What you should know, that you don’t know about generic medications

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The healing process starts with the assumption that:
1. The doctor has diagnosed a disease
2. Will treat it with a safe, effective and useful medication.

Why this course- Looking Back
- Historical generic vs brand problems include most classes of ophthalmic medications.
- Most problems are based on efficacy and safety and originate on formulation.

Disclosures:  
Dr Friedman  
• I Do Not have a financial interest in any of the products mentioned in this presentation.  
• Allergan, Bausch

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Course Objective:  
1. Understand the FDA approval process: New Ophthalmic drugs (original / branded / innovator), Generic counterpart (generic), OTC ophthalmic drops (non Rx).  
2. Understand equivalency and challenges related to generic and brand name ophthalmic drugs  
3. Understand historical and current controversies including legal and social issues regarding generic and brand name medications.
Looking Back – Moving Forward

Steroids - problems have been noted on:
- efficacy
- uniformity
- solubility
- dose

4. Springer R, Strop E. Case uniformity of topical corticosteroid preparations: physiological ophthalmic emulsion 0.1%

Looking Back – Moving Forward

NSAIDS - adverse events


Looking Back – Moving Forward

Glaucoma

- efficacy
- PGA’s and B blocker


Stewart WC, Sharpe ED, Shadduck JA, et al. The safety and efficacy of brimonidine 0.5% in xanthan gum versus latanoprost forming ointement 0.04%. Curr Eye Res 2002;24:247–51.

Sany J, Murali TK, Stewart JA, et al. Short-term tolerability and corneal toxicity of xanthan gum brimonidine tartrate 0.015% and glaucoma: brimonidine tartrate 0.015% in xanthan gum and latanoprost forming ointment 0.04% in glaucoma and ocular hypertension: a prospective, randomized, double-masked, active-controlled, three-period crossover pilot study. Curr Ther 2009;29:23–9.
Looking Back – Moving Forward

Antibiotics
- Manufacturing
- Delay in eradication
- Formulation ranges


Looking Back – Moving Forward

Combination products
- Tobradex


Let us understand why this happens and Why use Generic or Branded product?

Savings and cost
Is the OTC or Generic product identical in therapeutic benefit? or Outcome?

IF the therapeutic effect is less due to lower bioavailability and / or greater variability;
do the potential savings out-weigh the risks?
who is at risk (patient or physician)?
are there any legal implications?
• FDA Mission:
  - Security of the food supply
  - Advance Public Health
  - Fostering development of medical products to respond to deliberate and naturally emerging public health threats.

Drugs: Developed & Approved
• CDER - Center for Drug Evaluation and Research
• Evaluate new Drugs
• Provide Information to DR's and PT's on RX and OTC meds.
• Make sure that both brand name and generic, work correctly and that the health benefits outweigh known risks.

New Drug Application (NDA)
Answer this:
  - Is the drug safe and effective?
  - Benefits VS Risks.
  - Proposed labeling (package insert), and what it should contain.
  - Manufacturing and controls used to maintain the drug's quality, preserve the drug's identity, strength, and purity
Generics - ANDA

- Abbreviated New Drug Approval Application (ANDA) copy data and recipe.
- Bioequivalence

Clinical Trials:

- Test new medication or device
- Test different doses of a medication
- Medication or device for a new indication
- Compare effectiveness and safety than already used, standard medication or device ("the gold standard" or "standard therapy")
- Compare the effectiveness (therapy A vs. therapy B)

Clinical Trials, (Clinical Phase):

- Pre-Clinical: in vitro Animal models
- Phase 0: Pharmacodynamics and Pharmacokinetics in vivo
- Phase 1: Screening for safety
- Phase 2: Effectiveness, AE’s
- Phase 3: Effectiveness, AE’s, RMC
- Phase 4: Post-approval studies
Generics - ANDA

- Abbreviated New Drug Approval Application
- Bioequivalence
- Manufacturing
- Packaging
- Analysis

Are Generic Drug Equivalent?

- The Act makes it easier for generic drugs to gain approval.
  - Intention to reduce prescription costs
  - Save $ in managed care and patient
  - Assume equivalency to the branded product
  - Similar active and inactive ingredients
  - Assume --> safety and efficacy.

Innovator vs Generic

NDA - Brand
- Chemistry
- Manufacturing
- Controls
- Labeling
- Formulation
- Testing - Animal & Clinical studies

ANDA – Generic
- Chemistry
- Manufacturing
- Controls
- Labeling
- Reverse engineered
- ???
Non-prescription Drug Products
Over The Counter (OTC)

OTC drug monograph
• Must have a history of being safe
• Condition must be self diagnosable
• Regulated Labeling

Generics vs Innovator
Differences from the branded product:
Active ingredients
Same active ingredient!
No change in molecule

Generics vs Innovator
Differences from the branded product:
In Active ingredients
Same ingredient? ?
preservatives, stabilizers, buffers, viscosity agents, lubricants, vehicles
Generics vs Innovator

Differences from the branded product:
1. Route of Administration – a drop!
2. Dosage – Strength – same!
3. Labeling - Packaging
4. Excipients - Ingredients
5. Bioavailability and Bioequivalence
6. Orange Book labels A, B, or AT.

It is a drop, is it the SAME drop? size?
25ul to 70 ul, varies amount of medication
studies: Robert, Fiscella, Kaufman, Wittppenn

Generics vs Innovator

There is an acceptable analytical range of +/-5% giving ranges in efficacy!

- Generic latanoprost is 38% less effective
- Timolol generic less effective after 8 hrs
- Ciprofloxacin -16 to -34% variation


Generics vs Innovator

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Bottle size and design, affects drop size, leachables, expiration, evaporation rates all affect performance, concentration, safety, AE


Generics vs Innovator

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Generics vs Innovator

Excipients – Ingredients
- pH adjusters, antioxidants, thickening agents, buffers and tonicity adjusters,

ALL can be substituted
ALL can interfere with the pharmacokinetic and pharmacodynamic properties of active agents


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Generics vs Innovator

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Generics vs Innovator

Bioavailability and Bioequivalence?

Without head to head clinical trials it is difficult to evaluate performance and evaluate there are differences!


Generics Differences:

Same active ingredients (maybe, different recipe)


Consistency, Ph, Preservatives, Buffers, Vehicle, Stabilizers, Packaging: NOT required and variable!


Inactive ingredients can change effectiveness!


Bioavailability, Bioequivalence, Efficacy, Safety - never tested!

Generics vs Innovator

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I could not have said it better:

“When it comes to ophthalmic drugs, formulation really matters, it is difficult to evaluate its pharmacokinetics (how much drug is present) in the eye”.

Gary D. Novack, PhD.

Consider this scenario:

Patient does not improve and was “not informed” by his doctor that generic medications have not been tested via clinical trials in terms of safety, efficacy, or bioavailability.

U.S. Supreme Court on Generics

June 2011, US Supreme Court:

Generic drug manufacturers DO NOT have to be held accountable for:

Failing to warn consumers about a generic drug dangers.

U.S. Supreme Court on Generics
June 2013, US Supreme Court:
Generic drug manufacturers DO NOT have the
SAME responsibility as brand manufacturers to:
Update product labels when new problems arise.
Generic drug companies are protected from lawsuits due to adverse events.

Less safety information and less accountability for safety from generic drug companies (?).

Now consider this:
• Online ordering ?
• Facilitator pharmacy
• Counterfeit?

All samples were found to contain the declared drug.
Nine samples (27%) showed an under-concentration by 10% or less and ten (30%) showed an increased concentration of 10% or more than indicated on the label. 75% of the original drugs but only 12% of the generic drugs had measured concentrations within the standard advisory ranges of ± 5% from the nominal value.
**How do you . . .?**
- How do you address the patient about generics and brand name?
- Are patients informed?
- Do we need an Informed Consent?

**Why use Generic or Branded product?**
- Savings and cost
- Is the OTC or Generic product identical in therapeutic benefit? or Outcome?
- Pharmacy can substitute product in the same class.
- IF the therapeutic effect is less due to lower bioavailability and / or greater variability.
  Do the potential savings out-weighed the risks?

**Q and A session**