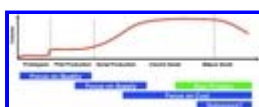


Increased disposable income

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Disposable devices for pharmaceutical manufacturing and point of care (POC) diagnostic products can offer lower costs but planning is needed to deliver that objective. Ian Fitzpatrick, manager of manufacturing innovation at contract developer and manufacturer Invetech Pty, looks at strategies evolved to ensure disposable components work and provide cost benefits

Pharmaceutical production facilities are introducing single-use production sub-systems to support greater product diversity and faster batch turnaround. While this creates new challenges to register facilities for multiple products, increased use of these major investments will continue to drive this behaviour.

The medical industry was the first to understand the benefits of using disposable devices, such as needles and syringes, to prevent risks of cross contamination. The technology was then extended to blood transfusion activities, and it was only 10–15 years ago that the biopharmaceutical industry started to use disposables. Disposable process technologies are commonly in place from early pilot to large-scale batch

production. Commonly these implementations are based on unit processes such as the fermentation step. Increasingly, integrated process stages are being assembled to deliver steps such as seed train development and clean-up operations.

Justifying and scoping these developments needs to anticipate the capital cost of disposable development and tooling to identify the configuration that can be justified. These strategies are radically changing the electro polished dedicated plant paradigm, creating opportunities for new drug production at substantially reduced costs using shared production facilities.

This story becomes richer where the need to manufacture multiple overlapping batches within common facilities occurs. Fully automated vaccine production systems built around disposable devices are enabling therapies targeting single patients. Batch record management, traceability, sterility, labour and many other costs that affect autologous and targeted therapies are substantially addressed through the use of closed, single-use processing systems. The commercial viability of these therapies largely lies in the strategies that disposable processing systems create (see figure 1).

POC medical diagnostic systems are commonly developed using the Razor/Razorblade model where a processing instrument is supplied at cost on the assumption that sales of the disposable components will provide the commercial return of the product. POC diagnostic technology includes portable, instrument-based diagnostic devices used in near-patient hospital and alternate care settings. Advancing technology provides opportunities for the traditional laboratory testing to move closer to the patient with testing and analysis taking place at the bedside. This has made POC testing increasingly valuable in many clinical settings (Figure 2).

hurdles to success

Many POC diagnostic products employ single-use disposable cartridges. Others use multiple-use disposable cartridges with up to 100 uses over 72 hours. Products aimed at POC applications face several additional success hurdles compared with lab-based diagnostic processes. The diagnostic is commonly initiated and managed by personnel not familiar with management of scientific equipment. Calibration against standards, sample preparation, and equipment status monitoring need to be managed by the device.

POC systems must reproduce many of the subsystems found in today's complex laboratory analysers without the support of skilled personnel to manage them. The expectation of immediate results by the user leaves no room for equipment malfunction. The absence of skilled technicians is a further demand on reliability.

One strategy is to include all the high-risk sub-systems in the disposable cartridge. In the event of a failure, replacement of the cartridge will replace the primary failure mode sources.

fluctuating demand

The active reagents and assay reference components supplied with the disposable cartridge are commonly present as small volumes within a container that has functions beyond storage. The cartridge shelf life can often be shorter than reagents for similar tests stored by traditional processes. This can add substantially to cost of test where inconsistent demand is experienced. Situations of inconsistent demand, where a local large scale laboratory and associated personnel cannot be justified, would seem to be ideally suited to the introduction of these POC systems. This is an example of the practical conflicts slowing adoption of the technology change.

Despite these challenges, POC instruments that employ disposable devices are developing acceptance. Test protocols of increasing complexity are being packaged. For example, onboard DNA separation and PCR amplification in a single use device is being developed for a range of applications (Figure 3).

High volume POC consumables and medium volume closed processing disposables are key to process function-ality. The capital cost of tooling and commitment to validation will restrict opportunities for changes to these products once the commitment is made.

The decisions made at design time will affect the viability of the product throughout its lifecycle. Equally, the opportunity is to create a design that delivers ongoing supply and reducing costs throughout its life. The

tools we use to realise these opportunities in the design process are described below.

Anticipation of the lifecycle needs of a product enables the choice of production technology to be set upfront with confidence that it will meet your needs. The quality testing systems required for the processes and the functional verification testing required before the design is signed off can be set up at the earliest stage of development. Material costs and assembly process planning allow production systems to be conceived and budgeted that deliver cost of goods estimates and capital demand profiles.

This can all be achieved very early in the product definition process and sets a clear direction for delivering uncompromised quality at the right cost supported by planned capital spending that responds to the achieved market performance. These planning activities create a clear direction for the development process; how quality will be addressed, how scale-up will be managed; the points where capital is needed; and a solid prediction of the product cost throughout its lifecycle.

The lifecycle view is illustrated using a POC cartridge application example (see Figure 4).

When developing a disposable cartridge platform for the in vitro diagnostics industry, there are many decisions taken early in the design process that need to anticipate requirements that affect the manufacturing cost throughout the product's lifecycle. By considering the stages of product evolution from development through to phase out, the advantages of disposable product use can be maximised.

product evolution

Prototyping: Early prototyping activity requires a rapid turnaround to enable design optimisation. The prototyping techniques need to deliver consistent components for representative verification. The prototyping processes need to lead to higher volume manufacture with low cost.

Establishing Product Quality: Moving from prototyping to early pilot production, the ability to deliver 'right first time' product quality is increasingly important. Often pilot lots will be used for clinical trials to verify product claims. Quality processes will be driven by the manufacturing process capability that can be achieved at this stage. For example, end of line quality testing quantities will be strongly driven by the process stability established at this time. Once the product is launched to market, the opportunity to change manufacturing processes is limited by validation constraints.

Product launch and scale-up: Products with high volume sales projections and healthy capital support can be established with production equipment fully developed for the planned market. Slower scale-up models with less certain market projections combined with a conservative capital plan, demand different approaches. For example, a manually operated assembly process, supported by automation of critical quality functions can provide a minimum entry level.

Lean manufacturing strategies such as flexible manning allow manually expedited processes to meet demand efficiently through early production volumes. Planned expansion of production capacity can identify sales volumes where the next stage of production capacity is justified and trigger the investment decision.

Incorporation of quality critical automation functions from earliest manufacture can minimise exposure to disruptive product re-validation in new production systems. These strategies allow a capital investment plan to be determined early, facilitating an orderly expansion of capacity as the market grows.

cost drivers

Mature production and cost reduction: As demand for the product plateaus, it is common to scrutinise the manufacture for cost reduction opportunities. A product's cost of goods is, however, principally defined at design time. Materials sourcing, processing and labour costs can be anticipated from early on in the product development. The cost of goods at the mature production level can therefore be estimated. This early understanding of product cost drivers enables cost of goods targets to be anticipated and achieved during the mature production phase. Failure to appreciate the cost drivers, such as end of line quality testing commitments arising from poor process stability, for example, can have a significant impact on product margin that is difficult to recover.

The decision to outsource can occur at any point through the product lifecycle. The organisation may strategically wish to avoid supporting a cGMP facility, or there may come a time where a new product is

being introduced and the existing mature production can be relocated to an external facility. In any event, understanding the manufacturing plan and the impact of product design and other decisions on that plan will facilitate negotiations on price and capital commitments with the manufacturer.

To create a plan for new product manufacture, the following tools deliver sufficient detail with relatively little effort:

- A design for manufacture review to explore competing component fabrication options
- A quality by design review that identifies design changes, manufacturing process features and quality test protocols needed to achieve 'right first time quality' for the product
- Manufacturing system configurations that address the range of production volumes. These are used to identify manning and capital requirements for manufacture
- A product cost model applies material costs and the manufacturing approaches to predict cost of goods driven by volume
- A manufacturing strategy is created to match the marketing scale-up plan. A capital spend profile then drives into the business plan

These tools deliver an implementation plan focused on right-first-time quality with capital expenditure appropriate for the volume. Like any manufacturing activity, successful implementation requires commitment from management, production and quality assurance teams.

The implementation of single-use systems into pharmaceutical manufacturing processes and diagnostic platforms introduces additional compromise decisions to be made at design time. Strategies that anticipate the product lifecycle can be introduced early in the design process to deliver robust outcomes.

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