- ASCRS 2021 Las Vegas
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- Disclosures: Consult Carl Zeiss Meditech & Leiters.
- Off label & non-FDA approved agents discussed
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- Antisepsis, Dilation and Wound Closure
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- Why Intracameral or Parenteral?
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- Compounding Issues
  USP Section
  797, 788, 789
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- Guidelines for compounded sterile preparations to reduce risk of:
    - Microbial contamination
    - Excessive bacterial endotoxins
    - Variability in concentration
    - Chemical and physical contaminants
    - Poor quality ingredients

- Indirectly affects multi-use of single use labeled compounded products in ASCs
- USP is interpreted and enforced by state and federal licensing agencies (JCAH, AAAHC, etc.)
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- How to confirm your product is appropriate
- Compounding error minimization by printed directions
- Know volume and concentration of your product each case!
- Confirm pH 6.5-8.5 (Edelhauser)
- Osmolarity near 300 milliosmoles (240-400 range ok)
- Sulfite concentration below 0.05% (epinephrine)
- Avoid Antibacterials: Chlorobutanol, BAK, methyl parabens
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- Know the provenance of bulk materials
    - USP FDA-approved bulk ingredients
    - caution with generic substitutes (Moxeza)
- Adulteration, excipients, active and inactive agents

- Moxifloxacin Cautions
- New moxifloxacin generics available
- (ANDA=Abbreviated New Drug Application)
- Sandoz is ok “authorized generic” licensed from Novartis
- Other generics could have different processes
- Moxeza Excipients>TASS>Severe Glaucoma

- FDA Orange Book
    - Approved Drug Products and their Therapeutic Equivalents
    - www.accessdata.fda.gov/scripts/cder/ob/
    - 2 doses available: 5 mg/ml and 1 mg/ml
- Do not flush using 5 mg/ml; limit to 0.1 ml
- Safer to obtain 503B 0.1% moxifloxacin and use at least 0.5 ml
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- **Why Not Vigamox**
  Particulates
- USP 788 and USP 789 guidance: particulates per unit [ppu] limits
- —USP 788 limit for ophthalmic topicals is: <300 ppu in injectable units of 10-25 µ
- —USP 789 limit for parenteral routes is: <600 ppu in ophthalmic topical units 10-25 µ
- Novartis has not confirmed to me that Vigamox nor Sandoz products meet USP 789 particulate standards*.
- *[Particulate approval data on Vigamox is proprietary to Novartis, so neither outsourcing facilities nor surgeons can know definitively whether

- Vigamox, nor the Sandoz brand authorized generic, meet the more rigorous injectable USP 788 standard for 503B outsourcing facilities, appropriate for an intracameral agent, instead of the less restrictive topical USP 789 standard.]

- **Therefore, Vigamox is not, a priori, acceptable as a precursor for intracameral use, per USP 789, and thus by FDA regulations**.

- **Why not Avelox**
  -Warnings on Avelox label
  -CONCENTRATION <0.5%
- “AVELOX IV should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.”
- Avelox IV is supplied as a 1.6 mg/ml concentration, which is well below the world’s standard concentration of 5 mg/ml, since the Espiritu JCRS article from 2006.

- **Therefore, Avelox cannot be used to prepare a 5 mg/ml solution.**

- **Additional reasons to retain moxifloxacin bulk API**
- 1. **Danger of batching multiple bottles**
- -Introduction of plastic particles from opening and removing fluid from the bottle.
- -Higher risk of bacterial contamination, as the bottles are not externally sterile.

- 2. **Patient Access**
- -This policy could create patient access issues because these types of drugs are bundled into the facility payment and not reimbursed separately. Therefore, increased costs could make it cost-prohibitive for ambulatory surgical centers.

- 3**. Drug Shortages**
- -Reduction in the number of FDA regulated sources of safe moxifloxacin to one supplier, Novartis will potentially lead to drug shortages.

- **Additional reasons to retain moxifloxacin bulk API**

- 4. **Improper Finished Drug Product Selection**
- -Use of FDP moxifloxacin 0.5%, other than from Vigamox or the authorized generic from Sandoz, by surgeons, surgical facilities, 503A compounders, or 503B outsourcing facilities, will increase the risk of substituting dangerous alternatives, which may not meet all the FDA and USP standards for injectable medications. Moxeza use was reported in the FDA warning in 2020, with devastating consequences.
- -Surgeons may not note that some generics may be manufactured using different processes or be equivalent to products other than Vigamox. The 503B labeling may not be on the unit-dose vial, but instead on the box or packaging. A 503a is not required to list the excipients in the source FDP.
- -A facility purchasing agent could easily request an inappropriate generic FDP unknowingly. If non-authorized generics are substituted, such as in the 10/29 TASS cases reported by the FDA in 2020, many patients could be harmed.
- **Additional reasons to retain moxifloxacin bulk API**

- 5. **Effect of Reduced Surgeon Use on Endophthalmitis Rates**
- -Lack of an API source for outsourcing facilities will be expected to lead to less surgeon or facility 503B use due to the inability to recover for items used incident to surgery. This implied reduction in access for beneficiaries would be expected to increase endophthalmitis rates 3 to 8 times, based on many large studies.

- 6**. Lack of FDA or 503B Guidance for Use**
- -Currently, outsourcing facilities believe they are not permitted to suggest a dose due to FDA regulations. The FDA should consider explicitly allowing 503B outsourcing facilities to include the appropriate one of these statements, supported by literature, with the specific product units shipped.
- **“Do not exceed a dose of 0.1 ml of this 5 mg/ml solution”**

- **“Use no less than a 0.5 ml dose” of this 1 mg/ml solution”**

- **Additional reasons to retain moxifloxacin bulk API**

- 7. **Access to cGMP Moxifloxacin**
- -Drugs compounded by outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements, FDA inspections on a risk-based schedule, and other important conditions that, according to the FDA, "provide greater assurances of the quality of their compounded drugs." For these reasons, we think it's essential that the FDA does not limit physician and patient access to moxifloxacin being compounded in 503B outsourcing facilities that have a higher assurance of safety.

- **Conclusion Regarding Moxifloxacin FDP**
- Currently, moxifloxacin API from an FDA approved manufacturer is used. As there is no moxifloxacin finished drug product (FDP) acceptable as a 503B source to compound from, moxifloxacin should be restored to the 503B bulks list.

Antisepsis
- povidone iodine

No resistance of any organisms to PVI in adequate doses
Low toxicity at typical concentrations 0.005-5%
<1% does not affect fibroblasts, 5% does
Bottle label concentration of “povidone iodine”: 5% or 10%
Active agent is not povidone iodine but “I_2“
- **~1/10th of labeled concentration is free I_2 (scrub brush labels)**

- Povidone iodine
  TOXICITY studies
- **Epithelial toxicity**
  - **related to concentration and contact time [AUC]**
  - **5% severe damage in rabbits, 1% only moderate damage**
- **Stromal toxicity**
  - **fibroblasts injured with PVI 0.25% x 2 min in vitro**
- **Endothelial toxicity**
  - **0.8% PVI intracameral damage, Not 0.1% PVI**
- **Retinal**
  - **0.05% to 0.5% is ok, 5% is not**
  - **0.025% tolerated in PPV infusion fluid**
- **Intravitreal**
  - **rabbit endophthalmitis model**
  - **0.1% and 0.3% were both tolerated and effective**

- **1% OK intact epithelium, <0.25% in AC, 0.025% vitreous**

- Efficacy in prophylaxis of Endophthalmitis
- **AC contamination is seen in 5-20% of cataract surgeries**
- **Most often commensal bacteria from patient's periocular skin**
- **90% Gram+, 9% Gram-, ~1% molds or fungi**
- **5% of endophthalmitis isolates have multidrug resistance (MDR)**
- **Low concentrations of PVI kills all of these!**
- Ruth Berkelman CDC 1980's
- **10% Betadine™ bottles rim cultures>bacterial growth**
- **A non-intuitive finding**
- **Berkelman examined PVI concentration dependence**
- **Percent PVI is not correlated linearly with bacterial kill**
- **Povidone binds bactericidal I_2 nonlinearly per Gottardi**
- **Lower percent PVI lead to higher free I_2 concentration**
- **Related to povidone stericity in solution**
- I_2 Biocidal targets
- **N-H amino acids and nucleotides**
  - **hydrogen bond locations blocked**
- **S-H cysteine no S-S bonds allowed**
  - **protein synthesis blocked**
- **Phenol group (tyrosine)**
  - **size of I atoms sterically prevents hydrogen bonding**
- **Unsaturated fatty acids binding**
  - **changes fluidity of lipids in the cell membrane**
  - **Multiple hits = no resistance!**

- Disinfection rate
  versus
  Disinfection capacity

- Lidocaine Gels Block Povidone Iodine Antisepsis
- Urojet gel Boden et al. JCRS 2018
- Akten gel Silas et al. JCRS 2015
- **Must apply gel after antisepsis with povidone iodine**
- 5% povidone iodine is painful without prior anesthesia with solutions
- Current common practice

- The Bactericidal concentration of Povidone Iodine
- **With no clinical signs of infection to warn the clinician, any preoperative patient might harbor more bacteria than can be killed by 0.25% iodine solutions.**
- **With a higher bacterial load, a low concentration of povidone–iodine might not have sufficient total available iodine to convert to free I_2.**
- **Shimada et al. found zero growth from the anterior chamber at the end of surgery using povidone–iodine 0.25% dosed every 20 seconds during surgery.**

Silas, et al. J Cataract Refract Surg 2017; 43:400–404

- Povidone Iodine
  Prep Protocol
- **Apply 1% x 3 to reduce surface load in preoperative preparation**
- **Flush 0.25% q20 seconds until after the speculum is removed**
- Povidone Iodine
  Prep Protocol

- **Topical anesthetics: Lidocaine drops are least epi toxic**
- **Lidocaine & Proparacaine last 20 min; Tetracaine 45 min**
- **Epi-Shugarcaine is an anesthetic**
- **Re-dose mid case topical and intracamerally**
- **Avoid viscous vehicles initially, as they block antisepsis**

- Povidone Iodine
  Prep Protocol
- Povidone Iodine
  Prep Protocol
- PVI Allergy or Toxicity
- Most povidone iodine sensitivity is due to toxicity from high concentration
- Those patients will tolerate 1% or lower PVI
- Consider a contact dermatitis dermatology work up
- Anaphylaxis does exist but extremely rare
- Even povidone can cause allergy including excipients (nonoxynol-9)
- Shellfish allergy does not relate to povidone iodine allergy
- Shellfish chitin may cause dose dependent anaphylactoid reactions

- Alternatives to Povidone Iodine
- Aqueous chlorhexidine 0.05% has been used as a primary antiseptic agent in Sweden for several years and has proven efficiency and safety.
- Similarly, chlorhexidine* has been administered in a large series of intravitreal injections in Australia and the endophthalmitis rates similar to those after the use of PVI.
- The evidence related to using other disinfectants such as picloxydine, a hypochlorous acid solution, and polyhexanide is scarce.
- Chlorhexidine 0.05% and 0.1% is not commercially available in the USA
-
- Contact Dermatitis Patch Testing
- If probably a toxic reaction to retained PVI scrub or paint in past
  Use dilute povidone iodine

- If contact allergy is suspected
  use 0.1% Aqueous Chlorhexidine dilute, and not alcohol-based
- Kanclerz, P., Myers, W.G. Potential substitutes for povidone-iodine in ocular surgery. *Eye*(2021). https://doi.org/10.1038/s41433-021-01447-8

- Optimal
  Wound Closure Options

- Stromal Hydration Errors
- Polyethylene Glycol (PEG) Patch
- PEG patch prevented pressure induced wound leaks in 95.9% of cases
- Sutures did in only 65.9% ($p<0.0001$) of cases.
- Preparation and application of the commercial sealant takes ~20 seconds.
- A wet incision reduces polymerization *in situ, so the bed must be dried first*
- Stromal hydration or an AC air bubble can stop active leaks prior to application.

- Fibrin and cyanoacrylate glue

- Fibrin glue consists of fibrinogen and thrombin. Fibrin is polymerized to form a hemostatic network and permits tissue adhesion.
- Commercially available fibrin glues contain aprotinin, an antifibrinolytic agent prolonging the sealant effect
- Effective for leaks in glaucoma and corneal procedures.
- Equal to cyanoacrylate glue for wound closure less pain
- International Ophthalmology 20: 323-328,1997.
  "Wong Way"
  intrastromal Pocket
- Anterior to the surgeon's normal clear corneal or limbal incision site, make one or two stabs into the anterior stroma with a keratome.
- The goal is to create a triangular pocket (its tip toward the pupil) that is approximately 1.5 mm long, 1.5 to 2.0 mm wide, and one-third the stromal depth.
- The main incision is made parallel to and posterior to the partial thickness stab incision

- Supraincisional Stromal hydration
- Supraincisional stromal needle hydration

- **OCT shows posterior bowing of Descemet membrane, with overlying stromal edema for 14 days.**
- **Discontinuity of the endothelium maintains stromal imbibition pressure.**
- **Endothelium slide>continuity>stroma compaction in 10-14 days**
- **Needle hydration may be superior to wound-face hydration, Wong pocket, and sutures, as the endothelial discontinuity lasts longer than in any of the other options.**

- Dilation and IFIS

Modern Iridology
- IFIS seen best with patient supine and an un-dilated pupil

• 1 Posterior bowing of the mid peripheral iris
• 2 Ectropion uveae
• 3 Iris pointing toward the incision due to poor rigidity
• 4 Vermiform iris flutter / billow on infusion of fluid stream

- IFIS manifests early enough to allow for controlled management using adrenergics, OVDs, hooks, or rings.
- Intracameral Dilation: History
- Intracameral Dilation: History
- Lorente et al. Intracameral Phenylephrine 1.5% for Prophylaxis against Intraoperative Floppy Iris Syndrome Ophthalmology 119 (10) 2012, 2053-2058

- Phenylephrine 1.5% and Lidocaine 1% PF Compounded
- Stable 2 months or longer at room temperature "ready to use"

- Buffered Epinephrine unstable at pH above 3.0

Degrades 1% per hour at pH 7

No benefit when placed in the bottle if a bolus is used

- Phenylephrine/Lidocaine ~pH 6; shelf-stable for 2+ months
- Cyclopentolate effective next day for toric IOL axis check
- Epi-Shugarcaine Formula (Emergency Use Only!)

9ml of BSS Plus (or BSS)
3ml of 4% preservative (MPF) free lidocaine
4 ml of 1:1000 bisulfite free, PF epinephrine
*(Lundberg/Behndig 2008)

- Bisulfites not for Intracameral Use
- Endothelium damage due to 0.1% bisulfite, not epinephrine.
- Corneas perfused with 0.05% sodium bisulfite:

No functional or ultrastructural endothelial damage.

- **Shortage of bisulfite-free preservative-free epinephrine for intracameral use.** Myers WG, Edelhauser HF, Journal of cataract and refractive surgery. 2011 Mar;37(3):611

- Conclusions
- Dilute Minims® Phenylephrine 2.5% at least 1:4 in BSS.

[Not available in the US]

- Neither the minimal effective concentration of epinephrine for prevention of IFIS, nor the maximum safe concentration of bisulfite in intracameral solutions is known.
- In the absence of available bisulfite-free preservative-free epinephrine, commercial 1 ml glass vials of epinephrine 1:1000 (1mg/ml) containing 0.1% bisulfite is probably safe when diluted at least 1:4 in BSS, or preferably in BSS Plus.

- 503b Compounded
  Phenylephrine 1.5%
  lidocaine 1%
- Available from many 503b outsourcing facilities
- 503b are FDA regulated and inspected
- Cost is about $15-25 per single-use vial in the US
- 0.3 ml is the typical dose after initial paracentesis
- Repeat intraoperatively for miosis, IFIS, or pain
- Adequate for pupil dilation without any topical drops.
- 3 bottles of drops when used single patient, cost less
- Tropicamide 1% topical for larger pupil at capsulorhexis

- Mydrane
- A fixed combination of mydriatics and anesthetic not available in USA, containing:
  - tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1%.
- 200 µL dose was well tolerated in rabbits with no ocular adverse effects on the corneal endothelium or retina.
- Intracameral mydriasis clinically effective in most cataract surgery patients
- Despite the acquisition cost of Mydrane®, predicted costs were neutral, including labor time and drops
- 95% maximum pupil dilation achieved under 30 s.
- Pupil diameter in the intracameral group remained stable
- Pupil size decreased in the topical group.

- Omidria
- 4-mL Omidria vial is diluted in 500 mL BSS, 0.0098% (phenylephrine) and 0.0034% (ketorolac).
- Omidria is 4-fold better than phenylephrine or ketorolac, in preventing pupil diameter <6 mm.
- Preoperative ketorolac is washed out during surgery.
- In a canine model, ketorolac uptake throughout intraocular structures is sufficient to ablate COX-1/COX-2 pathways for ≥10 hours postoperatively.
- Cost is high
- Covered under pass-through status with CMS.

- Dexycu
- Intracameral suspension dexamethasone (Dexycu®) FDA approved in 2018
- Similar efficacy to prednisolone drops in clearance of AC cells
- Higher rise in IOP over baseline than drops.
- Temporary corneal edema from migration into the angle, abutting the cornea.
- CME was reported as 3%, comparable to the placebo control group.

- Dextenza
- Dexamethasone impregnated canalicular plug (Dextenza®) approved 2018
- Phase 3 data showed superiority over placebo for pain and inflammation
- Reports of permanent canalicular obstruction and canaliculitis
- Williams, KJ et al. Intractable epiphora with the dexamethasone ophthalmic insert, JCRS 2021; published ahead of print
- Breakthrough iritis requiring topical steroid rescue

- **Pre and Intraoperative**
-
- **Antisepsis**
- **PVI 5% 3 min or PVI 1% x 3**
- **Dilation and IFIS Prophylaxis**
- **IC Phenylephrine 1.5% Lidocaine 1%**
- **Omidria**
- **Epinephrine 0.025% in bottle [~1 ml of 1% in 250 ml for MSICS**
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- **Postoperative**

- **Antibiotic**
- 1 mg/ml (not 5 mg/ml) moxifloxacin to fill seal and pressurize
- Seal wounds with intrastromal techniques or suture

- **Steroids**
- Caution injected steroids in severe glaucoma
- 4 mg TA subconjunctival inferior >5 mm routinely
- 8 mg superior for high-risk inflammation cases
- 40 mg TA posterior sub tenon's DR, Uveitis, and High risk for CME

- **NSAIDS Controversial**
- Small benefit per recent Kaiser study
- Rarely due to cost, except in high risk.
- Additional steroid more cost effective