

Aseptic Filling Expertise

High Quality
Pharma Technology Design



Introduction

Technological developments in the pharmaceutical industry have advanced rapidly over the last decades. One field of particular interest has been aseptic and sterile primary packaging. Primary packaging of pharmaceutical products often involves filling containers (including vials, syringes and bottles) with powders and/ or liquid solutions. Manufacturing staff, equipment and premises are all subject to stringent quality controls – and for good reason: patient safety.

In order to ensure the safety and quality of pharmaceutical products, every manufacturer in the pharmaceutical industry is compelled to adhere to the Good Manufacturing Practice (GMP) guidelines. Recently, a complete draft revision¹ of Annex 1 (Manufacture of Sterile Medicinal Products) of the GMP has been released. This document intends to provide information on the latest status, trends and technologies in parenteral filling equipment.

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How does the industry choose a sterile dosage form and how does this influence the packaging?

Pharmaceutical companies make their choices for a dosage form based upon the unique product features of the medication.

The dosage form for any medication needs to be correctly developed to provide proper administration for the patient to receive maximum benefit, and the conception of the therapeutic regimen is fundamental. The dosage forms are getting more specialized, constituting true systems that display characteristics to release the medicine at a rate that perfectly matches the real need in vivo for the duration of the therapy and to deliver the medication exclusively to its target site.

A parenteral dosage form is a sterile medicinal product. It can be presented as a solution, suspension, emulsion, or reconstituted lyophilized powder and needs to be suitable for administration by injection. For each medicine and dosage form, the most suitable packaging needs to be determined by the R&D pharmaceutical scientific team. Based on the unique product features of the medication and the preferred/optimal route of administration the most effective and efficient dosage form will be selected"



What does the pharmaceutical packaging industry demand?

Pharmaceutical companies are increasingly investing in their services and capabilities to span R&D through manufacturing, filling and packaging in their quest to differentiate the products based on the increased demand for

personalized medication and customer experiences. Therefore, the need for flexible small- to large-scale manufacturing, integration options and isolator technology for all sorts of dosage forms is notably growing.

What packaging challenges does the industry face as a result of the Annex 1^{III} regulatory framework?



The manufacture of pharmaceutical sterile products is always subject to special requirements as described in the guidelines and principles of GMP and its annexes published by the European Medicines Agencies. The latest draft of the Annex 1 guideline is centered around three key points:

Quick Response Manufacturing

Quick Response Manufacturing (QRM) refers to the ability to flexibly and immediately take action in case of safety breaches in the production process. The QRM strategy focusses on time management as the most significant factor in cost reduction and process optimisation.

Personnel

Personnel involved in the primary packaging of pharmaceutical products is required to possess the appropriate knowledge and expertise needed to adhere to the strict regulations in and around cleanrooms and other clean areas. The number of operator interventions needs to be reduced to a minimum to decrease the risk of contamination.

Quality Assurance

To comply with GMP and specifically Annex 1, Quality Assurance is of vital importance. QA encompasses a wide range of aspects that may affect the quality of the product.^{IV} It serves as a guarantee to the end-user of the product that this product is of consistent and reliable quality.

Part of QA is serialization and aggregation of pharmaceutical products for maximum traceability throughout the supply chain.

Now that pharmaceutical companies more often produce small quantities, they need flexible machines that can process small batch sizes with a variety in container types and dimensions. At the same time, it remains essential to maintain the highest-level requirements and follow these GMP guidelines to increase product quality, production environments and patient safety.

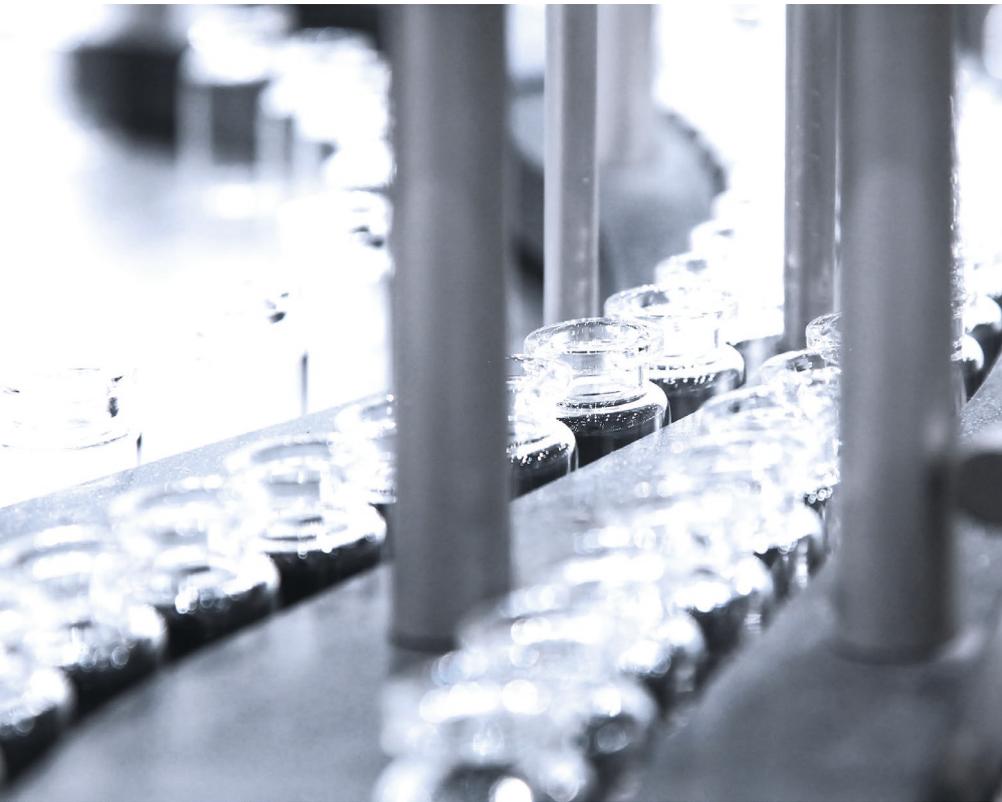
Filling Technology

„The total global injectable drug delivery market, in terms of value, is projected to reach USD 624.50 Billion by 2021 from USD 362.38 Billion in 2016, at a CAGR of 11.5% during the forecast period.“

In addition, the advanced developments in isolator technology (creating a sterile environment for the transfer of sterile products during the packaging process for example with laminar air-flow) supports the growth of parenteral dosage forms.

Manufacturers are now combining cutting-edge technology with the highest safety standards in their aseptic filling machines, in the smallest possible area to maximize hygiene specifications.

Pros and cons for the various parenteral dosage forms, e.g.; ampoules, glass vials, plastic vials, and pre-filled / dual chamber syringes, either in liquid, dry powder or lyophilized form, are being re-evaluated. Packaging forms need to be tested to exclude those at risk of interaction with the active ingredients in the medication and to narrow down to the most cost-effective and efficient packaging form for single dosage medication.^v



For highly potent and expensive molecules (biologicals), precision and accuracy are extremely important. This is driving the demand for aseptic liquid and/or powder filling equipment to handle various small batch sizes with extreme precision.

The need for differentiation for parenteral single-dose usage dosage forms is therefore significantly increasing. To this aid pharmaceutical production sites & CMOs are looking for flexible, easy to use and compact packaging solutions that also results in increasingly complex equipment.



Filling equipment solutions

The aseptic/sterile Fill-Finish equipment solutions need to be cGMP compliant, dependable and accurately designed to comply with the most recent revisions of the "Annex 1 Manufacture of Sterile Medicinal Products guidelines". Newly designed equipment needs to accommodate for small batches, various speeds and containers, including RTU / RTF (Ready To Use or Ready To Fill) bottles, vials, cartridges, syringes and pre-sterile nested trays.

Moreover, the filling equipment solution should also improve the ergonomic use for operators and maximize cleanroom efficiency.

Liquid and/or powder filling

For highly accurate and controlled filling and weighing, proven and reliable technology and equipment prevents costly overfilling, thereby increasing production efficiency.

Filling equipment solutions that accommodate for low as well as high speed or for large volumes at various speeds and with unique requirements are rare. A unique design and a modular integration approach are custom and practice in the pharmaceutical filling industry.

Dual Chamber Filling Technology Development

Traditional vials, ampoules, and cartridges are still the most popular delivery systems and the prefilled syringes are still experiencing the greatest growth in the market of any parenteral dosage form. Therefore, to advance the development program appropriately, pharmaceutical R&D scientists should

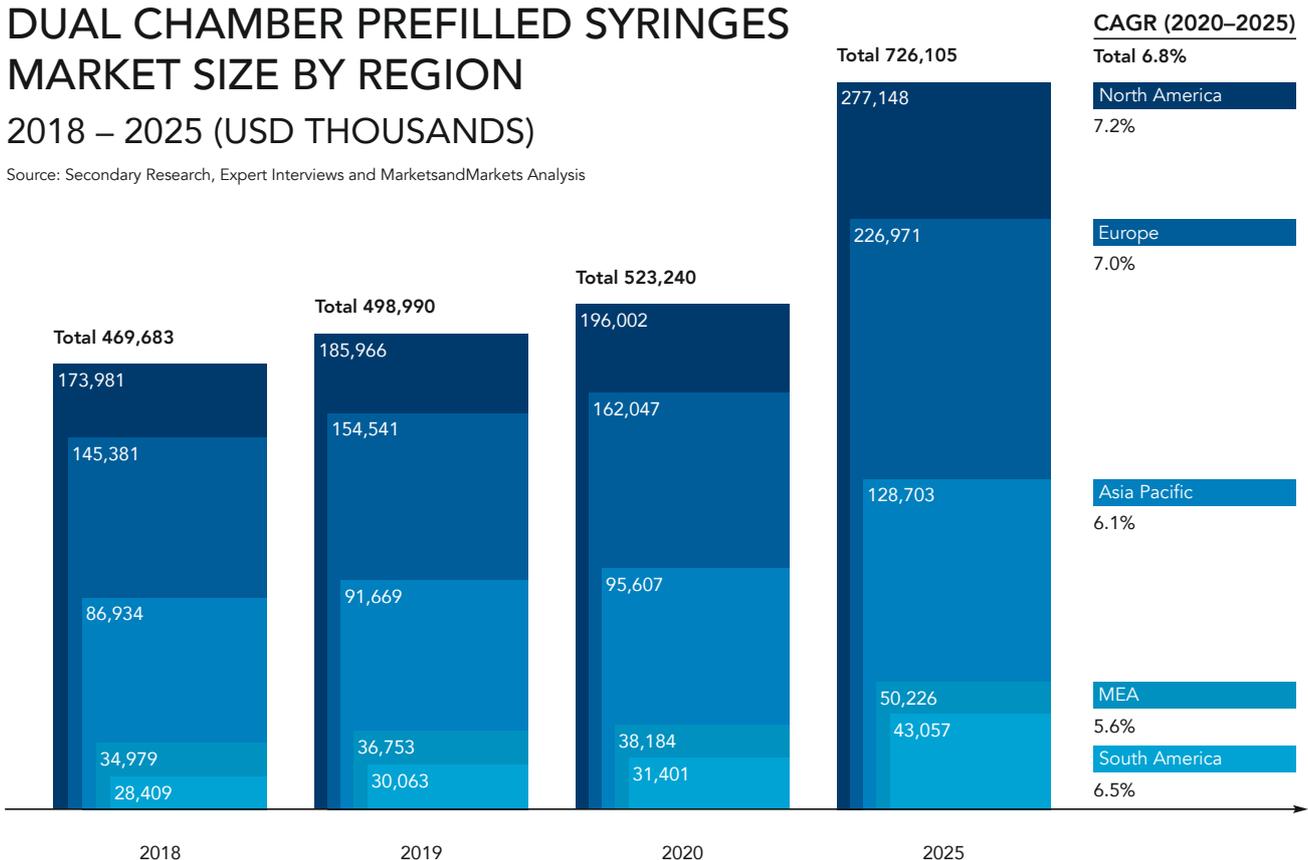
effectively leverage the advantages offered by each form of packaging and dosage.

A shift towards patient-centric administration of personalized medicines indicates new developments and trends towards new dosage forms such as Dual Chamber Filling technology.

This all in one type of dosage form makes precise and simple administration of medication possible. With this patient-friendly system, whether or not combined with an auto-injector device, the manufacturer can have a unique product differentiator.

DUAL CHAMBER PREFILLED SYRINGES MARKET SIZE BY REGION 2018 – 2025 (USD THOUSANDS)

Source: Secondary Research, Expert Interviews and MarketsandMarkets Analysis



Dual Chamber Filling Technology Development

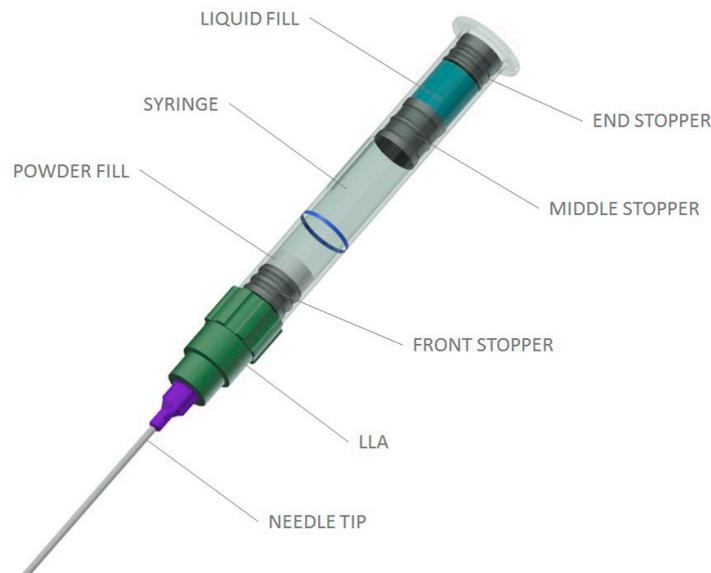
What are the advantages of newer dosage forms DCF^{VI}

Patient benefits of dual-chamber syringes (whether or not in combination with auto-injector devices) include:

- Self-administration
- Safe, predefined personalized dosage form
- Sustainable; less waste of active ingredient

As this is a variation on the traditional filling technology, the project approach for the technology development of equipment, containment and integration for pharma production sites is equal.

Differentiation in positioning, selecting and integrating the various modules for the complete production phase is based upon the unique requirements of the production site team.



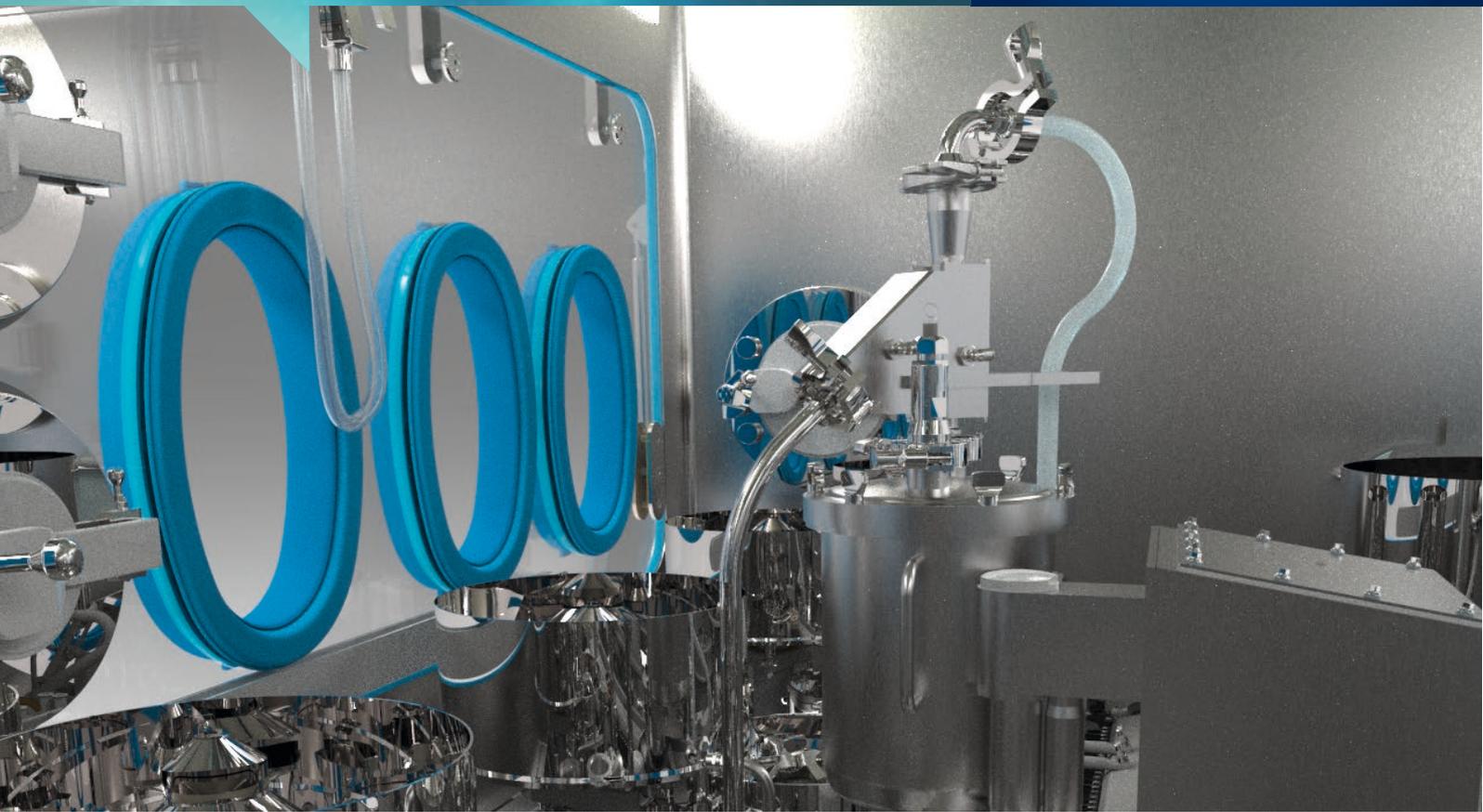
Challenges regarding new regulations

The draft Annex 1 on filling equipment and production processes in pharmaceutical primary packaging published by the EMA contains more detailed outlines that impact all primary packaging processes in various disciplines. In other words: all equipment manufactu-

rers need to be aware of the impact of these new guidelines for the industry as a whole.

Data management is becoming more and more important for audits and production performance measuring the

data storage and log systems. Whether filling is required with powder, liquid or freeze-dried ingredients, the process assessment is the key customer intelligence source for the development of any production line and filling equipment.



Filling expertise and developments in primary packaging

Dec's philosophy is to develop customer-specific modules and equipment. Starting with agreed project scope, intensive brainstorm sessions, strong design processes and (customer) reviews, the aim is to deliver an innovative filling solution. During the concept development, risk analysis is an important tool in the decision-making process. Frequent and intense discussions with the production site team (Q&A, R&D, Process development) and expert engineers are necessary to make the right decisions to achieve the best result.

In the Fill-Finish pharmaceutical industry, several technology solutions are in high demand. There is no fit-for-all solution; each production project is unique. The equipment filling solutions and modules need to be cGMP compliant, dependa-

ble and accurately designed to comply with the most recent revisions of the „Annex 1 Manufacture of Sterile Medicinal Products guidelines“. Moreover, all filling equipment and modules need to be configured for seamless integration into any production line and designed to accommodate various speeds and containers, including RTU / RTF (Ready To Use or Ready To Fill) bottles, vials, cartridges, syringes and pre-sterile nested trays.

Filling Technology Development

Dec's unique project approach for primary packaging filling equipment

With technology and process expertise in the pharmaceutical industry, it is crucial to listen intently, investigate and explore possibilities to come up with the best possible production solutions

and modules. When using a holistic approach, all aspects such as unique requirements and risk assessments need to be mapped and incorporated into any project. To ensure that the required

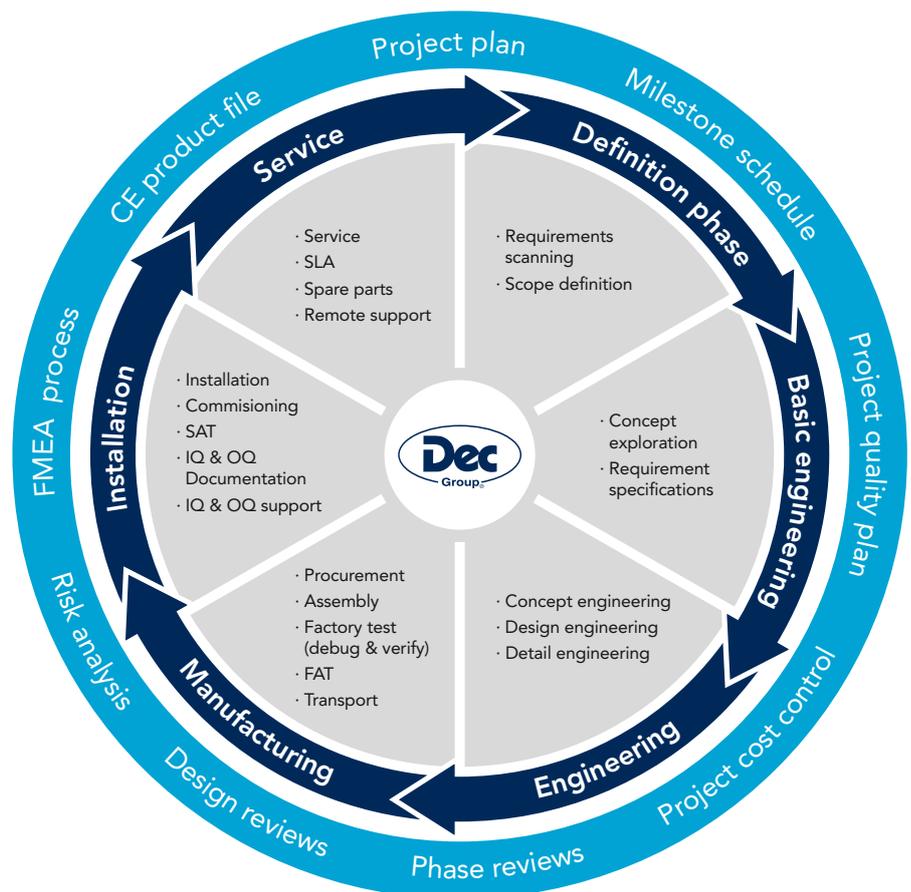
quality is achieved, the project will be managed through project phases, internal reviews, FMEAs (Failure Mode and Effects Analyses).

Thorough concept development | concept engineering phase

At Dec, we strongly believe that quality driven reviews are necessary in each step of any manufacturing process or project. With this unique approach we are able to design and deliver high-tech equipment to meet any unique specifications.

Before presenting our customers with a detailed study with recommendations, several components and processes need to be investigated in the Dec Concept engineering phase which consists of:

- A compact concept study, including FMEA review
- Investigation of the technical (onsite) complexities
- Functional process study and description
- Line concept study, including concept layout
- Input for final URS



Filling Technology Development

A ,fit-for-purpose' design methodology

The project deliverables and activities are part of our internal processes; the GAMP® methodology is strongly woven into our approach of project management. Applying procedures based on the Good Automated Manufacturing Practices method ensures that required quality levels are met for the highly regulated pharmaceutical industry. Dec engineers are experts in supplying

equipment and machinery according to customer specifications considering:

- Your User Requirement Specifications (URS)
- Any technical content complexity;
- Your required equipment specification(s)
- Modules selection

Dedicated taskforce for containment of turnkey filling equipment solutions

For any grade of aseptic environment, the complete filling production process needs to be mapped and assessed for the level of containment required to safely handle (toxic) medication. Isolators are designed to enclose the filling, stoppering and capping operations of

a Powder or Liquid Filling Machine while providing an ISO class 5 aseptic environment for the production process. Dec provides turnkey filling equipment and containment solutions for any aseptic grade.

Besides the containment open/closed RABS with UDF solutions and isolators for product & operator protection by airflow, Dec's process product range for primary packaging is endless, e.g.;

- VHP compatible equipment
- Autoclavable product parts
- Rapid Transfer ports (RTP)
- Glove ports including testers
- De-bagging
- De-nesting
- Environmental/microbiologic monitoring (viable and non-viable monitoring)
- oRABS/cRABS
- Process isolators
- UDF units
- Stopper selection and placement
- Capping
- Single lining
- Tray loading



Design verification methodology

A specific GMP/GDP documentation set prevents deviations at IQ/OQ/PQ. A smart way to save approximately 80% of the time needed for the documentation processes involved in qualification and validation.

Best in class equipment and modules selection with a strong partner network

Modular and variety design are the key elements in delivering state of the art equipment solutions. For this reason, Dec has built a strong partner network with suppliers for mechanical, electronic, software and robotic modules.

Conformity with all demanded industry standards for quality and safety

The reliability needs to be guaranteed. To this end, all equipment and modules are fully tested and supported by cGMP best practice documentation.

Why is Dec the trusted partner for design, construction and integration of Liquid & Powder Filling machines



As the equipment supplier to the global pharmaceutical industry and their contract partners, we offer decades of pharma technology quality design, modular equipment integration and production expertise in any grade of aseptic environment.

At Dec, we design smart, compact and reliable production equipment for the primary pharmaceutical packaging industry to maximise the ergonomic use for operators and to increase production and cleanroom efficiency.

Acknowledgements

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For more Information

To find out more about how your company can benefit, contact the aseptic filling equipment experts at Dec.

We design, build, integrate and operate primary packaging equipment to provide End-to-End Solutions to all challenges in Solids & Liquid Filling.

Dec supports the global top Pharmaceutical Manufacturers to reach their maximum potential.

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Sources

- I <https://www.gmp-compliance.org/gmp-news/revision-of-annex-1-manufacture-of-sterile-medicinal-products-published-for-comments>
Annex 1: Manufacture of Sterile Medicinal Products, 20 December 2017
- II Strategies to Modify the Drug Release from Pharmaceutical Systems,
- III <https://ispe.org/pharmaceutical-engineering/september-october-2018/new-improved-meet-annex-1-revisions>
- IV <https://qrm.engr.wisc.edu/index.php/what-is-qrm>
- V <https://www.marketsandmarkets.com/Market-Reports/injectable-drug-delivery-market-150.html>
- VI <https://www.persistencemarketresearch.com/market-research/double-chamber-prefilled-syringes-market.asp>

Primary packaging in the pharmaceutical industry includes aseptic and sterile filling of all sorts of medicinal dosage forms and with rapid developments in the fields of technology and personalized medicine, the need for flexible production options is notably growing.

Requirements of Primary Packaging Equipment

The use of injectable biologicals demands extreme precision, due to their high potency and cost. For highly accurate and controlled filling and weighing, proven and reliable technology and equipment prevents costly overfilling, thereby increasing production efficiency. In addition, packaging needs to be compatible with the ingredients to minimize the risk of interaction and to maximize cost-effectiveness and efficiency.

Compliance Challenges in Pharma

Manufacture of pharmaceutical sterile products is always subject to requirements of the GMP and its Annexes, including the "Annex 1 Manufacture of Sterile Medicinal Products guidelines", which is centered around three key points: Quick Response Manufacturing, Personnel, and Quality Assurance. In addition to being GMP compliant, aseptic/sterile Fill-Finish equipment solutions need to be dependable and accurately designed to comply with the most recent revisions of Annex 1.

Dec Filling Expertise

Through combined decades of experience in developing primary packaging equipment, Dec engineers are capable of delivering custom and fully compliant machinery to every customer. To this end, Dec applies a structured R&D trajectory which includes thorough reviews and risk assessments in every step. Dec provides turnkey filling equipment and containment solutions for any aseptic grade.

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