Phillips Medisize

Partnerships Built on Innovation

SCALABLE AUTOMATION FOR DRUG DELIVERY DEVICES

Today's medical device and pharma industry assembly concepts can be complex. Here, Bill Welch, Chief Technology Officer, Phillips-Medisize, outlines why, therefore, the company provides a comprehensive assembly concept, tailored to customers' needs. Scalability begins with early DFM/DFA philosophy integrated into the product development process.

It is commonly estimated that 80% of a product's cost and quality is determined during the first 20% of the product development timeline. As such, whether the commercialisation strategy involves in-house manufacturing or the use of a contract manufacturing organisation (CMO), early integration of a strong design for manufacture (DFM) and design for assembly (DFA) philosophy is critical to the device quality, cost and risk during clinical builds and commercial launch. A strong DFM/DFA philosophy ingrained within the product development process ensures manufacturing quality, cost, and risk objectives are met, without losing sight of HFE and the end-user device needs.

In a more general sense, DFx refers to "design for x", in which "x" may be any desirable attribute. At the component level, DFM, or the more specific design for mouldability for injection moulded components, refers to ensuring the product design conforms to the guidelines for the manufacturing process to be used. This is especially critical in drug delivery devices, since plastics are the most common material for mechanical components. Further, component-level DFM forms the backbone of the assembly process – regardless of the planned level of automation – since the process capability at the component level is necessary to reduce variation in the assembly process.

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Similarly, DFA is done concurrently with product design, with quality, cost, and risk of the assembly in mind. At the component level, this includes addition of features to make part handling, positioning, orientation, and inclusion into the assembly or sub-assembly. Component-level DFA ensures a mistake-proofing plan is established, which is also necessary to reduce variation in the assembly process.

Additional benefits are gained by concurrent DFM/DFA throughout the product development process, for example to reduce part count and eliminate high-risk assembly operations. Multimaterial, or multishot, moulding is one approach to combing components that eliminate complex assembly operations and provide an elegant solution to design problems such as sealing to prevent moisture intrusion. Early DFM/DFA team collaboration can then evaluate the return on investment of the upfront mould tooling costs to reduce assembly equipment and labour costs, prior to finalising the design.

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BOX 1: FIVE LEVELS OR CLASSIFICATIONS OF ASSEMBLY

In order to facilitate development of a manufacturing strategy, it is useful to leverage a high-level common language and terminology for tooling and assembly classifications. Such classifications are not intended to replace the actual specifications, but simply to ensure all team members can understand and agree in concept as to the initial, interim, and final approaches to be taken to meet engineering, clinical and commercial volume requirements.

Achieving conceptual agreement and alignment as rapidly as possible allows the tooling and automation engineering specialists to develop the detailed specifications right the first time, thereby eliminating rework that increases resources needs and timeline.

The table below shows the five classes Phillips-Medisize uses to describe different levels and types of assembly, and examples of Class II and III assembly lines are shown in Figure 1.

	Step Change Required	Step Change Required	Scalable Process		Prototype Process
DMC Classification	Class I	Class II	Class III	Class IV	Class V
Relative Description	CAM Driven, multi-up, fully integrated, high speed automation. Human precense required for monitoring only. Self diagnostic with built in compliance and integrity checks.	Rotary Indexing Table or Integrated Linear System, with automated part feeding/conveyance. Single or multi-up capable. Fully automated work cell. Limited human interaction.	Scalable Manumation with multiple station and multiple operators.	Manumation with a single operator station.	Manual Operation that may include hand press, special tooling, and part fixtures.
Types of Use	Automated Production	Automated Production	Combination of Full / Semi- Automated	Semi-Automated	Manual Operation
QA Requirements	Automated Inspection & DAQ	Automated Inspection & DAQ	Some Automated Inspection, No DAQ	Manual Inspection	Manual Inspection
Product Handling	Automated Conveyance	Automated Conveyance	Conveyor or Robot	Conveyor / Manual Transfer	Manual Transfer
Capacity	~ 20MM EAU	~ 5MM EAU	~ 1MM EAU	~ 0.50MM EAU	~ 0.10MM EAU
Capability*	Established Global Provider	Established Global or Regional Assembly Line Provider	Established Regional Assembly Line Provider	Regional or Local Assembly Line Provider	Regional or Local Assembly Line Provider
Cycle Time	1 PPS	10 PPM	5 PPM	5 PPM	2 PPM
	e.g. injection pens	e.g. safety syringes	e.g. filters	e.g. insulin pumps	e.g. IV-Sets

*Requires ASL Grading

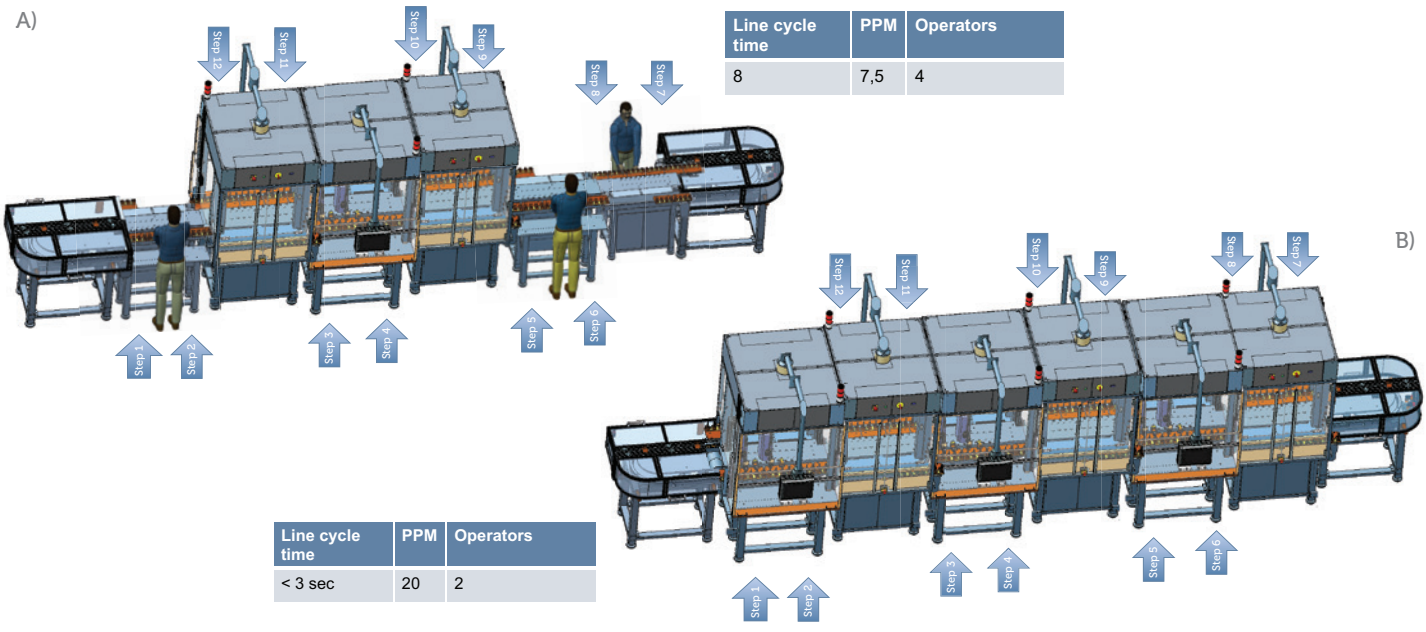

Figure 1: Examples of different classes of assembly line with A (top) showing a Class III line, partially automated with manual stations achieving 7.5 parts per minute (PPM) and B (bottom) showing a fully automated Class II line achieving 20 PPM.

While DFM/DFA must start at the component level to facilitate future scalability, the application of DFAA (Design for Automated Assembly) is also applied concurrently by the DFM/DFA team. DFAA is the next level, designing assembly processes in which components are oriented, handled, assembled, and transported through an assembly process without manual intervention.

- DFAA focuses solely on the automated assembly process, which is defined as "automated" only if the process does not require human interaction
- DFAA application makes interim manual assembly processes to support builds prior to automation build and validation easier. A device that is easy to assemble manually will lend itself to automated assembly. Component-level DFA alone does not develop processes suitable for automated assembly
- DFAA requires specialised automation engineering involvement in the beginning phases of the development process to ensure automated assembly is taken into consideration in parallel with other DFx.

Box 2 summarises ten often overlooked DFA/DFAA guidelines for drug delivery devices.

In summary, successful DFM/DFA needs to be an underlying philosophy truly integrated into the product development process. It cannot be viewed as a "checklist", step, or phase to be completed on the individual components after the drug delivery mechanism design is nearly complete. While at the component level an understanding of the DFM guidelines for the intended manufacturing processes is key, the greatest benefit comes from looking beyond component-level DFM/DFA to find system- or sub-system level solutions that enhance device performance while meeting human factors, quality, cost, and risk requirements.

SCALABILITY TO MEET END-VOLUME REQUIREMENTS

Increasing volume and varying production on a single system platform? Feasible! Scalability is the process to develop the manufacturing scale from the initial low-volume methods to the desired end-state volumes. In the case of a specialised, niche drug delivery device this may mean progressing from low-volume, 3D-printed components assembled by skilled technicians to a "manumation" assembly process conducted by a trained operator. In the case of a commonly used drug delivery devices, this typically means developing processes to support first engineering builds, then clinical supply, and finally a fully automated or high-speed automation process, supported first by developmental, single-cavity tooling and then incrementally higher multi-cavity tools.

Flexibility, while related to scalability, has its own definition as it relates to two primary concepts:

1. Ability to re-use assembly equipment modules when progressing from one scale level to the next, in order both to prove-out initial assembly concepts at lower scale, and save time and cost by leveraging that same equipment
2. Ability to use all or most of an entire base flexible assembly line to produce multiple, similar devices. In the case of pens and auto-injectors, this typically means matching up a device product platform with an assembly platform, with changes being primarily in the components presented to the line following a controlled line clearance and changeover process.

As with DFM/DFA, scalability considerations must be looked at concurrently with product development as part of a device manufacturing concept which is a device-specific plan to scale component and assembly production capabilities to a desired end-state, typically with iterations for both components and assembly to meet engineering, clinical, and commercial volume demand.

A well-constructed device manufacturing concept will not only consider the volume, costs, and timing of device needs, but also the regulatory requirements, risks, and geographic considerations with each iteration

BOX 2: TEN BASIC DFA AND DFAA GUIDELINES

While not all-inclusive, shown below are ten basic and often overlooked DFA and DFAA guidelines for drug delivery devices:

1. Ensure component-level DFM is applied to provide a stable and capable supply to the assembly process
2. Simplify the design and reduce the number of components, utilising techniques such as multi-material moulding for plastic components
3. Standardise and use common components and materials, both within and across drug delivery device assemblies, to minimise tooling, validation, and supply chain management costs
4. Ensure component-level DFA is applied for stable and capable orientation, handling, and placement
5. Minimise the use of fasteners, flexible components, interconnections, and adhesive / lubricant dispensing operations
6. Design mistake-proofing, part presence checking, in-line quality controls, and segregation of failed or rejected components, into the assembly process starting with initial builds
7. Design for robust assembly by minimising complex orientations and axes of assembly, beginning with components with suitable "lead-in" taper and location features
8. Manage final assembly cost and risk by strategic selection of sub-assemblies and modules in the assembly process, and ensuring high-value components and sub-assemblies are known to be of acceptable quality before integration into the next level of build
9. Design for flexible assembly to minimise time and cost associated with equipment, validation, and change-overs:
   a. Design components to use the same or similar bowl feeding, pallets, or other methods to introduce to the base flexible assembly line.
   b. Design components and assembly sequence to use the same or similar assembly and joining methods already included in the base flexible assembly line.
   c. Develop a standard set of product requirements to be subsequently inspected or tested on the base flexible assembly line
10. Design for high-speed, automated assembly:
    a. Use components that can be fed without tangling. In the case of springs, consider making the springs as part of the device assembly process
    b. Pre-orient the components when presented to the line to reduce cycle time
    c. Integrate finished device handling, packaging, and palletisation into device assembly and facility planning, since high-volume devices require purpose-built infrastructure beyond the assembly equipment itself.

of the scale-up plan. It provides clearly structured, modularly designed assembly lines which can be extended at any time, allowing fast retooling times. Essentially, the device manufacturing concept provides the "roadmap" to progress from initial, limited control engineering builds to the validated end-stage scale, meeting all quality system and regulatory requirements.

Core to the device manufacturing concept is a strong assembly systems foundation, starting with the earliest manual builds to ensure the manual process is feasible for scaling:

- Early manual builds need to establish the assembly sequence, fixturing, component orientation, and assembly operations that will be carried forward to subsequent scaling iterations
- Proper manual assembly is an enabler for higher level automation. Conversely, as mentioned above, a DFAA analysis may lead to a more robust manual assembly
- Collect and analyse reject / scrap data to reduce variation with each subsequent scaling iteration. It is imperative to ensure proof of concept has been achieved for each process before making further scaling investment
- The user requirements specification (URS) for a manual process needs to set the stage for the URS on the desired end-stage automation level. In some cases, it is helpful to draft the URS for the high volume automation first, and ensure as much as possible can be learned from the manual process.

In terms of flexibility, the re-use of assembly platform equipment is typically limited. For example, a core single-track assembly process cannot cost effectively become a four-track system such as that used for a typical high volume pen, but a single-track line platform may be scaled from manumation to semi-automation to full automation with upgrades to component feeding, orientation, assembly, and inspection / test operations which maintaining the single-track configuration.

Equipment and tooling supplier selection is an important factor of the device manufacturing concept, and consistent with DFM/DFA the suppliers should have early involvement. While ideally the same suppliers can be used for all iterations of the same equipment and tooling, in many cases this is not feasible or practical due to the technical focus, timing requirements, or global support capabilities of the supplier. For example, a quick-turn tooling shop and local equipment builder may be necessary to maintain timelines for single-cavity moulds and manual assembly fixtures, but they do not have high-volume capabilities or a global service network. In such cases, it is imperative that the manufacturing unit or CMO possess the project management, tooling engineering, and automation engineering skills to develop suitable URS and ensure any learning from initial stages is carried over to subsequent scaling iterations.

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It is critical to focus the URS on its intent, which is to define clearly and precisely what the equipment should do, and state any constraints. It is a requirements document, and not intended to be a technical document defining the system itself. Given that the URS will drive the validation requirements, it is recommended to take a modified "specific, measurable, achievable, realistic, and testable) SMART approach to URS development.

IMPORTANCE OF GAMP

The Good Automated Manufacturing Practice (GAMP) standard provides practical guidance to meet current regulatory requirements through efficient and effective use of industry practices. Given its purpose to facilitate interpretation of regulatory requirements and establish a common language and terminology, it can be tailored to a number of system types. The core principal of GAMP is that quality must be built into the manufacturing process and should not simply be measured after the product is made. Following GAMP ensures that process quality is a consideration when designing and fabricating automated assemblies and equipment.

GAMPs Key Concepts:

- Product and Process Understanding
- Using a Life Cycle Approach
- Scalable Life Cycle Activities
- Science Based Quality Risk Management
- Leverage Supplier Involvement

So what does this mean for automation and Phillips-Medisize customers? It means that our customers in the medical device, pharmaceutical, and life sciences industries are assured that our machines are designed and built under a quality management system. It begins with a URS for the machine, from which a functional requirement and a design specification is created. Those documents are the basis for the traceability matrix for the formal testing milestones of internal acceptance, factory acceptance, and site acceptance. Phillips-Medisize automation processes are GAMP-5 compliant, providing our customers the quality of service they require.

SUMMARY

Scalability for drug delivery devices begins with concurrent engineering via DFM/DFA and development of a device manufacturing concept. Use of common definitions for classifications of tooling and assembly equipment can be used to align the team on the concept, and enable the tooling and automation engineers to then specify, via the URS, the process requirements and select the appropriate suppliers for each scaling iteration. Therefore, the manufacturing unit or CMO must have the capabilities to provide effective DFM/DFA and development of a device manufacturing concept, in addition to capabilities for the project management and technical execution of the plan.

Phillips-Medisize has a long experience in managing different kinds of assembly concepts, from low-volume (smart assembly) through high-volume (high-speed automation) and is able to find the optimal assembly concept by looking at costs, volume and ramp-up schedule to meet the targets within budget, time and specification. Strategically-located resource centres support global manufacturing operations, and the companies´ global footprint allows flexibility in production while optimising capacity.