

Liquid pharmaceuticals

ANDREW SMITH REPORTS ON THE LATEST TRENDS IN PROCESSING AND PACKAGING EQUIPMENT FOR LIQUID PHARMACEUTICALS.

PROCESS EQUIPMENT

Custom vessels lift flexibility for Pharmasol

Two custom-designed process vessels supplied by Winkworth Machinery have improved manufacturing flexibility for Pharmasol, Andover, which specialises in filling creams and lotions and in contract manufacture of small-fill, high volume aerosols.

The nature of this work requires a highly adaptable production operation, which has been improved with the new 2000 and 500 litre vessels, as manufacturing manager Jim Tipple explains.

"We needed twin vessels because the type of creams and lotions being manufactured are dual-based, comprising a water phase and an oil phase. Often each phase is manufactured separately and then mixed together in the larger process vessel. Customer orders vary considerably in size and so the two vessels now provide us with optimum flexibility in manufacturing."

Pharmasol reports that the vessels have also enabled it to increase batch sizes, improve the control of heating and cooling rates and increase heat flow, resulting in better product consistency.

Each vessel is jacketed for heating and the 2000 litre vessel is side-scraped. They are installed in a purpose-built Class 10,000 clean room which is also a Zone 1 area.

A particular problem facing Winkworth during the design and manufacture of the larger vessel was the limited height available.

"Space in the room was so confined that Winkworth had to develop a design solution for the 2000 litre vessel which resulted in both the top and the bottom being adapted", explains Mr Tipple.

"This included reducing the height of the legs, modifying the outlet valve, reducing the



Extra flexibility: Pharmasol has installed two custom mixing vessels, purpose built by Winkworth Machinery

size of the bridge assembly supporting the scraped wall agitator and modifying the drive unit.

"Additionally, a special square lifting frame was designed which was used to move the vessel into the room with only 2-3mm clearance. Importantly, despite these modifications, the quality of manufacture and the manufacturing process itself has not been compromised in the slightest."

Stainless steel vessels

Also able to supply both stock and custom built mixing vessels is Adelphi Coldstream. All products are of pharmaceutical quality 316L stainless steel, which for evidence of conformity and traceability are etched with the material certificate number and supplied with a copy of the mill certificate.

The company says health and safety issues are an integral part of its vessel and mixer design, particularly relating to protection from

rotating parts, and it has developed a range of techniques to safeguard operators. These include physical barriers and the use of magnetic or mechanical interlock switches to ensure rotating parts are fully enclosed before the mixer can be operated.

Meanwhile the Ytron Y directed jet mixer – which won a PPMA Awards of Excellence in 2001 for its use in the production of tablet coating solutions – is being employed in a number of pharmaceutical industry applications where solids are to be incorporated and uniform mixing is of paramount importance.

One of these is in the production of dextrose and saline solutions for intravenous use, explains UK representative Ytron-Quadro.

The powder phase is introduced by a Ytron XC powder dispersion unit at the rate of 3000kg an hour into a liquid flow of 10,000 litres an hour. However, the high concentration requires a certain dissolution time in the large horizontal cylindrical vessel so a Ytron Y

directed jet mixer has been installed in the end of the vessel.

As a result, concentrations up to 30 per cent have been produced with constant uniformity over the whole batch, a fact confirmed by the lack of residues in the empty vessel points out Ytron-Quadro.

For further information:

Adelphi Coldstream
Winkworth Machinery
Ytron-Quadro

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FILLING AND CLOSING

Isolation technology in the forefront

Pharmaceutical filling is a multi-faceted "wish list". Precise accuracy is required to ensure correct dosage, but high speed is also demanded for line efficiency. Adjustable speed and overall line flexibility are also a must to cater for different container sizes and product consistency.

Fortunately, suppliers have lived up to this challenge and recent years have seen huge advances in filling technology, particularly in valve and pump design. Improved servo motors and their increasing use in filling machines has also done much to further precision, flexibility and speed.

Perhaps the biggest physical change, however, is the increased use of barrier/isolator technology. Fear of microbiological and particulate contamination in the pharmaceutical industry is no new phenomenon, but with increasingly sophisticated and commonly more expensive materials being used, coupled to ever stricter GMP standards, the problem is moving more to the forefront.

The rise of biotechnology has also resulted in an increase in toxic and other potent materials being used and in these scenarios product egress is of equal concern.

IMA is one company that has witnessed a particular acceleration in this trend and says there are three possible mechanical interfaces which can be used to integrate a filling machine with an isolator.

The most economic and simple one is to arrange the machine to accept the attachment of an isolator enclosure, keeping the standard machine base. Another possibility is to design

the machine base plate specially to allow a mechanical connection and seals above the machine base itself. This solution makes cleaning and draining easier.

The most complete solution is the so called 'six-walls isolator'. The company believes this represents the optimum choice in terms of cleanliness, draining and protection against leaks, but obviously involves more precise, accurate and complex design and construction concepts.

IMA says its experience in this field shows the best compromise to be the semi-integrated solution, both in terms of technology, construction time, costs and operational flexibility.

However, whatever configuration is chosen, it lists a number of engineering design criteria that are common for all equipment to work under isolation:

- The equipment must be designed from the outset to be integrated with an isolator enclosure.
- Completely integrated teamwork should be established throughout the supply chain: barrier, filling and sterilising system manufacturers.
- A dynamic pressure barrier must be installed between the different isolators in the line to avoid cross contamination.
- The control of all physical parameters involved, such as particulates, humidity, pressure and temperature, during all phases of operation, must be a primary issue.
- Preference must be given for a compact machine with reduced footprint in order to reduce isolator volume and facilitate access and maintenance.

To achieve the final point, ergonomic studies should be carried out in co-operation with the isolator supplier to decide the best positions for glove and rapid transfer ports.

Improved GMP standards

IMA also points out that particular attention to improved GMP standards is of paramount importance when dealing with barrier technology:

- All mechanical parts inside the machine must be "air-smoothed" – rounded shapes to assure a correct laminar air flow at a defined and constant speed, especially at the filling location.
- All parts must be designed in a way so as to ease unidirectional air flow and sterilant gas distribution inside the machine.
- Vial transport systems, starwheels and all size change parts must be designed to allow quick changeover, low maintenance and ease of transfer from the external environment.

- On the machine bedplate, the gaskets and seals must have the same mechanical and thermal properties. For example, parts in contact with the product or which cannot be sterilised in place, must be able to withstand autoclave sterilising cycles.

- Parts must be able to operate without lubricants in the aseptic processing area.

- All of the machine must be completely air tight in order to prevent leaks or communication points between sterile and grey areas.

- The compatibility of all construction materials with the sterilising agents must be established from the earliest design stage.

IMA also recommends that to reduce manual intervention further, the machine must be equipped with systems such as CIP/SIP, and checkweighing with automatic filling volume adjustment to ensure a higher filling accuracy.

Continuous motion vial filler

Launched at last year's Interpack, the company's latest machine is the Sterifill F2000. This has a continuous motion positive transport system making it suitable for liquid filling into cylindrical vials and stoppering at speeds up to 600 vials a minute.

IMA says it was specifically designed for operating under aseptic conditions either in a traditional class 100 area or in isolation technology. The machine has a compact, 850mm wide footprint and all operations can be carried out from one side, allowing against-the-wall installation.

The company believes the F2000 offers a number of advantages over traditional filling machines: dosing capacity from 0.25 to 500ml, an innovative stainless steel positive transport system with "dovetail shaped dowels", making it particularly easy to dismount and clean, plus statistical IPC of filled volume. The design also allows the entire transport system to be exposed to a sterilising agent, typically vapour phase hydrogen peroxide.

Blow-fill-seal specialist Rommelag has introduced Rovis, an electronic documentation system featuring password management and audit trail capabilities in compliance with 21 CFR part 11. All relevant records of documentation for equipment, spare parts list with drawings, machine maintenance, error analysis and other functions are available in electronic form.

The Bottelpack blow-fill-seal system makes sterile and pyrogen-free containers or ampoules directly from extruded polyethylene, polypropylene or PET in cooled blow moulds, then fills



Higher productivity: DT Packaging claims a 20 per cent advantage for its Technofill Premier filler

and hermetically seals them in a sterile environment, which assures a high degree of process and product security.

The Rommelag machines – available in the UK through FJ Pistol – are designed in a modular structure and have an integrated Class A clean room with additional grey/white machine separation. They are fully automatic, running either discontinuously with one and two moulds, or continuously with rotating mould chains. Up to 30,000 containers an hour can be produced, with sizes from 0.1ml to over 1 litre. Dosing is said to be very accurate and the machines are, in general, CIP/SIP capable.

GMP guidelines stipulate that ampoules should be subject to 100 per cent integrity testing and so Rommelag has introduced the HVLD high voltage leak detector for in-line testing. If there is a pinhole in the ampoule, the discharge current flows through into the container where it is detected and the ampoule is automatically rejected.

Handling systems, loading and unloading robots and, most recently, mirror welding machines for hermetically sealing Euro caps onto Euro head IV containers, are also available from Rommelag.

Ampoule filling machine

The first conventional ampoule filling machine was built in 1927 by the German company Rota, which later went on to develop techniques for safer filling of ampoules, including the flame-opening technology which is still in use today. Represented in the UK by Adelphi Manu-

facturing, Rota now has a full complement of ampoule and vial processing equipment, from washing, sterilising, filling and closing to labelling and inspection.

The fillers range from semi-automatic bench-top machines through to fully automatic lines with outputs up to 24,000 an hour. Dual function machines, which enable both ampoules and vials to be processed on the same unit for greater production flexibility, are also available. A variety of closures can be handled including rubber stoppers, droppers, caps and pipettes while the machines can be installed in isolators if required.

High speed sterile systems

The MAR range of pharmaceutical filling equipment is now available in the UK and Ireland through Ultrapac. The Italian company specialises in sterile, high-speed systems processing up to 600 units a minute with the capability of filling plastic and glass bottles, carpules, syringes and containers for diagnosis.

The M50 has been designed for filling containers with droplet counter closures or screw and pressure caps, as well as plastic and glass cannula. The machine can be fitted with a CIP/SIP system with ceramic syringes and runs at speeds up to 300 units a minute.

The M52 is for injectables and was originally designed for installations using isolation technology, but its compact size also makes it suitable for conventional settings where space is confined. It can be fitted with a statistical check weighing system and CIP/SIP with ceramic

syringes with a rotating piston. The M52 can also be integrated with the M12 capper. Speeds range from 150 to 600 units a minute.

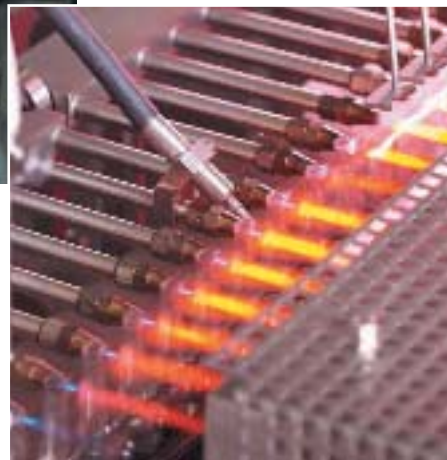
Again a compact model – 900mm wide – the M53 is available in various versions for production of injectables, and containers with droplet counter under-cap and screw cap. The machine operates at speeds up to 120 units a minute and transports containers to the various stations



Filling injectables: Above: Compact MAR M53 filler for vials. Right: Pre-heat and ampoule sealing station on the Rota eight-head in-line filler

infusion bottles. Maximum output is 320 containers a minute and it has a fill volume up to 500ml. The company has also developed an isolator for aseptic filling machines and at Achema it will be demonstrated with a bio-decontamination module which generates hydrogen peroxide steam, providing a “very short sterilisation cycle time”.

Meanwhile, a tabletop filling unit capable of handling a variety of viscosities and volumes from 100ml to 25 litres has been developed by RCS Filling Machines. The T1 gear pump is said to have easy programming of volume, be easy to clean and offer a wide range of nozzle types and sizes. With a modular structure, the unit can be tailored to customer specifications while retaining flexibility for future developments. A multi-head version to compete with traditional piston head fillers is under development.



with the aid of a handling ‘comb’ made from Arnite or 316L stainless steel. CIP/SIP and unitary checkweigher options are available.

DT Packaging Systems claims a productivity advantage of up to 20 per cent over conventional liquid fillers for its Technofill Premier machine, which it says has a number of applications in the pharmaceutical industry.

The machine now has a new nozzle bar lift mechanism featuring a programmable motorised drive to allow smooth motion. The nozzle movement can be programmed to allow variable speed and stepped diving action according to the product and container characteristics. The company says that combining this with an integrated variable conveyor speed provides the advantage of total control of the filling cycle.

Fill times are said to be reduced and output increased, even for foaming products and those that require filling into the neck of a bottle. The Technofill also has positive shut-off valves on each nozzle which prevents stringing and dripping and further enhances output speeds.

New from Robert Bosch is the FLC continuous filling and sealing machine for vials and

Sankyo Machinery Co’s stickpack technology for single dose liquid and powder pharmaceuticals is available in the UK through Springvale Equipment. Single lane to ten lane formats can be supplied and up to 800 packs a minute can be produced, depending on the properties of the product.

Stickpack advantages

Springvale says the stickpack offers a number of advantages, including low materials cost, ease of direct oral dose and aesthetic appearance. “Stickpacks are slowly creeping into this market as a preferred packaging choice,” says the company, “and as we have seen in other market areas, we predict this simple, but effective format will grow and grow.”

For creams and waxes, Kemwall Engineering now supplies stainless steel hot fill machines, ranging from basic heated dispensing vessels to

high speed, multi-pump units.

The dispensing vessels are available in capacities of 10-200 litres and can be supplied with specialised stirrers and flameproof electrics, or custom built to specification. Electrically heated with proportionally controlled thermostats, they heat up to 90deg C, ± 1deg C, and employ a three-phase stirrer motor with inverter drive.

The pneumatically powered pumping system has adjustable screw filling volume control and a hydraulic speed control for the filling rate. The pumps are available in four sizes, the smallest filling 0.5-15ml and the largest 5-250ml. If required, piston shut-off valves can be specified to eliminate dripping.

Options include automatic container loading, container pre-heating, after glazing units and cooling tunnels.

For further information:

- | | |
|-----------------------|------------------|
| Adelphi Manufacturing | enter 201 |
| Robert Bosch | enter 202 |
| DT Packaging Systems | enter 203 |
| IMA UK | enter 204 |
| Kemwall Engineering | enter 205 |
| FJ Pistol | enter 206 |
| RCS Filling Machines | enter 207 |
| Springvale Equipment | enter 208 |
| Ultrapac | enter 209 |

CASE STUDY: CP PHARMACEUTICALS

CP Pharma installs UK’s first LVI filler

The UK’s first Macofar LVI 4 liquid filler has gone into operation at CP Pharmaceuticals, Wrexham. Supplied by Romaco UK, the machine is being used to fill vials of a new painkiller, currently in the latter stages of clinical trials, which CP is manufacturing and packaging under contract from the licence holder.

New from Macofar, the LVI 4 is an automatic monobloc machine designed for the pharmaceutical and cosmetics industries and is said to set new standards of access for cleandown and simple operator size changeover. The monobloc concept also provides flexibility in the line configuration with separate filling/closure if required.

Contact parts are offered in a choice of AISI 316 L stainless steel or silicon and the four volumetric filling pumps can be supplied in stainless



First in the UK: The Macofar LVI 4 is said to set new standards of access for cleandown and changeover

steel or ceramic material. The dosing system comes with a choice of either ball or rotating valve and CIP or SIP systems are available as an option.

The LVI 4 incorporates features such as individual adjustment of the pumps and the ability to carry out all adjustments from the operator's side. Output is up to 4000 containers an hour, the fill range is 0.5-500ml and the machine is able to handle vials 16-85mm in diameter and 35-200mm high.

"We decided on Macofar because the machine offered high build quality, a high degree of flexibility in terms of the options we required and because Romaco offered the best all-round package in terms of supply and support," says CP Pharmaceuticals' production engineering manager, Jim Churchill.

Cost not an issue

"Cost was not an issue. We could have opted for more expensive machines but ultimately the LVI 4 proved to be the machine which best met our brief."

Although as an inhalant, the product does not need to be filled in classified cleanroom conditions, CP nevertheless wanted to create a controlled environment. The LVI 4 has therefore been supplied with a laminar flow unit and the

room in which it is installed is under controlled negative air pressure.

"We also wanted an option to clean the vials within the controlled atmosphere, which Macofar were happy to accommodate by incorporating an air blow/purge system at the first station," says Mr Churchill.

After filling, a nitrogen blanket is applied in the vial neck to protect the product and then a spray pump complete with aluminium closure is applied and rotary sealed.

For batch numbering, Romaco worked with ink-jet coder supplier Domino and a small print head was installed within the controlled area to apply the numbers to the aluminium closures.

More information - enter 211

CASE STUDY: VASQUALI

Back to basics for new filling machine

Italian manufacturer Vasquali recently went "back to the drawing board" to satisfy a major pharmaceutical company which required a new filling and capping system with the best possible GMP characteristics.

The customer wanted easy cleaning, minimal change parts, zero contamination and good laminar air flow around the bottle. After studying the problem, Vasquali – represented in the UK by Skerman Promac – decided to stick with its philosophy of simple, integrated design.

By using a skeleton main turret-indexing star wheel, the company says good GMP and excellent laminar flow around the bottle was achieved. This approach also reduces any spillage contact to a minimum by reducing the points of contact and, in addition, makes wash-down much easier.

Reducing contact points

Contamination of the bottles was also considered within the design by reducing contact points and fitting all drive systems for cap feeding, tightening and filling pumps below the main filling section, separated by seals to make cleaning a simple matter of washing the surfaces.

To cater for different liquids and gels, Vasquali designed a range of pumps that are said to be easily fitted, including a mechanical pump dosing system driven via the main machine drive, pneumatic systems for more viscous products and multi-lane peristaltic pumps for simple cleaning when zero contamination is required. For free flowing liquids, flow meters can also be used, connected directly to the filling nozzles.

The nozzle design prevents dripping or stringing by using a cut-off or closing valve to the tip end, providing advantages in terms of GMP and cleaning routines.

A pick-and-place method positions the cap directly onto the screw area, therefore reducing product contamination that could accrue if a wipe-on system is used. It also allows a minimum open period with good airflow before the electro-magnetic torque head tightens the cap.

Vasquali says the electromagnetic head was selected because of its accurate linear tool-free adjustment which is both maintenance and fibre-free to reduce contamination.

Push-on, snap-on or ROPP caps are a standard option.

Sensors to detect no bottle, no fill/no fill, no cap and missing cap are standard and linked to a reject station.

More information - enter 212

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LABELLING:

Pick-and-place helps handle unstable vials

Sessions of York recently came to the aid of Lithuanian-based Fermentas UAB which had a problem applying two labels to an unusually shaped and unstable vial. Standard labelling machines were not suitable for the job so Sessions designed a custom unit, based on its Spectrum labeller and using a pick-and-place system.

Operating at speeds up to 60 vials a minute, the unit places a label onto the vial cap and indexes round to the second station. The container is then spun at a speed synchronised with the second labeller which applies a wraparound label. The vial is then ejected into a hopper.

"As the vial is such an unusual shape and totally unstable, handling was a real problem," says Fermentas. "This machine has revolutionised our production."

Meanwhile, Newman Labelling System's VAL550 has been purpose-designed for



Syringe labeller: Newman VAL 550 showing the starwheel arrangement

labelling pre-filled plastic or glass syringes at speeds up to 350 a minute, using either paper or clear plastic labels.

The machine has a number of security features, including two reject station variants with their operation dependent on whether the syringes are fitted with plungers. Both use a 'positive accept' protocol with reject verification.

Microprocessor-controlled security systems have also been incorporated to meet MCA and

FDA GMP, including 21 CFR part 11 compliance requirements and a full package of validation documentation is supplied with each machine. Set-up options include complete line integration or standalone tray infeed and out-feed of syringes.

Herma's 040 wraparound labelling machine has been specifically designed for the pharmaceutical industry with product security a key feature. The machine uses what is said to be a "unique indexing star wheel concept" to transport products through the labelling and inspection stations, which "guarantees total product security as the products are tracked through the system using a shift register".

Reject product is ejected while still in control of the starwheel while labels not verified as correct by the optical Pharmacode and OCR systems are automatically rejected – with no need to stop the machine – before they are applied to the product. The machine will label cylindrical products at speeds up to 200 a minute.

For further information:

Herma UK

enter 214

Newman Labelling Systems

enter 215

Sessions of York

enter 216

CARTONING:

Bottle-in-box system handles 400 a minute

The Stealth range of cartoners from US-based MGS featuring the horizontal, continuous motion 'Bottle-in-box' system for healthcare applications is now available in the UK through Partners in Packaging.

The cartoners, which feature an automatic bottle reject system, automatically receive bottles into a servo-driven timing screw or star-wheel product handling device which gently tips and guides them into the carton infeed buckets for automatic loading into the carton. Cartons can be produced in reverse or straight tuck styles with full overlap. Economy glue end is also available.

The small footprint rotary machines operate at speeds up to 400 cartons a minute and employ a pre-break system using opposing vacuum cups. Controlled by an Allen Bradley SLC-5/04 PLC, the Windows touch-screen includes RSView 32 operating software and can produce a troubleshooting guide, production statistics, changeover recipes, schematics and assembly drawings.

Literature feeding modules for pre-folded, sheet or roll-fed labels are also available.



Speeds up to 400 a minute: MGS Stealth cartoner from Partners in Packaging

The CUC is a new continuous motion cartoner from Bosch which has an integrated bottle feed for pharmaceutical filling machines. The company says the most important innovation on the CUC is its fully servo motor driven product loading system in which all movements have their own drive axes and can be set to suit the products being packed. Code printers and readers are said to be easily integrated.

Stickpack cartoning

To complement Sankyo Machinery's stickpack technology (see Filling and Capping section), Springvale can also supply Lagenpac's collation and cartoning systems which have been specifically designed for pharmaceutical single dose sticks. Systems are available to collate

packs being produced on a number of multi-lane machines before cartoning on either an intermittent or continuous motion cartoner.

The Dutch company has systems for a number of different sizes of stickpack which can load up to 2000 sticks a minute into cartons of 2-100 sticks each. A wide range of carton designs can be accommodated and Langenpac also has equipment for monitoring complete batch integrity – with visual inspection of product, carton, and any inserts – as well as product counting systems.

For further information:

Robert Bosch

enter 218

Partners in Packaging

enter 219

Springvale Equipment

enter 220

CONVEYOR SYSTEMS

Conveying unstable nasal spray bottles

A specialist conveying system to handle nasal spray bottles – too small and unstable to transport on conventional conveyors – has been designed and built by Conveyor Systems for a leading multi-national pharmaceutical manufacturer.

It carries the polyethylene bottles – measuring 30mm in diameter x 105mm long – upwards and overhead through clean room conditions, at speeds of 200 a minute.

The nasal sprays are transferred from the filler-capper on guided 1.25in slat conveyors with variable speed drive and taken around 90deg bends to a side grip elevator.

From here, they are conveyed up onto an enclosed 2.4 metre high overhead conveyor,



Up and over: Elevator section of the spray bottle conveyor

which passes through the walls of a number of adjacent clean rooms, and back to floor level to collect on a rotary table.

Among features designed by Conveyor Systems to maximise line efficiency and prevent possible blockages are two 'fallen bottle chicanes' built into the slat conveyor at either end to evacuate and capture toppled bottles.

Both the sidegrip elevator and discharge lowerator, along with the joining high level transit conveyor over the clean room, are completely enclosed in clear polycarbonate.

More information - enter 221