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MES

When microns matter...

MICRO OPHTHALMIC OCULAR IMPLANTS

More often than not, the smallest component in a medical or pharmaceutical implant or device is the enabling component. Micro manufacturing (micro injection molding, micro machining, and micro automation) has blazed the trail for many new developments, implants, micro surgery, and robotic surgeries today. This article, by Donna Bibber, Plastics Engineer & Chief Executive Officer of Micro-Engineering Solutions, explores one such market segment in which micro manufacturing has played and will continue to play a significant role in worldwide growth in the next five years ... ophthalmic devices.

Age-related eye diseases such as cataracts, diabetic retinopathy, glaucoma and macular degeneration (to name only a few) continue to cause loss of vision either significantly or completely. Driven by a baby boomer aging population, technology innovations and vast, rapidly emerging markets in China and India, the ophthalmic devices sector is expected to attain a double-digit growth. Ophthalmic and intraocular implants are largely made up of many micro sized and highly precise components and assemblies. This market sector continues to remain one of the largest and fastest growing micro medical and pharma micro device sectors, globally.

MARKET DATA

The global ophthalmic device market was valued at $10 billion (£6 billion) in 2008 with the US market comprising $5.5 billion of this. Driven by growth in the vision care and cataract surgery market categories, the market is forecast to grow by 8.5% annually during 2008-2015 to reach $15 billion worldwide ($9.8 billion in the US).

On the downside, due to reduced consumer discretionary spending in the US, the market continues to grapple with growth decline in refractive surgery. On the upside, the treatments for other conditions are the major factors for the vastly emerging growth markets worldwide.

Major players in the ophthalmic pharmaceutical space include:

- Alcon (now part of Novartis)
- Allergan Inc
- Bausch & Lomb Inc
- Daiichi Pharmaceutical Co Ltd
- Genentech Inc
- Inspire Pharmaceuticals Inc
- ISTA Pharmaceuticals Inc
- Johnson & Johnson (Vistakon Pharmaceuticals LLC)
- Merck & Co Inc
- Pfizer Inc
- Santen Pharmaceutical Co Ltd.

Major players in the surgical ophthalmic space include:

- Abbott Medical Optics
- Alcon
- Bausch + Lomb Inc.

CONDITIONS AND TREATMENT

The eye is a complex and sensitive organ. There are many structures and targets, located closely together and sometimes, in terms of targets for treatment, these structures are conflicting with one another in their proximity. Existing in the eye are significant defense mechanisms, such as the tear film and the cornea, which present challenges for medication to enter. Specifically, the vitreous fluid is difficult for injected medication to traverse to reach the posterior of the eye.

A number of conditions of varying seriousness and interest are:

1. Glaucoma
2. Cataracts
3. Diabetic retinopathy
4. Age-related macular degeneration
5. Dry eye syndrome
6. Uveitis
7. Retinal detachment

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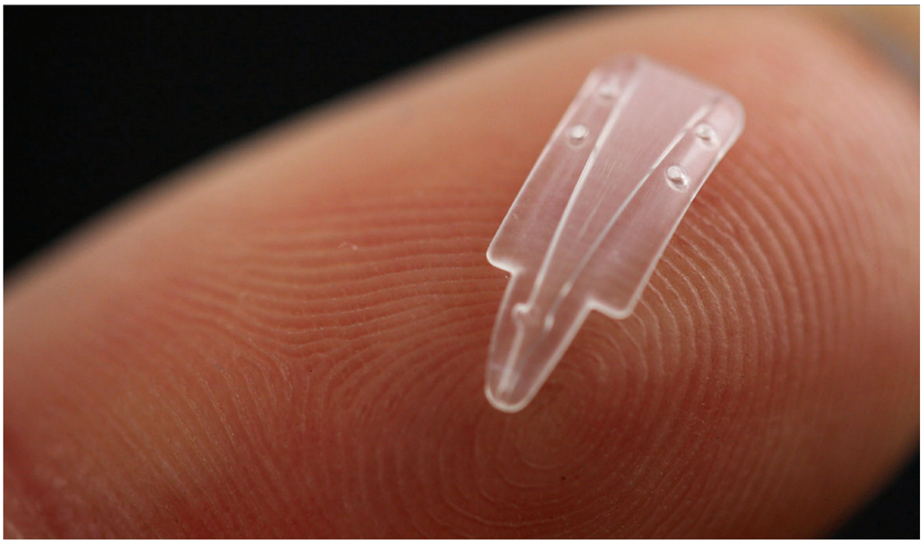

Figure 1: A micro-injection moulded glaucoma drain (shunt).

8. Advanced age and lifestyle diseases; still an extremely high level of unmet need
9. Others of lesser importance can be treated / managed with eye glasses, OTC medication, antibiotics, and specific hygiene protocols and, in limited instances, with surgery.

Treatment often requires contributions from two or more parts of an inseparable therapeutic triad:

- Ophthalmic pharmacology
- Surgery of the visual tract
- Implantable ophthalmic medical devices.

Highly innovative specialist companies dominate pharmacological development. Innovative companies on the drug delivery side are equally important. Industry development occurs through a large number of highly-focused, research driven specialist companies, often very small and funded through innovation-support funding programs. Such companies can need to be able to easily find a large marketing partner as big pharma is often funding this development externally in lieu of doing it themselves in-house.

Highly innovative specialty companies define and epitomise the requirement for treatments for these conditions that comprise micro sized and ultra-precision components and assemblies. Anyone who has ever worn corrective contacts and/or been on the bad end of a windy day near an outdoor fire pit, you have probably noticed that the smallest speck in your eye can cause you severe pain.

The reasons for intraocular implants being micro sized then are to provide the eye an extreme level of comfort with the least invasive, yet compliant implants in the human body. The thin and delicate structures of the eye require paper thin and flexible components that are nonetheless strong enough to withstand extreme fluid pressures in and behind the eye. The successful creation of a device that is both paper thin and strong is an engineering challenge that requires the skill and expertise that only micro moulding and nano surface specialty companies can understand and implement. Let us explore this micro requirement specifically for some of the more common conditions/treatments.

For example, glaucoma, the "sneak thief of sight", affects many elderly, African Americans, and those with a family history. Considered the second leading cause of blindness (after cataracts), glaucoma is principally caused by elevated intraocular pressure within the eye. Micro surgical devices and intraocular implants are used if eye drops are not an effective treatment. Micro components and surgical treatments include:

- Trabeculectomy (laser surgery) is most common approach; creates a hole in sclera to allow fluid to drain into the outer cyst
- Conventional surgery can also be used to create a drainage hole in the white part of the eye if laser surgery is unsuccessful
- Implant surgery positions a device to aid the drainage; estimated that several thousand are performed each year in the US
- Canaloplasty places a microcatheter into Canal of Schlemm to enlarge the natural drainage channel for healthy eyes.

Figure 1 shows a glaucoma drain, commonly known as a shunt. This shunt is injection moulded, spherically shaped with a wedge-shaped radial side action in the tool that creates the drain geometry. At the end of the side action travel is a 250 μm orifice whereby no moulding flash can be tolerated. Shunts are mostly tubular, however this one is shaped and designed for placement in the sclera (side of the eye). It is designed to act like a venturi system which uses the pressure of the eye to push the discharge from glaucoma to behind the eye where it can drain. In addition to the 250 μm entry orifice, there are 4 suture holes of 250 μm diameter (2x a human hair) moulded into the top of the implant. These suture holes also must be free and clear of particulate or flash to prevent sutures from cutting during implantation or after surgery.

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Age-related macular degeneration (AMD) is the leading cause of permanent impairment of reading ability and loss of fine detail for those over age 65 years. The macula is the central portion of the retina used for seeing fine detail and can be destroyed in one of two ways beginning at age 60.

In 2004, 1.5% of adults over age 40 experienced advanced AMD and 6.1% had intermediate AMD (1.8 and 7.3 million adults, respectively). The dry form is most common form of AMD but it can become wet form which is more destructive. In dry AMD light sensitive cells in macula break down. Dry AMD is treated by oral ingestion of high dose of anti-oxidants and zinc.

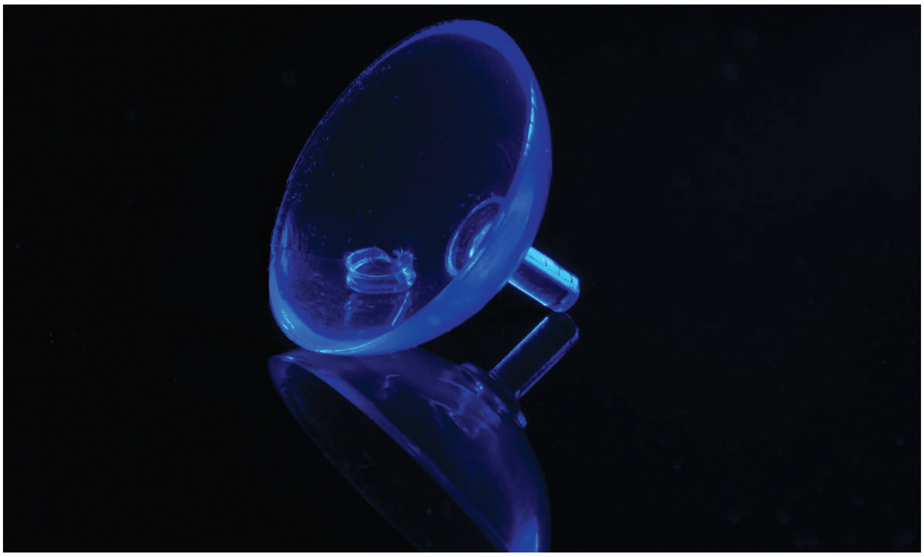

Figure 2: Macular degeneration laser guide.

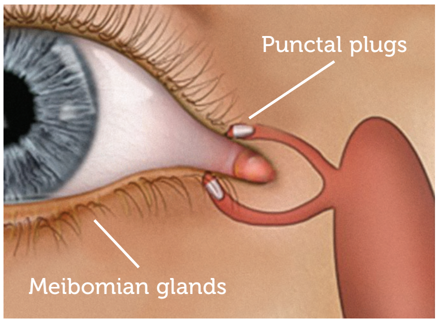

Figure 3: Punctal plugs placed in drainage channels of the upper and lower eyelids (Source: allaboutvision.com).

Wet AMD is characterised by growth of abnormal blood vessels behind retina. Laser surgery is used in small proportion of patients to destroy these vessels but the treatment also damages the retina. Another treatment approach involved intravenous injection of a photo-activated drug (into the arm). When exposed to light in the eye the drug is activated and it destroys the unwanted new blood vessels. Injections into the eye to block growth of abnormal new blood vessels are also available.

Prior to 2007, medicine was not available to treat AMD; in 2007 the market was estimated to represent more than $1.2 billion in sales.

Figure 2 shows an AMD guidance device used in laser surgery. The spherical radius sits on the cornea and the lens underside must be free of flash, mould parting lines, and surface imperfections. The 300 µm laser hole shuts off on the spherical radius and blending these geometries three-dimensionally in steel to produce the polymer micro injection moulded component is very challenging.

In this case, material selection was also a key factor in providing the rigidity required to hold the guide in place during laser deployment. USP Class VI materials (they have previously been used in medical products) are necessary and also require OEM testing even if they are shown to be Class VI compliant.

Dry eye is one of the most common reasons for an appointment with an ophthalmologist. Dry eye condition is defined as an irritation of the eye due to an inability to produce or maintain/retain enough tears on the surface of the eye. It can result in damage to the front surface of the eye and impair vision. The causes vary from specific diseases (such as Sjögren's syndrome or lacrimal and meibomian gland dysfunction) to other causes including age, gender (women are more susceptible), medications, certain medical conditions, environmental conditions such as exposure to smoke, wind, or dry climates, and other factors such as prolonged use of contact lenses or refractive eye surgeries (LASIK).

Treatment, may require micro components (approximately a quarter of the size of a grain of rice) including punctal plugs (see Figure 3) whereby a plug is surgically placed in both the top and lower eyelid to prevent fluid in the eye from draining, thereby keeping the eye hydrated.

> "New methods combine traditional top-down methods with futuristic bottom-up methods to provide medical and pharmaceutical device companies with enabling products to treat the likes of glaucoma, macular degeneration, cataracts, dry eye, and even diabetes around the world"

Additional treatments use OTC eye drops or prescription lubricants and anti-inflammatories. These medications are extremely costly and if not administered properly (balancing the dropper over the eye and making sure it all gets into the eye) defeats the purpose and wastes consumer and healthcare costs. Much effort is put into micro pumping and micro administering of these fluids with aspirators, implantable pumps, and slow release polymers that release the drug in timed increments.

DESIGN CONSIDERATIONS

Many drug delivery devices are now manufactured in non-traditional ways such as silicon wafer technology, MEMS, and ground-up manufacturing methods. These methods are then matched to more traditional top-down methods to provide medical and pharmaceutical companies with differentiated and strategic value. These processing techniques are typically developed using "conventional" single micron level positional accuracy using current work holding devices. These methods are inadequate in preventing cross contamination of actives in capillaries and other microscopic microfluidic assemblies.

Nanometre-positional accuracy was not available to the mainstream even 2-3 years ago. Even today, traditional pallet-holders coupled with automatic X, Y, Z probing can barely guarantee a one micron positional accuracy. It is also strange to think this isn't good enough for the eye, but the surface finish is absolutely necessary, orders of magnitude tighter tolerances than seen in conventional or macro manufacturing.

So it is evident that developing ophthalmic and intraocular implants requires thinking at the scale on which the human body operates, and the human body operates at the scale of nanometres. White and Red blood cells on average range from 8-100 µm in diameter and

"Top Down" Methods	"Bottom Up" Methods
Laser Machining	Genetic Code
EDM-WEDM	Complexity Theory
Ultrasonic Machining	Self-assembly
Ion Machining	Biological Cell
Grinding	Proteins
CNC Machining	DNA and RNA
Chemical Milling	LIGA
Photochemical Milling	3D Printing
Electrochemical Machining	

Figure 4: Summary of Micro-Engineering Solutions' micro and nano manufacturing methods used today and in the future.

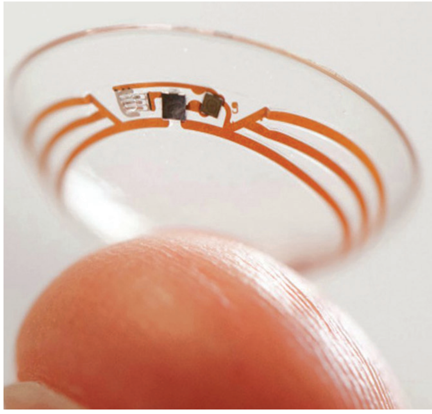

Figure 5: Google's smart contact lens (Source: Google Inc).

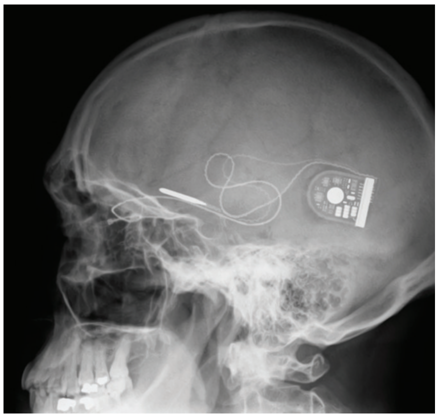

Figure 6: Retinal implant (Source: Institute for Ophthalmic Research at the University of Tübingen).

DNA can be as small as 2-3 nm. In between these two range a great deal of discovery and science that we cannot begin to understand without simulation outside the body, for example mimicking strands of DNA and blood cells working together. It is for this reason that ophthalmic, intraocular, drug delivery and pharmaceutical device companies are looking for help from manufacturers to push the boundaries of what is possible to achieve features and tolerances in the nanometre range.

As shown in Figure 4, what we have discovered in the micron range has certainly helped us to learn some top down methods that didn't work, and some bottom up methods that worked but needed some refinement using a combined top-down/bottom-up method.

Growing structures (i.e. bottom-up methods) to create geometry was also not mainstream until 2-3 years ago. A good rule of thumb is that material and process marrying will force a top down methodology until we can mill, grind, edm (electrical discharge machine), diamond turn, and etch no more. We have already used LIGA (German acronym meaning lithography, electroplating, and moulding) for many years as a bottom-up method. However, with the emergence of 3D printing, at some point in the near future, we will be looking that technology to create geometry, surfaces, and – when the materials are available and 3D printable – even human organs. This will push micro manufacturers and macro manufacturers beyond our current capabilities in top-down methods, or there might be a "marriage made in heaven" employing both methods.

For example, in the area of diabetes, Google is developing a smart contact lens for measuring glucose in tears (see Figure 5). Google said the lens comprises "chips and sensors so small they look like bits of glitter, and an antenna thinner than a human hair". The chip and sensor are embedded between two layers of soft contact lens material. A tiny pinhole in the lens allows tear fluid from the surface of the eye to seep into the glucose sensor. The prototypes currently being tested can take glucose level readings every second. The project was co-founded by Brian Otis and Babak Parviz who worked together at the University of Washington (Seattle, WA, US) before moving to Google.

One can't help imagining that, beyond diagnostics, completely encased electronics placed onto the cornea may one day bring vision, gaming, web browsing, and social interaction to a completely new level.

Alternative methods are coupling neuroscience with ophthalmic science as seen in Figure 6, which shows a retinal implant embedded in the eye that restores vision to the vision impaired or the visionless.

Non-traditional methods for manufacturing such as nanometre positional accuracy and dust-specked sized injection moulded, machined, and assembled components are spawning technological advances in ophthalmic intraocular implants and intraocular drug delivery devices. These new methods combine traditional top-down methods with futuristic bottom-up methods to provide medical and pharmaceutical device companies with enabling products to treat the likes of glaucoma, macular degeneration, cataracts, dry eye, and even diabetes around the world.

Areas unknown can be explored with micro manufacturing – restoring lost vision, enhancing vision, hydrating eyes in harsh conditions, gaining less invasive, viable ways to cross the elusive blood-retinal barrier, micro-electronics and eyes controlling the brain to control prosthetics, and even controlling motion for paraplegics. Imagine a technology allowing people to see...... people they haven't seen in years, objects in a room, light in a sky, food on a plate, and to recognise a smile. We are fortunate to be well positioned in micro and nano manufacturing to play a part in enabling these treatments and products that contribute to worldwide health.

ABOUT THE AUTHOR

Donna Bibber is a Plastics Engineer and CEO of Micro Engineering Solutions, a micro-focused design and manufacturing company providing micro moulding and micro automation/assembly services to start-up and Fortune 500 companies alike. Ms Bibber has published and lectured on hundreds of technical papers on micro moulding medical and pharmaceutical devices, and associated topics worldwide and was voted onto the MD+DI List of 100 Notable People in Medical Devices in 2008.