual electronic signatures (for counterchecking). The human machine interface (HMI) will have password protection and time-based auto-logoff. Access will typically be based on authorisation levels (eg administrator, supervisor, operator, engineer). All these functionalities will form an audit trail for each drug batch.

CONCLUSION

So, is engineering of a pharmaceutical project more challenging? The answer is no.

However, it does require a level of attention to detail, as well as fully understanding the process and project requirements. This is because each pharmaceutical project is unique, and therefore requires care and attention to ensure successful design, install, and operation ultimately. Clear communications and realistic time management are key, as with any other engineering projects. Good luck, have fun and enjoy the opportunities! ■

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