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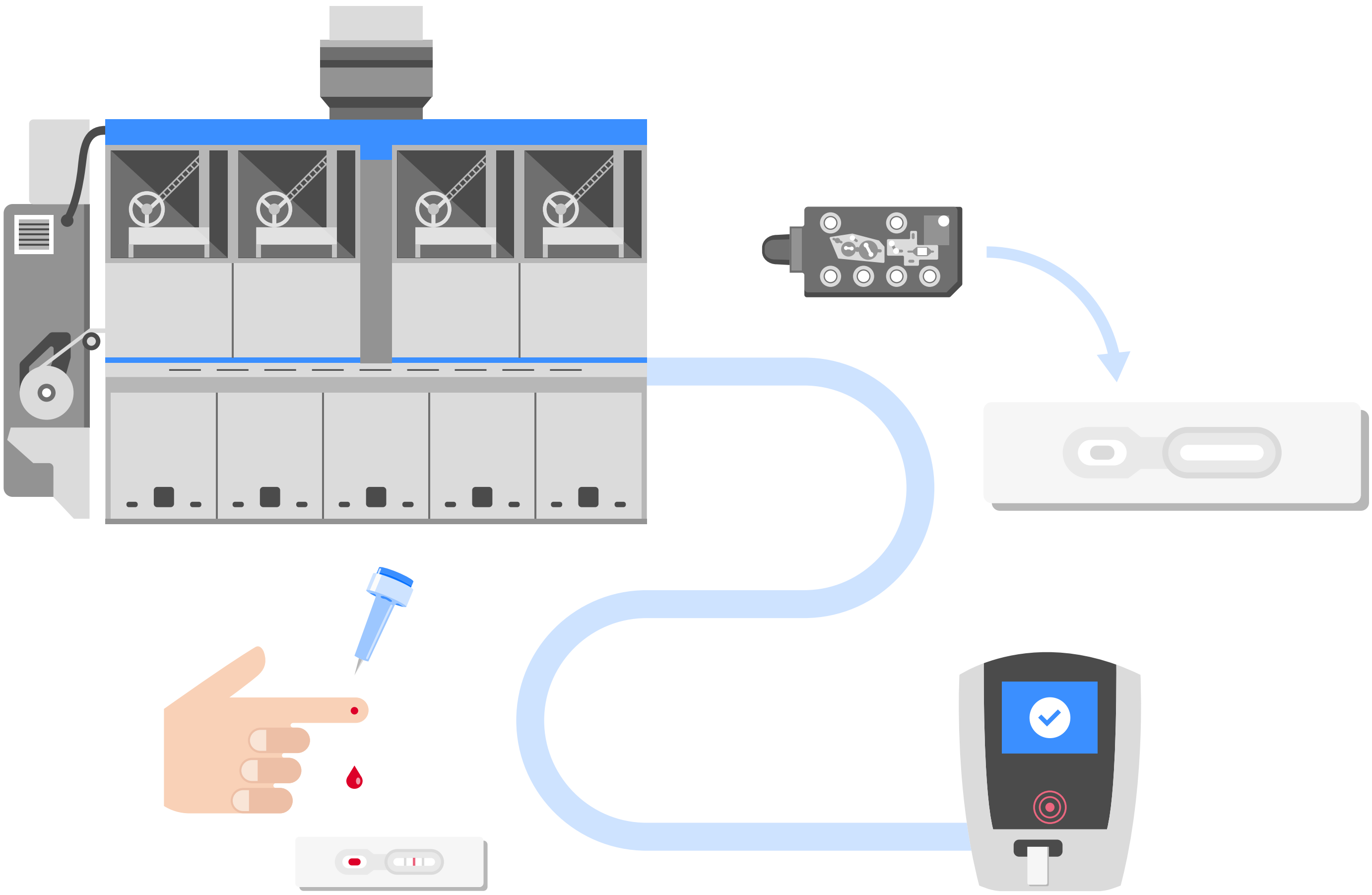


Microfluidics – designing in the lowest cost

By Steve Brown

You've developed a new assay. After considerable effort, resource and investment, it's been shown in the lab to be accurate and consistent and promises to be a genuine solution to a real problem. Now it's time to consider how it might manifest itself as a product. The problem is that the effort, resource and investment are set to continue. Poor design decisions at this stage will turn a viable product into a non-starter. The opposite is also true, as wise decisions now can turn a good idea into a world-beater. Commercial success will require a cost per test and ease of use better than the opposition (we'll assume the lab work has already demonstrated the performance benefits we'll need).

Typically, products will consist of a disposable cartridge element and an instrument to read it. Provided the instrument is not too large or expensive and is easy to use it shouldn't be a problem and will form only a small portion of any profit. A good lab-on-chip will utilise a small sample volume and will be designed around microfluidic principles. Good cartridge design will be what provides the profit.

Where do we start? Let's look at the functions required of a typical microfluidic chip.

Sample preparation

Different sample types (blood, urine, saliva, nasal swab, faecal sample etc) require different processes to extract the ingredients of interest. If multiple inputs are required this normally necessitates a separate disposable sample preparation unit for each type. We'll discuss these in a separate article.

If the expected input is from a single source (say, blood from a finger-prick) the sample prep function could be incorporated into the cartridge. Any sample preparation would then be carried out within the cartridge and would be invisible to the user. This would be a key consideration if attempting a CLIA-waived development program.

Reagent storage

Two options here, on-chip or off-chip. On-chip will require a robust storage receptacle, normally a blister pack, which will add cost.

Multiple reagents will require multiple blisters and will soon incur significant costs. An alternative approach is to dry down reagents onto the chip and rehydrate to order from a single, large blister pack containing only a common buffer solution. Off-chip storage (i.e. bulk reservoirs within the instrument) would seem to be a more cost-effective approach but require the user to top-up periodically and the inclusion of a low reservoir detection and warning system. Furthermore, we must be concerned with how reagents are then transferred to the chip. Open ports allow fluids in but will also provide a path out for pathogens or waste materials in the form of fluids or aerosols. The possibility of contaminating the instrument will have to be eliminated and implementing solutions to these issues can exceed any cost savings made from removing blister packs in the first place.

Fluid motion

We need a method of moving sample and reagents around the fluidic channels. There are many approaches we can use here:

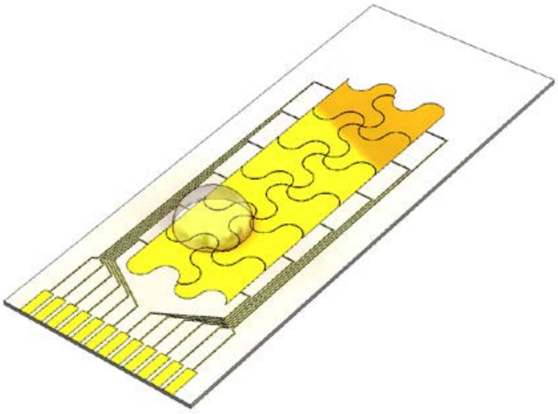
Capillary action. Limited in its functionality, providing a relatively low motive force, but is very inexpensive as it requires no external actuation. Channels do not necessarily need top and bottom surfaces to work (fountain pen nibs provide a constant flow of ink very consistently).

Positive/negative pressure. This can be provided from a micro-pump within the instrument or by inclusion of on-chip bellows and valves (more later). An on-chip solution is preferable as it eliminates paths (and therefore possibilities for contamination) to the outside world.

Gravity. Simple and inexpensive. However, at microfluidic scales, surface tension effects will exceed gravitational forces. Motion under gravity can be assisted with the inclusion of hydrophobic coatings or by centrifugal motion.

Surface Acoustic Wave (SAW). This technology can generate high forces and fast response times but it relies on close coupling between generator and sample. This is often difficult to achieve inexpensively and consequently, the functionality will reside on-chip, which will inevitably add cost.

Electrowetting. This is also referred to as Digital MicroFluidics and uses an electric field to locally switch a hydrophobic surface to a hydrophilic one, and thus enable the movement of droplets. If a "checkerboard" arrangement of electrodes is utilised, then the path of droplets becomes controllable from software rather than limited by physical pathways. On the downside, top and bottom surfaces of the working channel need to contain conductive layers, insulating layers and hydrophobic coats. To all intents and purposes, each of these is an additional part in the bill of materials and an extra manufacturing operation. There is therefore a potentially significant cost penalty for the additional versatility.



Mixing

Clearly, when bringing together say, a sample and a reagent, the primary desire is a homogeneous mixture, but a good mixing technique is also required to rehydrate dried-down reagents or microbeads. Furthermore, once the dried material has been liberated and entered the fluid, the mixing technique must be robust enough to break up any remaining clumps. Some approaches to be considered are:

Static mixer. Pushing fluids back and forth through a serpentine path is a simple way of mixing. However, long channels or long times are often required as these still mostly depend on diffusion, which can be slow for large molecules. Also they are best at mixing two fluids side by side, rather than the front and back regions of a fluid volume.

Magnetic bead stirring. Paramagnetic microbeads will form strings in the presence of a magnetic field. Rotating the field causes the strings to spin and impart a stirring motion. Larger diameter "helper beads" can also be added if additional energy is needed.

Mechanical agitation. If the mixing chamber has a flexible top or bottom surface, then applying a mechanical squashing action can be a simple but effective method of mixing.

Ultrasound. This is commonly used as a mixing method on a macroscopic scale and can be down-sized to microfluidic scales. Best performance is achieved when the generating components are in direct contact with the materials to be mixed. Like SAW, having an off-board ultrasound source introduces coupling issues and drastic losses in performance.

Coefficient of Variation (CV) of reagents and fluids

Whether macro scale or lab-on-a-chip, our assay requires a consistent and known droplet volume in order to be accurate. Our chip design will have to include a method of drawing off a known (and preferably predetermined) volume regardless of whether the source is a bulk reservoir in the instrument or smaller on-chip store such as a blister pack.

Polymerase Chain Reaction (PCR)

Moving to the smaller volumes which make a microfluidic consumable so attractive gives us two issues which are of less significance in the macro world:

a) The increased surface area/volume ratio means evaporation becomes a concern. We therefore need a method of either sealing the sample in a chamber or locally raising the vapour pressure.

b) The mass of the container is large compared to the sample mass. Therefore, we must make sure that the heat we supply to the consumable is efficiently transferred to the sample. Furthermore, having an on-board temperature sensor is unlikely to be a luxury we can afford so any internal temperatures will have to be inferred from thermal modelling and rigorous optimisation.

Further optimisation will be required to balance the cycle time vs temperature overshoot. This will be achieved by designing in good (and consistent) thermal contact between instrument and cartridge and also by setting up the PID (Proportional-Integral–Derivative) control properly. In figure 1, the red curve gets to temperature quickly but massively overshoots the target temperature and risks damaging our chemistry. Eliminating the overshoot (the purple curve) means time to temperature increases by a factor of 10 but the target temperature is never exceeded.

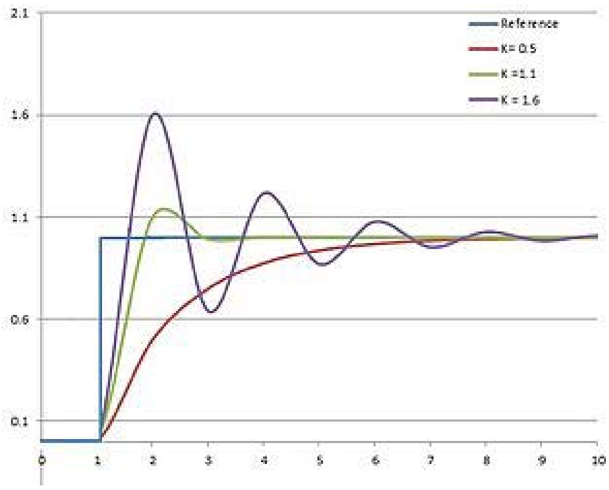


Figure 1
The green line is an optimised performance – allowing a small overshoot to enable a much quicker time to temperature.

Manufacturing approaches

Ultimately, we are trying to achieve the desired performance at the lowest cost, even if it means transferring some of the functionality to the instrument and increasing the instrument cost a little. As with most things in manufacturing, it all comes down to annual quantities at the end of the day – the more we're making, the more options for cost reduction we have. We should also consider the nature and geometry of the features we're including. Creating features smaller than around 50 microns becomes very challenging using additive manufacturing or CNC machining so different techniques would have to be employed to create microwell arrays, for example.

There are many methods of constructing our microfluidic chip. Here is a round-up of some of the most commonly used:

Additive manufacturing (e.g. SLS, SLA, FDM)
Useful for quick turn-round, low initial capital outlay and complex shapes. Slow process speeds make it unsuitable for more than 10's of parts. Fine features and finishes are not feasible but could be added as a second machining operation or by the insertion of elements made by different techniques. Some materials are porous and will have to be coated to seal them.

Casting

Often overlooked as a low volume, fine tolerance approach. A flexible mould can be created from a high cost, finely toleranced master part and used to create cast replicas. A mould will have a relatively short life (<10 cycles) but will produce identical parts. The master can be used adinfinitum to create new moulds without detriment. The master could be created to include several copies so the casting process will produce multiple parts per run. Care must be taken to ensure air bubbles and air pockets are eliminated and parts often require hand-finishing to remove the fill witness. A fast and effective method for making high quality moulds is vacuum casting. A key benefit is that the vacuum draws out all the air, removing any bubbles and forcing resin into the entire volume of space.

CNC machining

Usually the go-to technique for cost-effective production of up to 100's of parts, this approach will struggle with smaller features. Cutters capable of creating 30 micron channels are available but these are extremely delicate and require high speeds and slow feed rates. Furthermore, there is a limit on depth of cut. A good machinist's rule of thumb is that holes should not be more than three times their diameter. This means overall production rates are low and costs relatively high.

Early phase moulding

Injection moulding is a very attractive method of producing 100's to 1,000,000's of parts. Injection moulding can be considered two ways, early phase moulding and production moulding.

With the rise of additive manufacturing, many injection moulders have streamlined their services to be more competitive. They now offer 4 – 6 week turn-round times and parts off a mould tool for around £10,000. Simple parts could be more like £5,000. Tools of this nature tend to be made of aluminium because it is quicker to machine and are therefore not as hard-wearing as fully hardened steel tools. It is reasonable to expect 10,000 parts off an aluminium tool before tool wear becomes an issue. Parts will be indistinguishable from those off a hard steel tool.

A prototype tool also enables exploration of materials. Parts can be moulded from different materials and although shrink rates will vary, it should still be possible to use parts for wear tests, compatibility trials, to test optical clarity, aesthetic appeal and to carry out dummy assembly runs etc.

The really attractive aspect of moulded parts is that the addition of extra functions comes free (almost). Alignment features, access ports and joining elements can all be designed in and because they are moulded at once, will be consistently positioned.

There are companies that offer a range of generic microfluidic mouldings off the shelf. If you are lucky you may be able to get the functionality you require from a moulded part without the expense of a mould tool.

Production moulding

Moulding prototype parts predominantly has two functions, to uncover unexpected issues and to get something into assay developers/lab technicians' hands to start using. It is therefore worthwhile trading some risk for speed. When moving to production tooling, it has to be right. This will likely be an expensive tool and parts produced off it will be used for laboratory trials which may form part of an FDA submission. Changes to the tool will require retesting of the assay. Therefore, more design effort will be invested in it. But that time will be well spent as we can exploit more of the features a moulding can offer:

Multicavity tooling

Can have a drastic effect on cost. The two main components of moulded part cost is the amount of raw material used (we're already addressing that by moving to a microfluidic solution) and cycle time, i.e, the length of time it takes to fill, freeze and eject from the tool. Creating a 32 cavity (say) tool enables 32 times as many parts to be produced as a single cavity tool.

Family tool

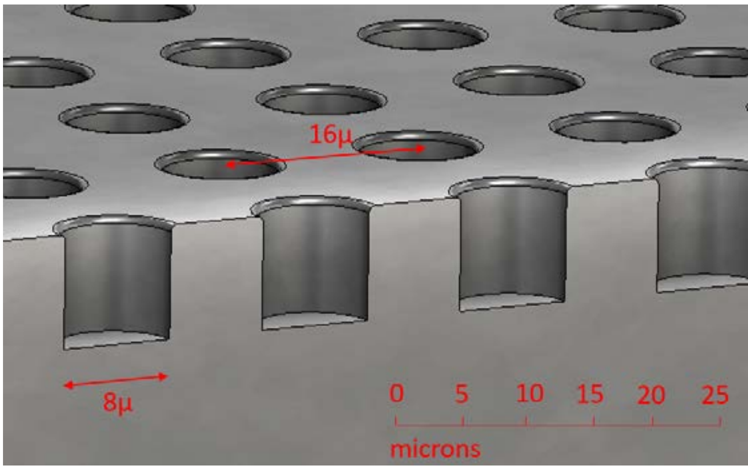
Useful where an assembly will only ever use a complete set of parts (for example a top moulding, bottom moulding and an insert of some description). All three parts would be moulded at once and could be held together as a set by a thin sprue. This enables easier colour matching (as the family will be moulded from the same batch of material) and ease of stock control (you should never find yourself in the position where you run out of stock of one of the components.

Two-shot tooling
With this technique, instead of ejecting the moulded part from the tool, it is retained in one half of the tool. Then, the tool swivels and engages with a second, different half. This will enable a second plastic injection to take place and we end up with a single homogeneous part comprising two elements of different materials (and therefore properties). This is how the soft rubber gripped toothbrushes (for example) are made. We can use this combination (usually a rigid/pliable pairing), to provide built-in gaskets, soft touch buttons and grip features and, when contrived to include a chamber below, as miniature bellows. This last feature opens the possibility of creating an externally driven pump. The advantage to this is that the fluid path is entirely self-contained, there is no open port to the outside world.

Advanced functions
With extra design effort comes the possibility of adding living hinges (and other deliberately flexible geometries), snap features, break-off features and sacrificial elements.

Surface finish
There are games to be played with surface finish too. Typically, parts are delivered with a “light spark finish”. This is the imprint of the finish left by the spark erosion process on the mould tool. But there’s no reason why we can’t specify a different finish from the moulder. The tool can be polished to provide a much smoother, slippier finish. It can be locally polished, which, when applied to a clear plastic, will create an optical window in an otherwise translucent part. We can make it rougher to alter its behaviour when rubbing against a second part or to promote adhesion. There are companies who can modify mould tool surfaces to mimic the super-hydrophobicity found in nature and thus avoid the cost of applying coatings as second operations.

Microwell arrays
A regular mould tool manufacturer will quail at the thought of making a tool which incorporates sub 10 micron features. That’s not to say they can’t be moulded - it is entirely feasible to create a microwell mould lithographically and drop it into the macro mould tool as an insert.



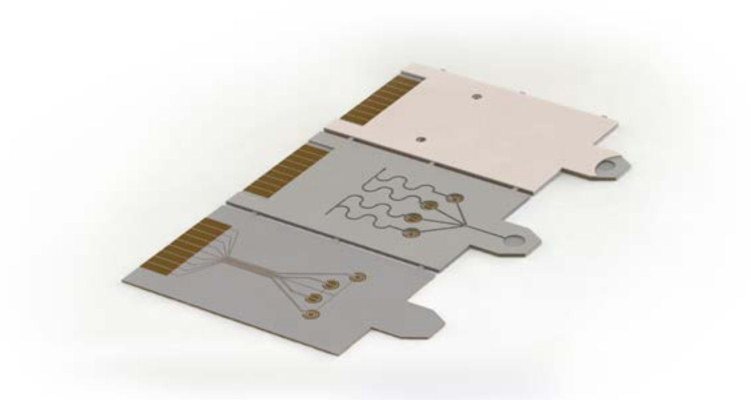
A fully hard production tool will take longer to design, longer to manufacture, be subject to more stringent testing and, in the case of a two-shot tool, be significantly more complex. It will therefore be significantly more expensive than a prototype tool. It should, however, last for 1,000,000’s of cycles.

Embossing
Shallow features can be embossed into a plastic part. This needn’t be done using a hot tool, it is possible to permanently emboss at room temperature, eliminating the need to heat the tool or to allow the part time to cool.

Film
It is possible to laser cut (or mechanically stamp) plastic film and laminate them together to create microfluidic channels in a three-dimensional component. Film is an exceptionally inexpensive material and easily processed. It’s even possible to create electrodes and passive circuitry by taking metallised film and partially removing the metal coat (by laser ablation) to form conductive paths. Laser (or die) cutting and ablation can all be carried out on a web-format and can be incredibly fast. Assembly, however, is a specialised activity. Material variation and tolerance build-up mean that it is difficult to laminate several webs together. Normal practice is to use one web as a base and cut, pick and place parts from the other webs onto it.

Although attractive for very large volumes, laminated chips do not lend themselves to every microfluidic application. If you need on-board reagents for example, they will likely be in blister packs and will need to be captured, protected and include the means to puncture and direct their contents to the right place on the chip. That needs a moulding.

There are other ways to fabricate microfluidic components than those mentioned here. And, of course, you aren't limited to one method. There's no reason why we can't use several techniques and create a hybrid. For example, we could create a moulding which incorporates all the useful geometry, functionalise it by adding the blister pack(s) and dry reagents and then sealing it all together using film.



Assembly

One of the metrics used to assess the cost of an assembly is the Cost of Goods (CoGs). As it implies, this is the cost of acquiring all the parts comprising the bill of materials, whether they are manufactured in-house, sub-contracted out or off-the-shelf items. However, this only gives us part of the picture. A key cost inextricably linked with the CoGs is the cost to assemble and test. Sometimes it makes sense to increase the cost of the component parts if the effect is to reduce the cost of assembly by a larger amount.

Also worth bearing in mind is the choice of manufacturing partner. Bringing everything in-house avoids paying mark-up to a third party but not all companies have the resource or expertise to do that. The Far East is the traditional place to find cost-effective manufacturers but dealing with companies so far away and in a diametrically opposite time-zone is sometimes unpalatable. Eastern Europe labour rates aren't as low as those in China, but companies typically invest more in automation to reduce costs. An alternative location for low-cost manufacturing is North Africa – there is a growing consensus that the region's growth is on an upward trajectory, fuelled by investments in infrastructure and proximity to the EU. Places like Costa Rica have a growing medical device manufacturing presence and are very accessible for North American companies.

Don't ignore the benefits of manufacturing locally. The COVID-19 pandemic has revealed how reliant the West is on Chinese manufacturing and there is increasing focus on reshoring. The increased costs are somewhat offset by the hidden benefits of shorter lines of communication, quicker transportation, greater flexibility and more effective control of intellectual property.

Back to the details. It's inevitable that our chip will contain multiple components. They will therefore have to be held together as a single entity in such a manner that it is leak-tight (both to prevent contaminants entering the assembly and invalidating the integrity but also to prevent any infectious or dangerous materials leaking out). The complete unit should be tamper-proof where possible. So how do we join it all together and how does it seal?

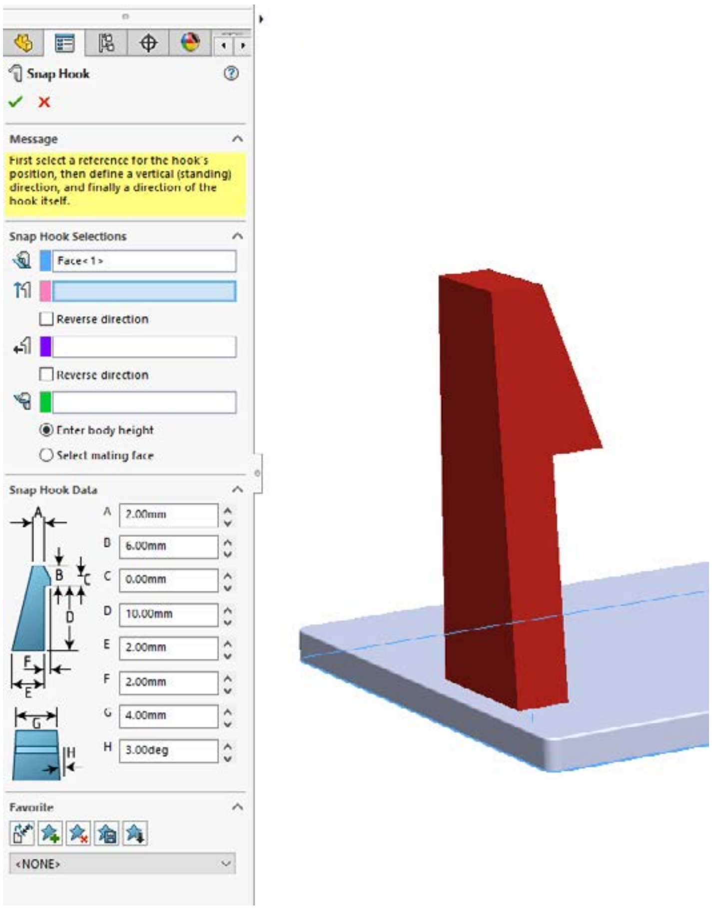
Adhesives

Adhesive used to hold parts together is an additional part on the BoM and will have to be handled, applied and cured. Each of these is an additional cost. But sometimes there's no alternative. UV-cured adhesives are almost instant and enable us to avoid a lengthy stay in an oven. Adhesives can be applied on a batch basis by a glue robot (inexpensive and mature) or by stamp transfer for continuous flow assembly. Glued joints have benefits in that they are genuinely tamper-proof and form their own seal if properly applied in a continuous bead.

Fasteners

Again, to be avoided if possible as they'll be an additional part on the BoM and have to be handled on the assembly line.

Snap features
Take some time to get right but are very effective (and free) when designed correctly. (There's even a tool in CAD packages to help get the design right first time:



Placing them on the inside of a moulding makes them tamper-proof. Sometimes it's possible to design lips into a moulding which will provide adequate sealing (like soda bottle caps) but more complex geometries or demanding applications will need a compliant gasket. If you have a two-shot moulding, the gasket could form part of the second shot, effectively eliminating a part.

Heat staking
Moulded posts and holes can be used to align parts and once assembled, the protruding part of the post can be heated and formed into a rivet head to hold everything together. Cheap and automatable.

Ultrasonic welding
Is quick, clean and easy and needs no additional parts on the BoM. A dedicated tool (called a horn) is required to focus the energy into a sacrificial welding lip but these are relatively inexpensive, and the resultant joint has the same integrity as the rest of the moulding.

Laser welding
Some materials (and combinations) are more suitable than others for laser welding but provided appropriate materials are selected, this is a flexible joining method. Changes to the design and the weld line can be accommodated in software without the need to retool. Be aware though – laser welders aren't cheap so expect a hefty capital outlay.

Hot plate welding
This is a simple approach which is cheap and effective but does not have the finesse of laser or ultrasonic welding. It is much easier to keep the heat to a localised area with laser or ultrasonic welding. A useful rule of thumb though - similar materials will create a permanent weld, dissimilar materials will create a peelable weld.

Ready to go? We can help you.
Sagentia is a product development company with extensive experience with diagnostic devices. We have moulding designers, systems engineers, software engineers, scientists, analysts, optics wizards and mathematicians. We can assemble a team to assist you through the whole cycle – from concepting through to transfer to manufacture. In this article we have focussed on the design of the cartridge but in the real world it cannot be dealt with in isolation – it is inextricably linked with the instrument and the assay. We can also design and develop your instrument with you and even consider the dynamics of your assay, providing a useful review stage.

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