HOYA
SURGICAL OPTICS

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The Best of Multiple Worlds?

The HOYA 4-in-1 multiSert™ delivery system preloaded with Vivinex™ IOL offers unmatched IOL delivery flexibility and consistency, but how does the Vivinex™ IOL perform over the longer term?

Here, leading experts in their field share their surgical experiences with the multiSert™ as well as the available scientific and clinical evidence of the Vivinex™ IOL platform's PCO performance.

Featuring:

Professor Gerd Auffarth, International Vision Correction Research Centre, University Eye Clinic, Heidelberg, Germany
Professor Dominique Monnet, Université Paris Descartes Hôpital Cochin, Paris, France
Dr Khiun Tjia, Isala Clinics, Zwolle, Netherlands
Professor Michael Wormstone, University of East Anglia, United Kingdom.

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The Surgeons in this supplement are delighted by the performance of the 4-in-1 multiSert™ delivery system preloaded with the Vivinex™ IOL but, following uneventful surgery, patients expect to benefit from an IOL that performs optimally over the long term; after all, sophisticated surgery is wasted if the patient's sight is impaired within months.

Causes of post-operative visual degradation include IOL glistenings and posterior capsule opacification (PCO). The latter, which remains a major long-term issue for cataract patients, is a consequence of lens epithelial cell (LEC) activation and migration. Hence, PCO prevention strategies (Sidebar 1) might include attempting complete LEC eradication, prevention of LEC activation, or facilitation of barriers that exclude LECs from the posterior capsule.

But what evidence is there that the IOL surface can mediate reduction in PCO frequency? And, what decisions should surgeons make, given the current IOLs available to them? At the 2018 European Society of Cataract and Refractive Surgeons (ESCRS) in Vienna, leading experts came together to examine and answer precisely these questions.

Part I: Comparative PCO performance analysis: HOYA Vivinex™ versus a leading competitor IOL

Professor Michael Wormstone, University of East Anglia, UK

"PCO is a cell biological problem – a wound-healing response to the trauma of cataract surgery. This trauma initiates changes to the lens cells resulting in enhanced sensitivity to stimuli through receptor activation. Surgery also induces local expression of wound-healing activators. In addition, disruption of the blood-aqueous barrier allows serum proteins to access the aqueous humor and provide further signals to drive functional responses leading to the formation of PCO (Box, Figure 1). To study PCO in vitro, we require laboratory models that enable the study of PCO development accurately." Professor Wormstone's lab has a long history and deep expertise that has continually improved on ex vivo models to simulate PCO development post-cataract surgery. Using human donor eyes, Professor Wormstone's lab established a capsular bag model system that allows IOL implants to be studied in spatial configurations as that of patients (3, 4, 5). "This system has allowed the identification of a number of growth factors that can drive PCO related

Etiology of PCO

- Cataract surgery disrupts lens integrity and evokes a wound-healing response
- LECs are stimulated to proliferate and migrate to all available surface including the posterior capsule
- Pro-fibrotic stimuli drive cells to transdifferentiate to a myofibroblast
- Cells present on the central posterior capsule will deform the matrix and aggregate, which will contribute to light scatter
- In time cells can also differentiate to form Soemmering's ring and generate Elschnig's pearls, which further degrade vision

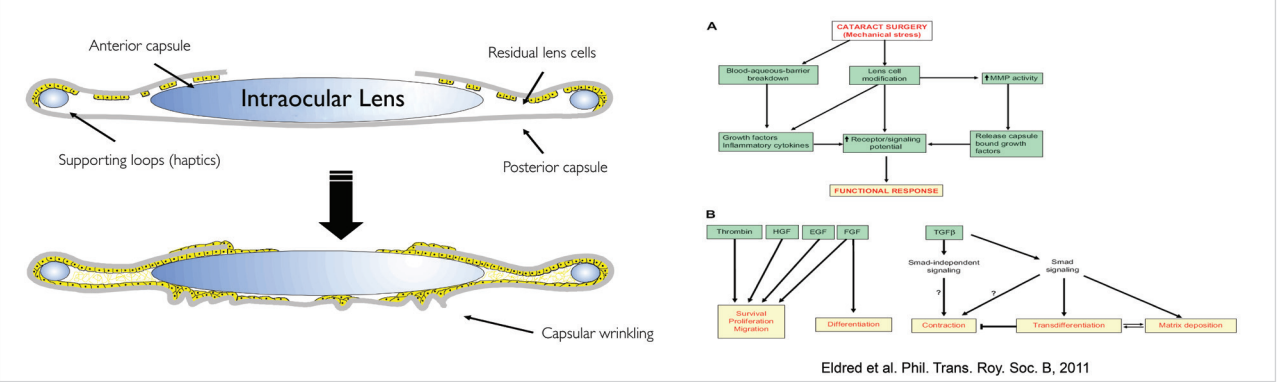


Figure 1(a). Schematic of post-surgical capsular bag, illustrating LEC proliferation and invasion: note cells and wrinkling on the posterior capsule (1).
Figure 1(b). Cataract surgery causes a cascade of events culminating in a functional response: growth factors promote LEC proliferation, migration and differentiation, and TGF-beta promotes LEC transdifferentiation to a myofibroblast and fibrosis (2, 3). Cell invasion of the central posterior capsule, fibrotic changes and formation of structures such as Elschnig's pearls causes vision degradation.

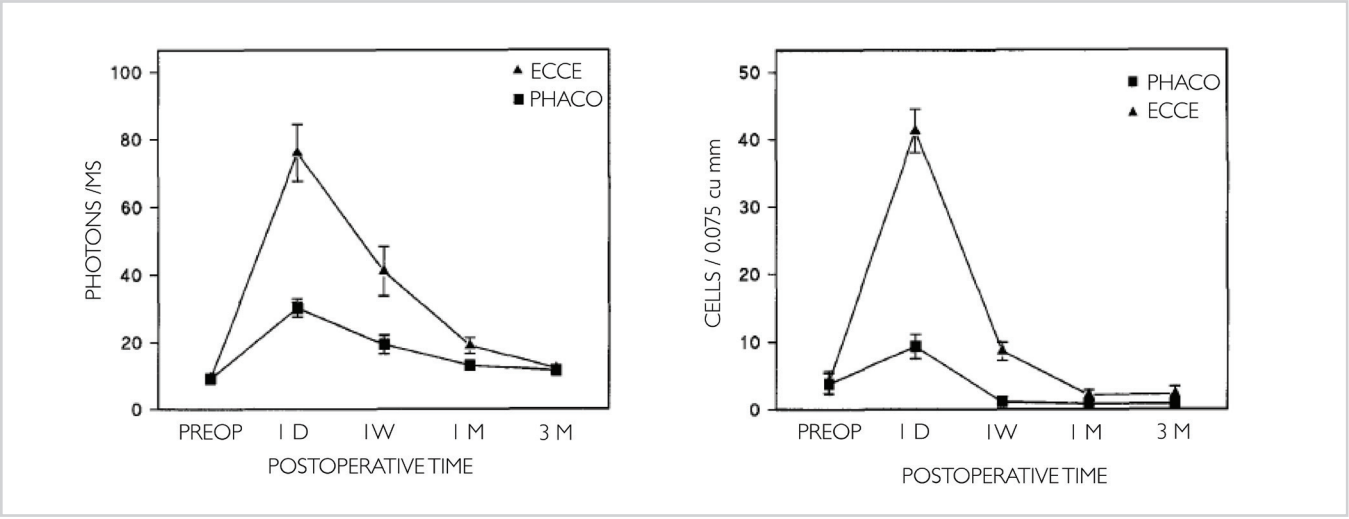


Figure 2. Reference from Pande MV, Spalton DJ, Kerr-Muir MG, Marshall J., J Cataract Refract Surg. 1996;22 Suppl 1:770-4.

functional responses, and serves as a valuable tool to understand the biological systems regulating PCO. As such, it is also possible to test and evaluate IOLs in the capsular bag model. Improvements over the last 20 years include, but are not limited to, pinning down the anterior capsule to enhance the optic edge-capsule interaction and humanization of the capsular bag system with the use of human serum and growth factors in place of bovine-derived sources (6). In collaboration with HOYA in 2018, the model has been further improved upon with the introduction of a graded culture system that reflects the transient nature of inflammation in patient's post-cataract surgery."

The transient nature of inflammation has been reported in clinical observations, high levels of inflammatory proteins in the first week post-surgery are followed by a decline to base levels (Pande et al., 1996, JCRS, Figure 2). The new graded culture system, capsular bag model allows a systematic study of IOL designs and provides detailed insights into PCO development over a truncated timeframe of four weeks as opposed to long-term clinical observations of 2-10 years in patients. Furthermore, the human capsular bag model reflects PCO development realistically compared to the aggressive and enhanced wound healing nature of the in vivo rabbit model. Clearly, the graded culture system presents a significant improvement of tools that enable superior IOL design and testing, particularly in measuring PCO development.

"Comparing Vivinex™ with the market-leading IOL of similar square-edge design and hydrophobic acrylic material, our graded culture system allowed us to measure cell growth on the IOL via direct microscopy. We also measured light scattering, which directly correlates to capsular bag wrinkling

Sidebar 1: Approaches to PCO prevention: hope versus experience?

- *Eradication of capsular LECs*
  - Hope: Remove cells responsible for PCO
  - Experience: Difficult to achieve, and likely to be counterproductive (equatorial LECs are required for stable IOL fixation on the zonular fibers)
- *Avoid LEC activation by 'open-capsule' method of surgery*
  - Hope: Reduce exposure of LECs to growth factors, thereby preventing the cascade of cellular events that result in PCO
  - Experience: Little commercial interest in this approach
- *Exclude LECs by 'shrink-wrapping'*
  - Hope: Inhibit LEC migration by ensuring IOL is closely apposed to the posterior capsule
  - Experience: Requires optimal IOL design, but is often impermanent (development of Soemmering's rings may disrupt capsular leaves within a few years)
- *Exclude LECS by fibrosis induction*
  - Hope: Promote formation of a fibrotic barrier that blocks ingress of LECs
  - Experience: Promising; higher PCO rates after anterior capsule polishing may be caused by inadequate fibrosis related to removal of LECs

and matrix remodeling on the posterior capsule. The studies showed that Vivinex™ has a square-edge barrier that retards cell growth on the posterior capsule better than does the competitor IOL. Furthermore, light scatter on the posterior capsule is consistently lower on Vivinex™ compared to the competitor IOL when measured at the study endpoint of four weeks. Most strikingly, Coomassie Brilliant Blue staining at the study end-point reveals that cell migration onto the IOL is extensive on the competitor IOL, but not on Vivinex™. The extensive presence of cells on the IOL may disrupt light passage through the otherwise optically clear central visual axis, causing fair concerns about light scattering and the performance of the competitor IOL in providing good visual acuity."

Prof Wormstone concluded that the graded culture system mimics post-surgical inflammatory events and allows assessment of PCO following IOL implantation. "Overall, Vivinex™ appears to retard cell growth on the posterior capsule, which results in less light scatter in the central visual axis. The differences in cell growth on the IOL surface are striking: LECs are clearly less likely to populate the Vivinex™ surface than the competitor IOL surface. Thus, results from this system suggest that Vivinex™ is better able to manage and influence the biological processes that lead to PCO than the competitor IOL."

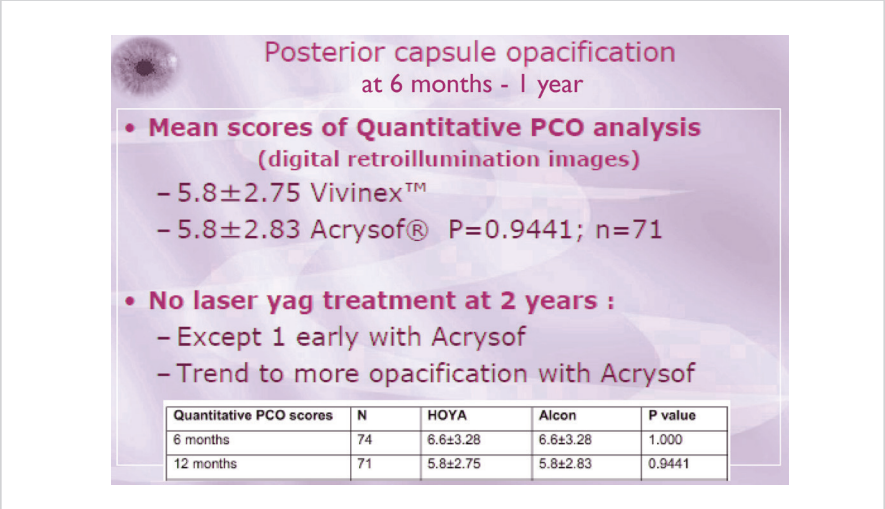
Part II: Comparison of two hydrophobic intraocular lenses: a prospective study

Professor Dominique Monnet, Université Paris Descartes Hôpital Cochin, Paris, France

"PCO remains the most common long-term complication associated with IOLs with a frequency of between 2 and 51 percent at three years. Furthermore, standard PCO treatment (YAG laser capsulotomy) carries its own risks: induced glaucoma (6 percent); retinal detachment (1.4–2 percent after five years); macular oedema (1.23 percent); and IOL damage (7, 8, 9). Factors known to influence PCO include IOL material, IOL design, surgical technique, drug coatings and surface treatments (10, 11). Of these, IOL material may be particularly important: for example, hydrophobic IOLs have lower PCO and laser capsulotomy rates than hydrophilic IOLs at both 1- and 2-year time-points (11, 12). The latest innovation in this field is a manufacturing process, designed to alter IOL surface chemistry (Sidebar 2); the process results in new functional groups that are thought to facilitate IOL-LEC-capsule adhesion, ultimately resulting in a superior barrier to LEC migration.

Does this advanced IOL surface bring any clinical benefits? Since July 2015, we have been part of a three-year, multicenter European study (Sidebar 3) to compare HOYA Vivinex™ with Alcon Acrysof®, with particular regard to PCO and glistening rates.

At 6-12 months, PCO incidence was low in both groups (Figure 3), with a trend towards more opacification in Acrysof®; the single YAG laser



Quantitative PCO scores	N	HOYA	Alcon	P value
6 months	74	6.6±3.28	6.6±3.28	1.000
12 months	71	5.8±2.75	5.8±2.83	0.9441

Figure 3. Prospective clinical study, 12-month time-point. Acrysof® ™ and Vivinex™ have similar PCO rates.

Figure 4. Glistening levels one year after implantation (n=73 patients). Note that all of the Vivinex™ IOLs remain in the lower 2 categories.

procedure was in the Acrysof® group.

Furthermore, we have found significantly less glistenings in Vivinex™ than in Acrysof®, both at one year ($p<0.0001$, Figure 4). This is consistent with previous work indicating that glistenings are extremely common in Acrysof® (33.5 percent were shown to have moderate glistening levels, and 26.9 percent high glistening levels [14]). Surprisingly, however, we found subsurface nanoglistening in 92 percent of Acrysof® lenses – but never in Vivinex™ lenses.

"PCO remains the most common long-term complication associated with IOLs with a frequency of between 2 and 51 percent at three years."

In my opinion, therefore, ozone processing of the IOL seems to be an effective mechanism of preventing PCO; our study reports no YAG procedures up to three years after implantation, suggesting PCO is now under control. Furthermore, in the Vivinex™ material, glistenings are much reduced and subsurface nanoglistenings have been eliminated altogether.

In conclusion, the Vivinex™ IOL's unique combination of attributes, together with the new preloaded screw-push injector, make for a perfect system (Figure 5)."

Sidebar 2: The Vivinex™ surface modification

- During Vivinex™ manufacture, IOL material is UV-irradiated (185 nm and 254 nm), producing ozone
- Ozone forms -OH and -COOH groups on the IOL, thus making the IOL surface more reactive

NB: This approach is not a 'coating': there is no possibility of surface constituents being released from IOL

- The ozone-modified acrylic is reported to be a superior substrate for cell adhesion (13)
- Therefore, HOYA's process would be expected to encourage IOL-posterior capsule adhesion, thereby facilitating barrier formation and inhibiting PCO

Sidebar 3: Prospective clinical study: Vivinex™ versus Acrysof®

- Intent-to-treat population: 85 patients
- Similar initial visual acuities
- Different IOL implanted in each eye, same patient
- Standardized surgery:
  - 2.2 mm incision
  - capsulorhexis overlap
  - capsule polishing
- Follow-up at six months and yearly thereafter
- Outcome measures: PCO quantification, glistening evaluation, best corrected visual acuity, refractive outcomes.

Options	type	Influence	Vivinex Hoya
Raw Material	Hydrophobic > hydrophilic	PCO – capsular bag retraction Long term stability **Risk of Glistening**	**Yes** **No**
Square Vs Round edge	Square >>> Round edge	PCO --	**Yes**
Optical Diameter	**Effective** 6 mm	Quality of vision	**Yes**
Spherical vs aspherical	Aspherical Negative	Quality of vision	**Yes**
Haptics - optic	Design	PCO --, rotational-refractive stability	**Yes**
Yellow chromophore	Blue blocking	Long term Retinal protection ?	**Yes**
Preloaded Injector system / Incision size	Preloaded ≤ 2.2 Convenient	Infection / Surgical induced astigmatism	**Perfect**

Figure 5. Vivinex™ provides a unique combination of advantageous attributes.

Part III: Performance of the new HOYA multiSert™ injector system for the Vivinex™ IOL

Professor Gerd Auffarth, International Vision Correction Research Centre, University Eye Clinic, Heidelberg, Germany

"IOL delivery systems appear to come from two different worlds; we have either push devices or screw devices. But now HOYA has attempted to provide the best of both worlds in a single device – and I believe they have succeeded. With multiSert™, it doesn't matter which world the doctor comes from, as no aspect of the surgeon's procedure needs to change unless the surgeon wishes it.

A defining characteristic of the multiSert™ injector is its flexibility of operation. Surgeons can use it single-handedly (push method) or with both hands (screw method) (Figure 6). The former mode allows clinicians to use the free hand to stabilize the eye with a spatula, make a paracentesis, or do anything else they require. In situations where the injector must be kept very steady, however, the two-handed screw mode provides a very high degree of control over pressure and speed of delivery.

MultiSert™ also benefits from the 'insert shield,' which provides further flexibility of operation (Figure 7). With the insert shield advanced, multiSert™ functions similarly to a wound assist implantation device, stabilizing the injector inside the wound. Alternatively, retraction of the insert shield permits lens implantation at the capsulorhexis level. So whether surgeons wish to avoid deep injection or inject into the capsular bag in one step, the multiSert™ accommodates their preference.

At the David J. Apple Laboratory in Heidelberg, we have examined the delivery of Vivinex™ multiSert™ into human autopsy eyes and porcine eyes eyes using an intraocular endoscope, and into human autopsy eyes using the Miyake-Apple view (Figure 8). In the

Figure 6. Surgeons can use multiSert™ in push mode or in screw mode according to their own preference.

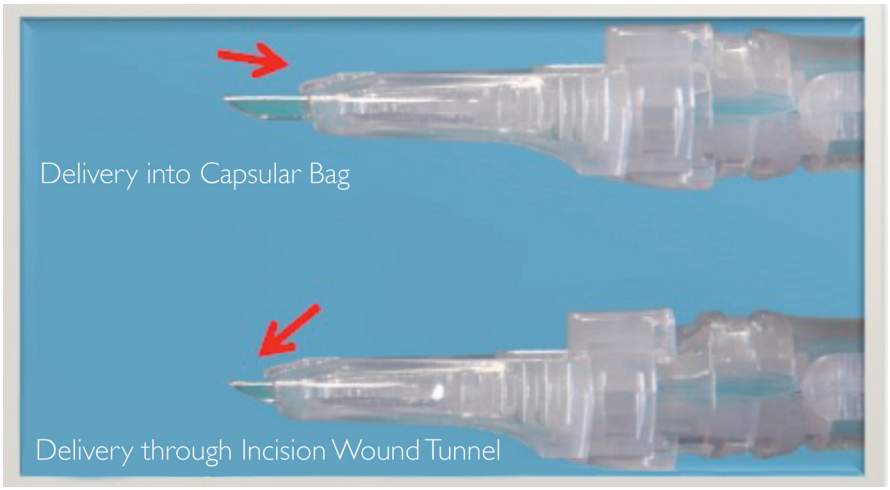


Figure 7. Into the capsular bag or into-the-wound – multiSert™ accommodates both approaches

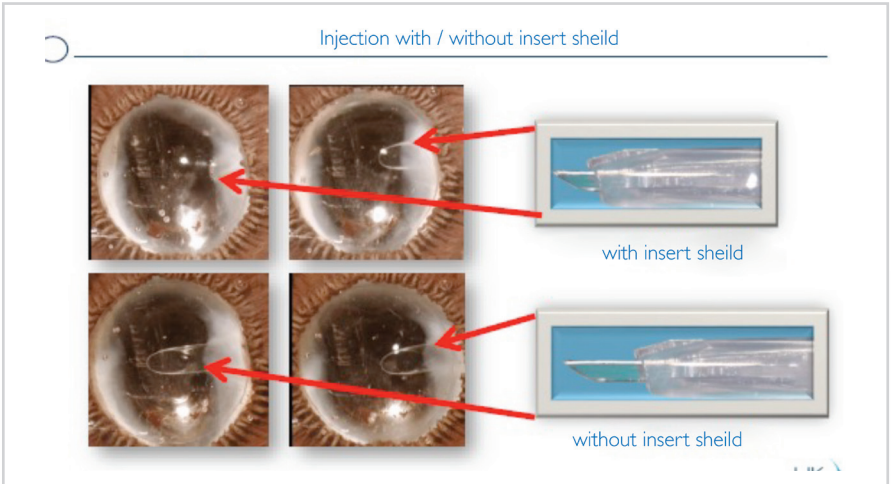


Figure 8. Miyake view of human autopsy eye receiving Vivinex™ lens from multiSert™ injector. With the insert shield, multiSert™ delivers the leading haptic into the capsular bag, and the surgeon can then push out the second haptic. Without insert shield, the surgeon can insert the lens directly into the capsular bag.

porcine eye, we placed the endoscope in the anterior chamber; in human eyes, we observed from the posterior.

Our key finding is that multiSert™ induces little deformation of the capsular bag, suggesting that it should be associated with a lower frequency of capsular and zonular weakness, and enhanced safety. It is easy to use, and unique in combining both screw and push modes. The insert shield is an excellent feature, and effectively stabilizes the injector tip in the clear cornea wound. Importantly, the surgeon always has a choice: to use the insert shield with tight incisions, or to dispense with it and go straight to the capsular bag, via the capsulorhexis, with larger incisions. Overall, our laboratory work suggests that multiSert™'s consistency and safety makes it a leader among preloaded IOL injectors."

Part IV: First-hand experience of multiSert™

Dr Khiun Tjia, cataract surgery specialist, Isala Clinics Zwolle, the Netherlands. Dr Tjia performs over 2000 cataract procedures annually, including challenging cases referred to him from around the country, and teaches cataract surgery to residents. He also helps evaluate innovative products, including phaco instruments and preloaded IOL injection devices.

"In my clinic, we usually use Alcon AutonoMe™; however, I recently tested multiSert™ in eight procedures. I found that it had various advantageous features that are of the utmost importance for both patient outcomes and surgeon comfort.

- It combines a through-the-wound insertion technique, and maintenance of good incision integrity, with a 2.2 mm incision size, which is very important for limiting the risks of surgically-induced astigmatism and endophthalmitis.
- It causes only very limited wound stretch, and requires no stromal hydration of the incision.
- It provides an unprecedented degree of control during injection. Direct tactile control of the plunger is combined with effortless plunger movement; I felt no significant pressure increase during injection, nor any sudden pressure drop on IOL release.

Specifically, multiSert™'s unique ability to switch between push and screw modes not only enables tight control of the procedure, but also eliminates injector blockage (a drawback of wound-assisted insertion in other devices). Furthermore, I would expect that the very slow advancement permitted by 'screw' operation would be advantageous in challenging situations, such as zonular weakness. Finally, the versatility of multiSert™ is further underlined by the 'insert shield,' an innovation designed to limit incision stretch to corneal stromal fibers caused by the injector tip. That said, I did not require this feature, as multiSert™ tip control during injection was impeccable.

In summary, the multiSert™ is truly 'best-in-class.' Tip control during injection is impeccable, ease of use is simply stunning, and the elimination of failed insertions is very encouraging. This device will stand out in any evaluation, and should be rapidly embraced by ophthalmologists."

My experience with multiSert™ – Dominique Monnet

- "I find that multiSert™ is safe and trustworthy, and always results in smooth IOL release.
- The push mode is consistent across all dioptres: no 'rocket' effect.
- Injections 'into the wound' require only low pressure (unlike competing one-handed, hydrophobic lens injector systems).
- There is a short learning curve; it's easy to use in all four modes."

Q&A

Who might benefit most from multiSert™?
Prof Auffarth: "Everyone! Experienced surgeons can try a new mode, while new surgeons will gain experience in both modes and won't end up restricted to one specific method of operation."

What is the main advantage of the insert shield?
Prof Auffarth: "It gives surgeons the ability to adapt their approach for the eye in question; for example, they may prefer to avoid a classic wound incision in a high myopic eye in case they penetrate the anterior chamber. It provides surgeons with more options and more freedom."

Why choose a 28-day end-point for the graded culture model?
Prof. Wormstone: "Our understanding of PCO is informed by post-mortem tissue from a patient who died 28 days after cataract surgery, so we try to follow that time-frame in vitro. Also, 28 days is a reasonable timeframe; we don't want to wait too long for the answers!"

Conclusions

What should ophthalmologists take from this event? First, an in vitro model designed to replicate post-surgery PCO indicates lower

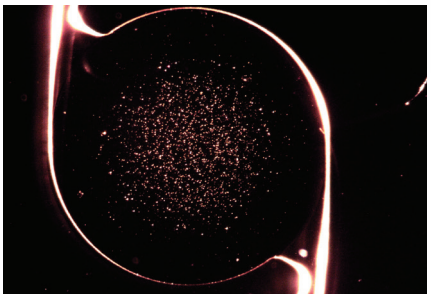


Figure 9. An example of an Acrysof lens exhibiting glistenings.

cell growth on Vivinex™ than a market-leading competitor. As Michael Wormstone puts it: "My opinion is that Vivinex™ performs far better than the competitor control IOL in our graded culture model."

Second, strong PCO performance is also seen clinically with Vivinex™ IOLs: "PCO is now under control," asserts Dominique Monnet. "The lower levels of glistenings and complete absence of nanoglistenings in Vivinex™ are also highly encouraging (Figure 9)."

Third, the multiSert™ system impressed the group. Gerd Auffarth, who draws on both direct clinical experience of the injector and on in vitro tests on enucleated eyes: "Although this is the first version of a combined push-screw injector, it is nevertheless very mature; every surgeon, whatever his preference and clinical circumstances, will find the stability he needs with this device." Furthermore, Professor Auffarth's laboratory studies suggest that multiSert™ causes little deformation of the capsular bag compared to other systems, and hence should have safety benefits.

Khiun Tjia agrees, admiring the limited wound stretch caused by the device, and the unprecedented level of control it gives the surgeon. "As a clinician who has worked with industry to develop numerous medical device innovations over the years, including designs of preloaded insertion systems, I am confident in saying that multiSert™ represents best-in-class performance of any preloaded system for delivering IOLs."

In short, the panelists believe that HOYA has developed a system that suits all surgeons, regardless of their push or screw backgrounds, while providing better vision for their patients, over longer time-periods. Thus, IOL delivery is no longer fragmented into two worlds – but united by a single innovation from HOYA.

multiSerttm is not currently available in Germany

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