THE MANDREL CHALLENGE – LABELLING VERY SMALL CONTAINERS

Here, Tamara McCartney, Technical Associate & Senior R&D Leader (North America), and Jos van Noort, Senior Application Manager Pharmaceuticals & Healthcare, explain how the rigorous technical, regulatory and quality requirements of the pharmaceutical industry impact on labelling, including how the very small diameter, curved surface – the mandrel – of a prefilled syringe presents particular labelling challenges.

The way non-oral medication is delivered to patients has changed dramatically over the last 40 years. There are many more types of injection devices, driven by increased demand for injectable biopharmaceuticals. More and more biological medications are now available to treat diseases such as cancer, autoimmune conditions and diabetes. Devices now in common use include ampoules, vials, prefilled syringes, auto injectors and pen systems. Prefilled syringes deliver benefits that include dosage accuracy, reduced drug waste and the assured sterility that improve patient safety.

> "There are very significant hurdles to overcome when attaching a label reliably to prefilled syringes."

As with any medicine, reliable identification of a prefilled syringe is paramount. Patients, pharmacists and doctors need to have complete confidence that a device contains the right drug, for the right person, with a label that shows a clear description of contents, instructions for use and expiration date.

This is not such a straightforward requirement as it might initially seem. There are very significant hurdles to overcome when attaching a label reliably to prefilled syringes. Such syringes are very small containers, with difficult surfaces for adhesion, and often with the presence of an anti-adherent coating on the surface (like traces of silicone). A standard stationery label of the kind used in offices falls far short of the performance required.

THE LABELLING CHALLENGE

Several criteria must be met when labelling a prefilled syringe:

- Production efficiency must be optimal
- Labels must remain firmly adhered to a container with a very small diameter
- The adhesive has to be compatible with 'low surface energy' materials, notably some plastics (COC/COP)
- Information must remain legible for extended periods of time
- Labels must withstand environmental variations, such as temperature and moisture changes
- Nothing in the label should interact either with the syringe material or the syringe contents.

Sterilisation-friendly products are also required for some applications, with labels that are able to withstand heat, steam and chemicals. As far as possible, the label

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should also be easy to process, so that costs are controlled.

Some of the criteria listed above act in opposition to each other. For example, an arbitrarily strong adhesive could be used to ensure permanent adhesion to a syringe. However, such an adhesive might not meet the need for migration resistance of label components into the syringe – and a label that contaminates the drug it is labelling is of no use. An adhesive also has to be practical for production purposes, enabling high speed manufacture and trouble-free end use. To take another example, a label using a highly aggressive but overly thick layer of adhesive, which 'oozes' and contaminates production equipment, would be slow and costly to produce.

Perhaps the most difficult single labelling challenge is posed by the very small diameter or "mandrel" of a prefilled syringe. Mandrel performance can be viewed as a tug-of-war between two forces. A retractive force arises from the stiff, adhesive-coated facestock (or label). In opposition to the retractive force is the adhesion force provided by the label's adhesive. The label will lift at the edges if the retractive force is greater than the adhesion force.

Factors that need to be taken into account when designing a label material for good mandrel performance therefore include the modulus and thickness of both facestock and adhesive, and the radius of the mandrel. Materials such as polypropylene (PP), cyclo-olefin polymer (COP) or cyclo-olefin co-polymer (COC), with low surface energy, make good mandrel performance more difficult to achieve because adhesives are not strongly attracted to such surfaces.

The surface energy of a substrate has an impact on the so-called wetting of an adhesive to the surface. Favourable wetting characteristics mean an adhesive can flow out onto a surface, which has an impact on both initial tack and final adhesion. A low-surface-energy substrate typically reduces the wetting properties of an adhesive. Good wetting characteristics are achieved at the expense of the modulus properties an adhesive needs to perform well in mandrel applications.

> "Pharmaceutical labelling is also subject to very strict qualification, and so drug manufacturers want to avoid changes to adhesive formulation whenever possible."

In order to understand mandrel performance and other factors, it is worth briefly reviewing how self-adhesive (or pressure sensitive) labels are made and used.

PRESSURE-SENSITIVE LABELLING

A basic pressure-sensitive labelling laminate contains the facestock, which can be made of film or paper, an adhesive layer, a release liner (to hold the label until ready for dispensing) and a silicone-release coating that facilitates separation of the label from the release liner (Figure 1).

A laminate of this kind is made in large rolls by a label manufacturer, and subsequently turned into sheets or rolls of labels by a label converter – a specialist printing firm. Individual labels are then dispensed from their release liner, either manually or automatically, onto containers. Productivity is important throughout this chain. Labelling materials should convert as quickly and cleanly as possible, and offer good printing and dispensing characteristics.

Adhesive technology is pivotal in label design. A balance has to be struck between an adhesive's ability to adhere to a container and its ability to release from the liner during dispensing. For pharmaceutical applications, migration properties are also crucial – with no contamination of the container's contents from adhesive, facestock or ink.

Three adhesive systems are commonly used in pressure-sensitive label manufacture:

- Solvent-based processes dissolve the adhesive ingredients in a solvent before application to a web of material, after which the solvent dries out.
- Hot-melt adhesives use thermoplastic rubbers, compounded with tackifying resins, antioxidants and oils – coated onto the web at elevated temperatures.
- The emulsion process uses adhesive ingredients that have been emulsified in water.

Adhesive formulations further include rubber-based, acrylic and modified acrylic adhesives, using non-latex rubbers, acrylic polymers and acrylic polymers with additional components respectively.

Solvent acrylic-based adhesives have been the pharmaceutical industry standard for years, but developments by the chemical industry have resulted in new emulsion acrylic polymers, and adhesive properties that match pharmaceutical industry requirements very closely.

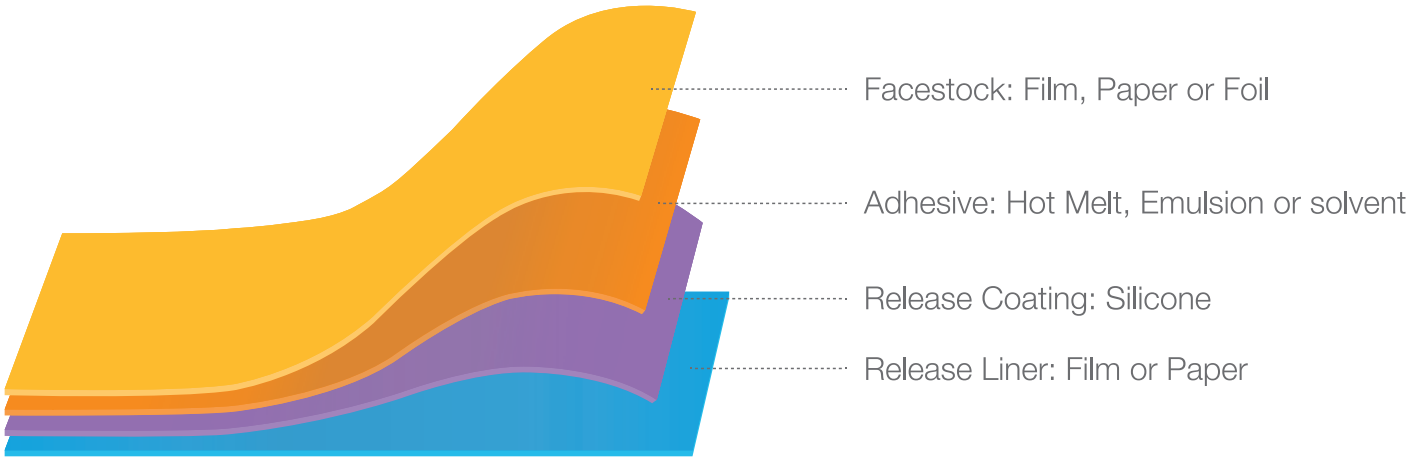

Figure 1: The basic pressure-sensitive label laminate.

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For example, S717P is a tackified acrylic emulsion adhesive developed by Avery Dennison for pharmaceutical applications. When combined with low stiffness paper or filmic facestocks, it gives the mandrel performance and low migration properties needed for prefilled syringe labelling.

AVERY DENNISON S717P ADHESIVE

S717P offers a range of benefits for pharmaceutical labelling. The most significant benefit for prefilled syringe applications is far lower levels of edge lift, all the way down to diameters of 7 mm. Figure 2 shows how the adhesive holds the label firmly in place on a 1 mL PP syringe.

The Avery Dennison Research Centre in Europe, located in Oegstgeest, the Netherlands, uses an extensive set of equipment to test new developments such as S717P in a way that reflects real-world conditions as closely as possible, using international FINAT, DIN or ISO test protocols. Different aspects of adhesive performance are assessed using FINAT Test Methods (FTMs) 1, 2, 9 and 13. For example, the test method used for adhesion and loop tack (FTM 9) is shown in Figure 3.

Relevant tests are performed on various kinds of substrates, and on objects that range from standard panels to syringes and vials. Substrates are also subjected to different treatments when appropriate,

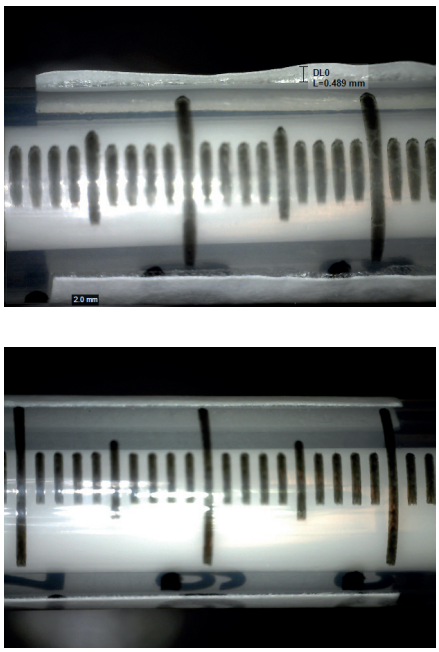

Figure 2: Comparitive edge-lift performances for (top) a conventional adhesive and (bottom) S717P.

for example by cooling down and allowing condensation to develop. Applied labels are also stored under varying conditions, and tests are conducted using equipment familiar in the pharmaceutical segment, such as fridges (down to -85°C), climate chambers and a steam sterilisation machine.

A microscope with a measurement system determines any resulting label lift to a high degree of accuracy (following FTM24). Figure 4 shows an example of the results from an FTM24 test, comparing S717P mandrel hold performance with a commonly used commercial adhesive, on 1 mL, 2 mL and 5 mL PP syringes. In each case, S717P delivers far lower levels of edge lift.

Good performance across a range of criteria is needed for a production-ready label, and Table 1 shows the performance improvements (or parity) delivered by S717P.

Next to the choice of adhesive, selecting the most appropriate facestock is also important. It is not uncommon to see standard laser printer papers being used on syringes by end users. Unfortunately, a paper of this kind has to be stiff enough to survive passage through a laser printer, and the result is significant label lift when it is used on a small diameter container. Figure 5 shows mandrel hold for different facestocks, illustrating the significant improvements seen when using a more flexible material.

ADDITIONAL PHARMA DEDICATED PRODUCT FEATURES

Pharmaceutical labelling is also subject to very strict qualification, and so drug manufacturers want to avoid changes to adhesive formulation whenever possible. This safeguards production continuity and avoids additional testing costs. The "P"

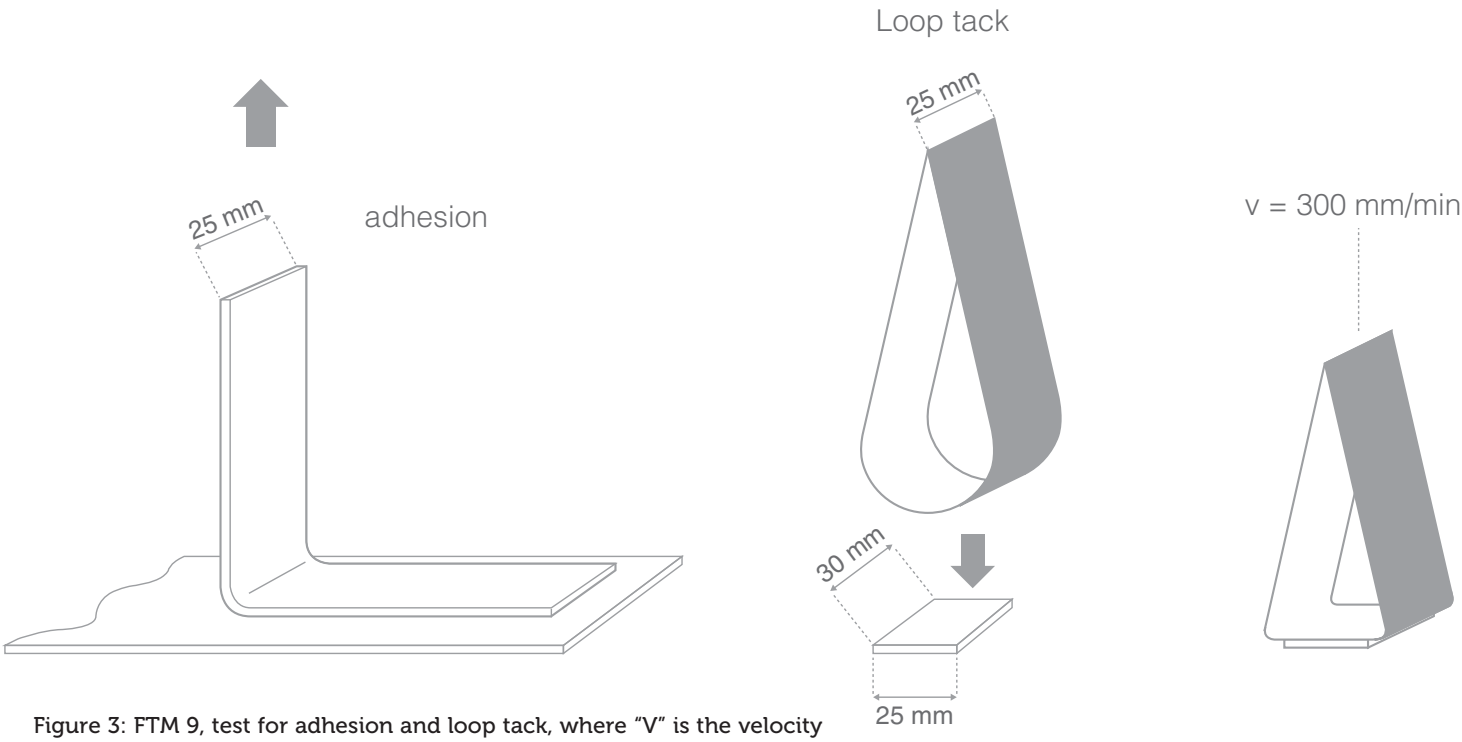

Figure 3: FTM 9, test for adhesion and loop tack, where "V" is the velocity of the tensile tester as it descends onto and then pulls up the test sample.

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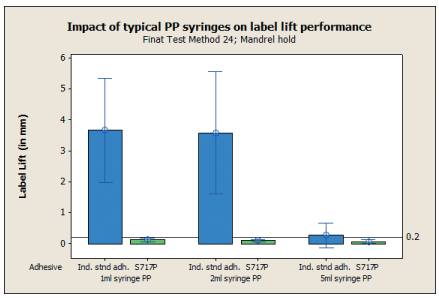

Figure 4: Mandrel hold on PP syringes: S717P versus commercial adhesive.

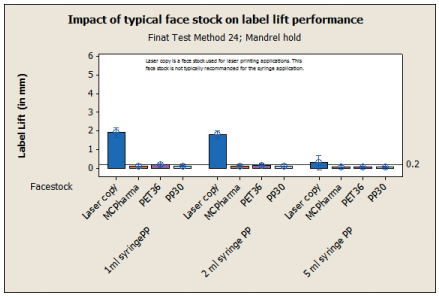

Figure 5: Mandrel hold for different facestocks.

suffix (for "Pharma") on S717P confirms that S717P adhesive benefits from Avery Dennison's change management control. It is planned to retain the proprietary adhesive in the portfolio for at least five years, and if for any reason this is not possible then change notification will be sent out a year in advance. To support the qualification of S717P, a complete set of certificates (among others, migration and toxicology) is available together with the option of conducting customised analytical tests in our central laboratory.

CONCLUSION

The unique labelling requirements of prefilled syringes, with their small diameters and difficult labelling substrates, mean that a very high performance labelling material is needed. S717P adhesive provides excellent adhesion and low migration. It offers label converters and end users a convenient and reliable way to label prefilled syringes, vials and other packaging with all of the information required to safeguard patients. With its S717P innovation, Avery Dennison has solved the mandrel challenge and created a label suitable for small pharma containers made from many different types of material.

ABOUT THE AUTHORS

Jos van Noort is a Senior Application Manager at Avery Dennison Materials Group Europe. He first worked on new polymer chemistry at Royal Shell in the Netherlands, before moving to the R&D department at Avery Dennison to work in analytical chemistry and product development. Mr van Noort now leads pharma label innovations.

Tamara McCartney is a Senior R&D Leader at Avery Dennison Materials Group North America. She has worked on new product development at Avery Dennison for 24 years, specialising in pressure-sensitive adhesive technology across many different market segments and applications including pharmaceutical; variable information; beer & beverage; and removable label innovation. Ms McCartney also holds a Project Management Professional (PMP) certification.

Application		S717P	Typical Industrial Standard Adhesive
Adhesion	Room temperature	+	+
	Moist substrates	0/+	0
	LSE substrate	+	0
	Cold substrates (< 5°C)	0	0
Mandrel	Syringes/vials (Glass)	++	+
	Syringes/vials (HDPE/PP)	++	0
	Treated surface glass vials	++	0
Sterilisation	Syringes (PP/Glass)	++	+
	Vials (PP/Glass)	++	+
Extractables	EtOH (10%, 95%)	++	+
Application	Service temperature	-60°C to >135°C	-50°C to 120°C
	Minimum application temp	10°C	10°C

Table 1: S717P adhesive characteristics. "0" = average performance and "+" = above average.

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A labelling solution for demanding pharma applications

THE PHARMA LABELLING CHALLENGE

Label 'lift' is a major challenge for pharma applications such as plastic, treated glass syringes and vials. Low surfaces energy and/or small container diameters place enormous demands on the label adhesive – and changes to manufacturing designed to raise productivity can mean that an existing labelling solution no longer performs adequately.

As a pharma labelling solution, the adhesive S717 offers excellent performance on difficult containers and a rapid re-certification process. S717 is part of the pharma dedicated range that offers a robust change management control to make sure that components do not change and notification times are in place if a change has to be made.