MANAGING COSTS AND SCALE-UP RISKS FOR **MEDICAL DEVICES**

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Much has been written about the use of Quality by Design (QbD) during the development of pharmaceuticals. The same principles can equally be applied to medical device and drug/device combination products.

This blog describes a methodology to ensure that QbD and Design for Manufacture (DfM) are considered in a pragmatic way at all stages of development. The resulting medical products can be brought to market faster and, crucially, at lower ongoing manufacturing costs. The methodology also ensures seamless scale-up between clinical supply and commercial volumes. We believe these ideas are also applicable to ATMPs.

THE CHALLENGE OF NEW MEDICAL DEVICE DEVELOPMENT

Successful new product development (NPD) projects drive company growth and sustained competitive advantage. It is widely recognised, however, that all industries have intrinsic NPD risks. Medical device and pharmaceutical NPD projects also have to consider the complexity of regulatory regimes and the requirement for clinical trials. These risks and some of the common ways of mitigating them are summarised in Table I.

TYPE OF RISK	MITIGATED BY
Technical - “will it work?”	Prototyping and clinical trials
Market - “will it sell?”	Market studies, and/or voice of the customer (VOC) interviews. For medical products, preliminary research to understand the reimbursement for the product is important and can vary significantly by region.
Intellectual Property - “freedom to trade?/ Protected from copies?”	Patent searching and applying for patent protection
Regulatory - “Are we allowed to sell?”	Planning the submittal process and preliminary discussions with regulators. For products that will be launched into regulated environments regulatory acceptance of the product is critical
Supply chain - “can we make it at an affordable price?”	Considering the manufacturing methods early within the product development. Prototyping the manufacturing process

Table I: Typical NPD risks

Unfortunately, supply chain risk and DfM are often ignored until late within the NPD process. Blog author Dr David Seaward, 3P Founder and Projects Director, has observed two recurring reasons for this oversight: first, a lack of automation experience within device development teams, which are often clinically led, means that the early phase development team is unaware of the impact of their design choices on the ultimate cost of goods: secondly, the “funding gap” — or so-called Valley of Death — between initial research and the commercialisation of a new medical device means that DfM is perceived to be unaffordable. As a result, high costs can be incurred late in a development programme that would have been eliminated by a low-cost investment much earlier. Does this sound familiar for ATMPs?

This is a particularly short-term view for medical devices, wherein early product design decisions adversely “lock in” expensive long-term manufacturing costs. Once clinical studies have been done, there is a natural reluctance to change even minor product features to make production more efficient and reduce the cost of goods.

The perceived and real need to repeat clinical studies with inherent timescale delays and additional costs prevent late-stage product changes that could improve production. Yet, ignoring DfM early in the product development lifecycle leads to higher than necessary costs of goods for the life of the product. The author believes that there is “better way” that can be applied to medical devices and combination pharmaceutical products.

QBD AND PAT

This "better way" uses many of the concepts found within the pharmaceutical industry's QbD initiative and Process Analytical Technology (PAT). These, in turn, draw heavily on the experiences and methodologies developed within other industries (such as Six Sigma). This change in mindset was driven by absolute need of the drug production sector to ensure the availability of safe, effective and affordable medicines. Traditional regulation and validation had led to low-efficiency manufacturing that "tested in" quality, resulting in inefficient and outdated manufacturing processes ... and expensive medicines.

The industry had been reluctant to introduce novel and more cost-effective technologies owing to regulatory uncertainty. But, the governing framework changed in 2004 with the publication of the US FDA's PAT Guidance[1]. This has been supported with a number of guides from the International Conference on Harmonisation of Technical requirements for pharmaceuticals (ICH, ich.org). Again, does this sound familiar for ATMPs?

THE "BETTER WAY"

Any risk is best mitigated by recognition and proactive management. The following methodology identifies manufacturing risks early when costs and impacts of change are low. This leads to the early elimination of unfeasible options such that development projects become easier to predict and forecast, both from a cost and schedule perspective. Although the production of many ATMPs is based on laboratory processes, it's still possible to make automation changes that reduce the cost of goods ... IF the process is understood.

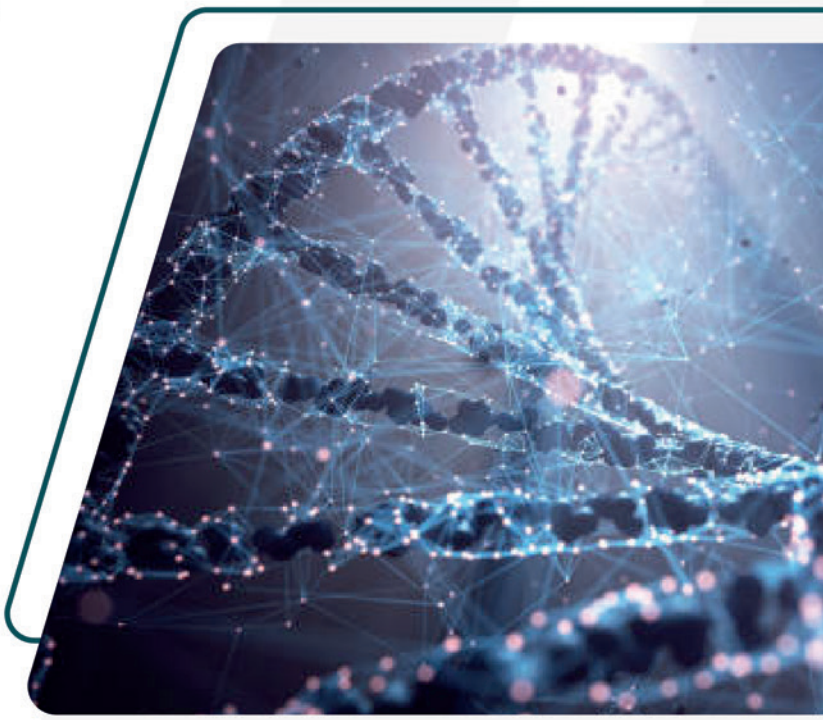
Ensuring that a manufacturing process is efficient, offers low reject levels and relies on robust processes that operate well within their specifications is the very essence of Six Sigma. Of note here is the concept of Critical Quality Attributes (CQAs): these are properties or characteristics of the product that should be within an appropriate limit, range or distribution to ensure the desired quality.

Medical devices, for instance, can be considered to comprise a number of subcomponents that are brought together using a number of processes or unit operations (such as assembling, mixing, sealing, filling, coating, heating, gluing, etc.). For ATMPs, these unit operations might include cell harvesting, apheresis, cell preparation, selection, cell expansion, centrifugation, filtration, purification, chromatography, controlled heating, controlled cooling, fill/finish, controlled freezing/thawing, in-process testing, storage, lyophilisation and product release testing.

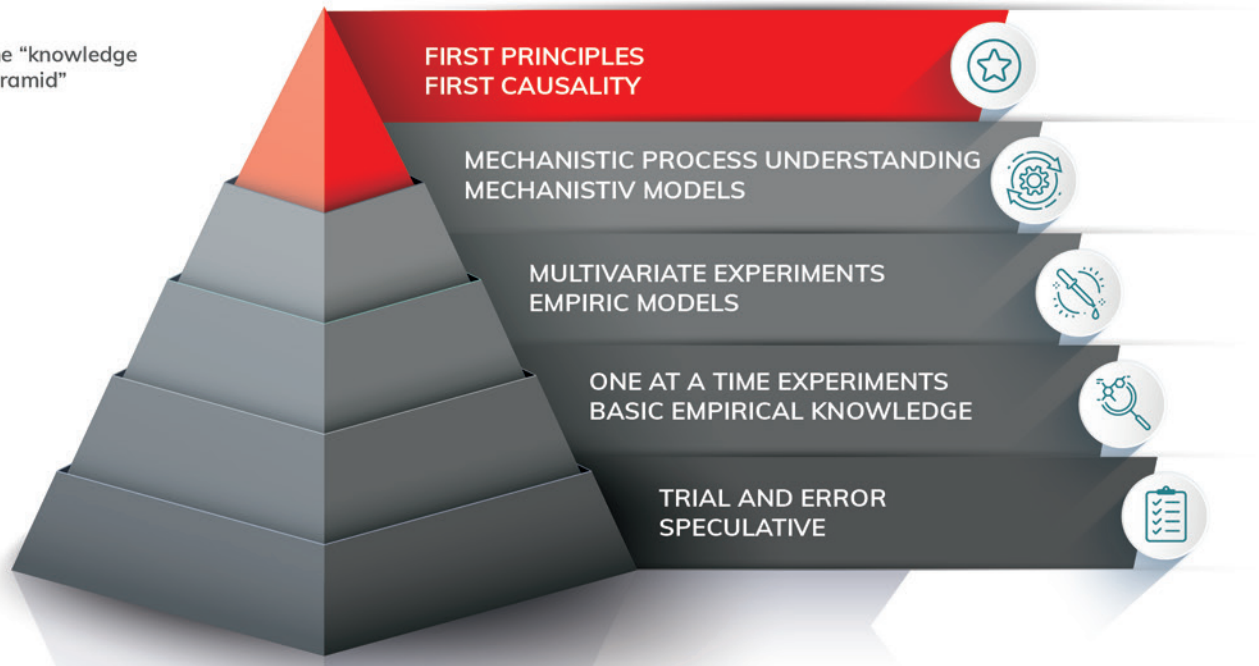
Every procedure will have desirable (promote) and undesirable (eliminate or identify and reject) transformations that the process may generate. For example, when considering a medical device made up of plastic parts, a desirable transformation would be the clipping together of two plastic pieces, whereas an undesirable one would be a mechanical clash leading to component damage. Similarly, during cell expansion, a desirable transformation is the creation of sufficiently viable cells whereas an undesirable one would be cell mortality.

Now would be a good time to introduce Critical Process Parameters (CPPs): these are independent process factors (such as position, time, temperature, pressure, etc.) that can be controlled in a production process and that are most likely to affect the CQAs. As life science automation specialists, 3P's engineers focus on CPPs. These are the things we can control as engineers within our machines/systems.

In an ideal world, the interrelationship between CQAs and CPPs would be fully understood and described by formulaic relationships. However, the real world is multidimensional with interrelationships that are often poorly understood — particularly when it comes to producing novel product such as ATMPs. Given that batch sizes are often "one," it becomes challenging to run any form of design of experiments (DoE) to build a statistical model.



The "knowledge pyramid"



As described earlier, the way a product is to be made may have been ignored during early development. The level of understanding of any process can be described schematically as a "knowledge pyramid." At the base of the pyramid, information is obtained via trial and error and assumptions are made regarding any links between CQAs and CPPs (so-called Dark Arts). As one travels up the pyramid, more precise links between inputs and outputs are derived. During any NPD, the aspiration should be to travel up the pyramid. All too often, though, core processes that are key to a product's efficient manufacture remain near the base.

PROTOTYPES TO MITIGATE RISKS AND THE USE OF INSTRUMENTED AND SCALABLE PROCESSES

"Will it work" risks can be mitigated by generating working models and prototypes, doing functional tests and, ultimately, running clinical studies. 3P are great believers in "fail early, fail fast" and have developed ways of working to front-end load risks as a way of minimising them. A series of blogs on the subject is available on the 3P website within the blogs section (www.3pinnovation.com/media-events/blog).

The increasing use of functional prototypes has enabled product developers to test many different designs rapidly and cost-effectively. What took many months to accomplish a decade ago can now be done in a few weeks and at low cost. There is an equivalent methodology for process development and DfM that involves prototyping the manufacturing process: a rapid prototype can also be used to mock-up the assembly and production processes.

So, how does one move up the knowledge pyramid to ensure robust processes and low cost of goods? It's a challenging and complex multidimensional problem. The author has found that a number of relatively simple and straightforward activities will significantly increase a team's understanding of product manufacturing processes. The activities also identify any risks that need to be addressed (see Sidebar).

In any manufacturing system, there will typically be a number of connected machines. Mapping and flowcharting these processes will provide an initial indication of the numbers and types of equipment that may be required. In essence, any machine can be thought of as a sequence of unit operations, during which only a limited number of working parts — end-effectors — interact with the product.

3P has developed a way to identify the critical end effectors and their motions, and build them into simple, manually driven tooling. Crucially, this is done in a way that is scalable to commercial capacities. Techniques such as poka yoke can also be introduced.

Operators load and unload components into tooling (sometimes referred to as pucks or nests) and all subsequent actions are done by simple levers, slideways, etc. Any specialist processing elements (such as sealing or gluing heads) can be mounted on the tooling. Crucially, the operator is not normally allowed to perform the process directly — only indirectly via mechanisms.

When specific process understanding is required, additional sensors are added. For example, the real-time trace of force when two parts are clipped together can provide invaluable insight into the process robustness.

The torque to activate a lever provides similar insights: the pressure and flow can be used to detect leaks or to quantify the size of a small orifice. Process sensors can provide data to support product design changes: often, very minor amends to component design can lead to significant improvements in product function and/or manufacturability.

One high-volume example saved 3P's client more than £250,000 a week in terms of production efficiencies between an old product developed using traditional techniques and a new one developed using a 3P instrumented assembly fixture.

A range of labour-intensive product process development machines

It will be appreciated that a manual production line can be put together by linking a number of individual assembly systems. This is ideal for low-volume sample production. For ATMPs, for example, using the "hub and spoke" methodology for production (more of which later), these small pieces of equipment act as perfect stepping stones to benchtop scaled-out equipment in the spokes. For some projects, 3P has seen that such systems were so successful that multiple units were produced to enable the rapid and low-cost manufacture of higher volume batches ... albeit with more operators.

When settings/tolerances are important, the equipment can be designed such that tolerances can be mis-set in a controlled manner. Using this methodology, process robustness can be determined and managed early within a product development lifecycle. This enables DoE, which provides process understanding.

In QbD terminology, the "design space" and "control space" can be determined. The standard deviation for CPPs and CQAs can be ascertained and the robustness of a given process assessed. It is not uncommon for unit operations to be found wanting with one or two sigma capability. As mentioned earlier, once a process is understood, very simple changes to the process and/or the product can convert a poor procedure into a robust (Six Sigma) one. The saying that you "can only control what you can measure" is very true.

Most medical devices contain a number of interacting injection-moulded plastic parts. Initially, these will be prototypes. Single cavity moulds will be used for higher clinical volumes and multicavity moulds will be used at commercial scale. It is normal to see wider dimensional variability from a multicavity tool than from a single cavity mould. It is also normal to see differences in the mean dimensions with different coloured parts (the colourant, usually referred to as the masterbatch, changes the level of post-injection shrinkage): one colour may be dimensionally different to another made from the same mould.

By using manual tooling early within a product development process, tolerances can be identified at the outset; making minor changes to the product design early during development often convert a borderline process into a robust one. The most appropriate datum features within components and subassemblies can be identified and, again, minor changes made to accommodate them. Manual assembly systems are therefore used as valuable product development tools.

There are occasions when the motion profile of the end effector is a critical process parameter in its own right. There are also occasions when very high volumes of samples are required beyond those that can be practically made using non-automated systems, and yet which do not justify the investment in commercial, high-output ones. An intermediary solution between manual and fully automatic systems exists in semi-automatic assembly. In a semi-automatic system, the operator loads components into tooling or a puck. The components in the puck can then be manipulated with a series of automatic (pneumatics, servomotors, robots and the like) or manual operations as required. In both situations, additional sensors can be used to provide process understanding.

With knowledge of the target commercial machine, one key advantage of semi-automatic systems is the ability to fully replicate and mimic the process used in a commercial system, albeit at lower capital cost and throughput (although output speeds will be lower than the commercial system, the process speeds can be representative). What does this mean? Using a puck-based semi-automatic system eliminates scale-up risks between clinical and commercial volume manufacture whilst providing a cost-effective route to clinical sample supply.

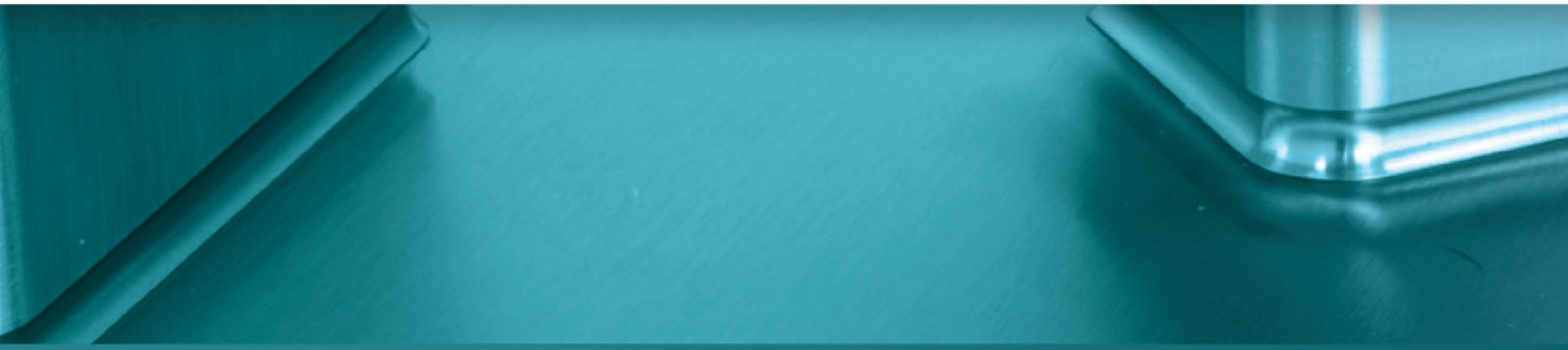
The implementation of the above methodology ensures that medical devices are developed with the needs of manufacturing from the outset. This, in turn, leads to high efficiency, high quality processes with low rejects, all of which helps to reduce the cost of goods. Prototype manufacturing systems also provide the additional benefit of a low-cost method of producing initial low volumes of samples for clinical trials.

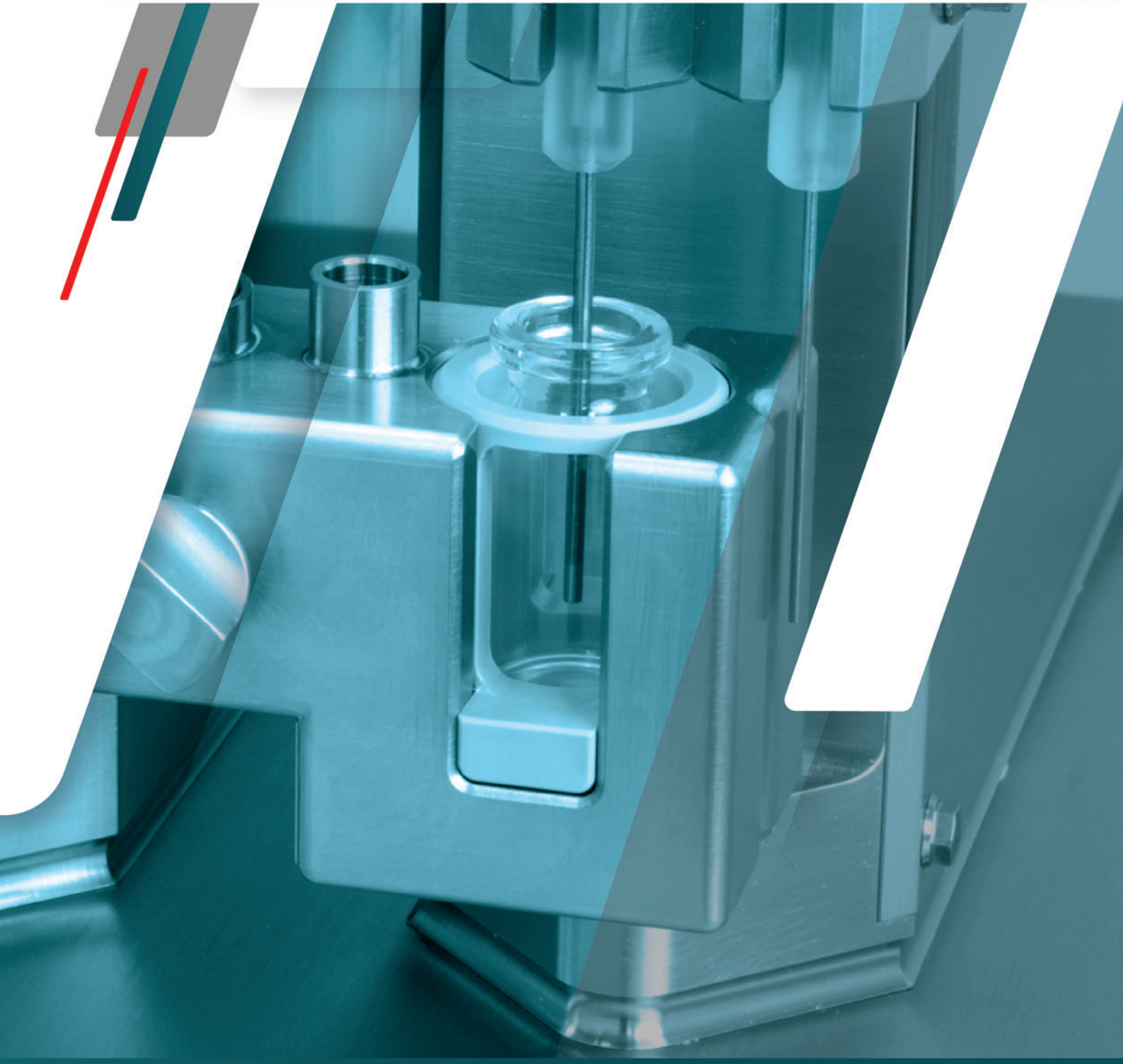
A range of semi-automatic product process development machines

CONCLUSION

The medical device development process often ignores DfM, resulting in inefficient commercial production and relatively high costs of goods. 3P propose a “better way,” whereby the requirements of automation are considered early within the medical device development process. A DfM methodology using QbD principles has been provided.

The concept of prototyping the manufacturing process using instrumented manual and semi-automatic assembly systems has been proposed. This also provides a low-cost method of providing clinical samples from a scalable process, all of which leads to lower ongoing costs of goods.





SIDEBAR

Suggested activities to ascend the knowledge pyramid

Generate and then maintain a list of CQAs for the product: This will evolve with the product development and ensure that any known tolerances and methods of measurement are also recorded.

Generate a list of all possible unit operations: There will always be alternative processes with pros and cons — such as clip, glue or screw together. For ATMPs, the unit operations are likely to be "locked and loaded."

Identify plausible ways to link the unit operations together to form routes to manufacture: Again, for ATMPs, these will be defined and unalterable.

List the inputs (product materials and components) and outputs (subassemblies and intermediaries) to each unit operation: Are there any methods to measure and control the unit operation?

Consider all the transformations the unit operations can generate (both intended and unintended): Often, the best way to gain process understanding is to discuss "what goes wrong" as opposed to "what goes right."

Generate a table for each transformation and subjectively list the expected directional links between process parameters and transformations: Identify any likely CPPs that related to CQAs. Often, experts have an intuition about these links but are unable to quantify them numerically. The insight is valuable; for example, it would be useful to know that the optimum temperature at which to harvest cells is also the maximum!

Generate and maintain a risk log, which is continually updated: Identify what could be done to mitigate the risk.

REFERENCES

1. https://www.fda.gov/media/71012/download