Preserving Pharmaceutical Products:

Patrick Crowley

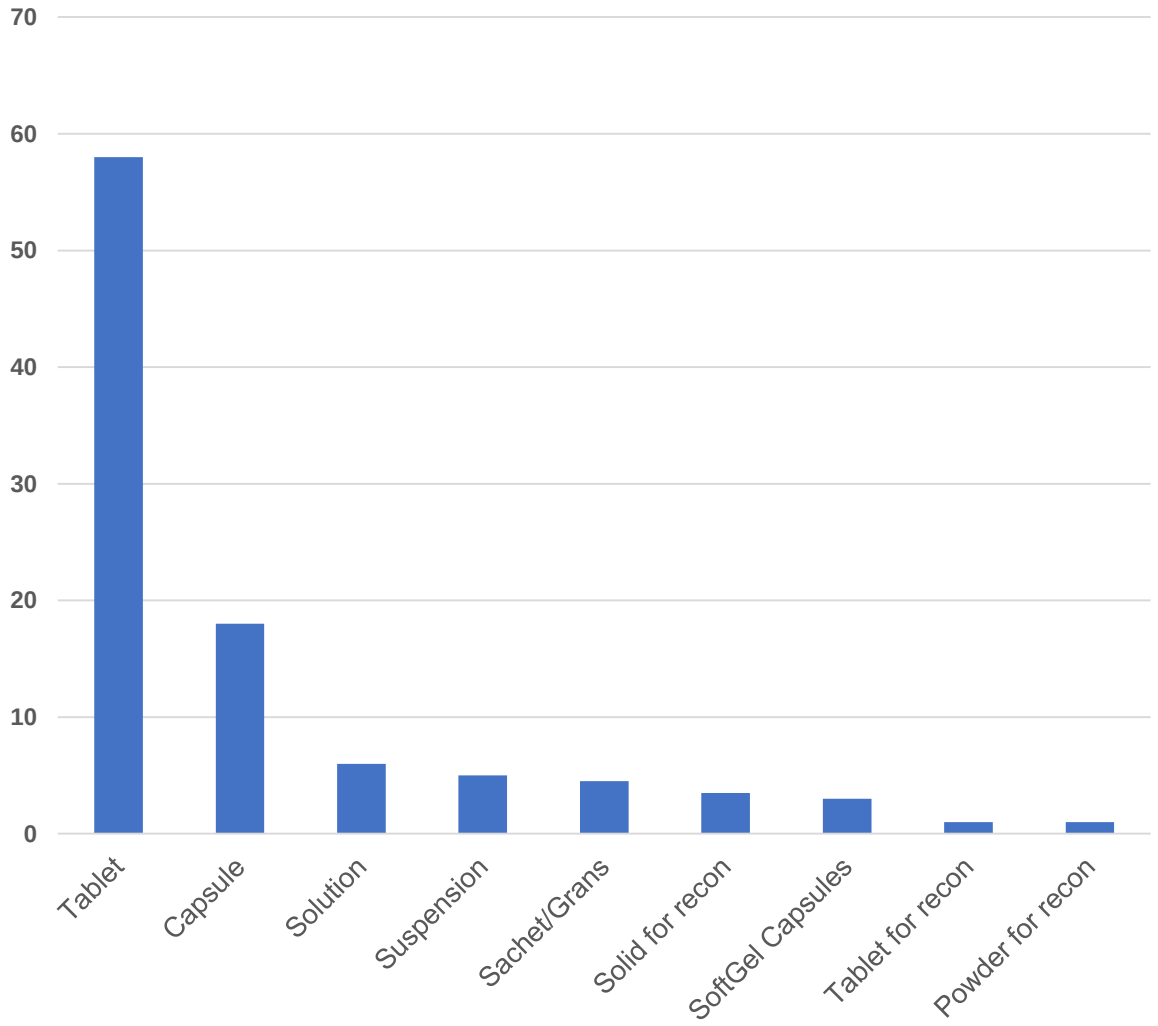
Pharmaceutical Products

- Modes of administration vary
  - Oral
  - Injection or infusion (parenteral)
  - Inhalation (oral
  - Intranasal
  - Applied to skin (“topical”) - creams/ointments/lotions)
    - may be applied to mucosal surfaces
    - may be applied to damaged tissue
  - Ophthalmic Products
- Generally have long shelf lives
  - 3-5 years in many cases
- Some product components possess “intrinsic” antimicrobial activity.
  - eg antimicrobial drugs
- Other product components may confer or aid preservation

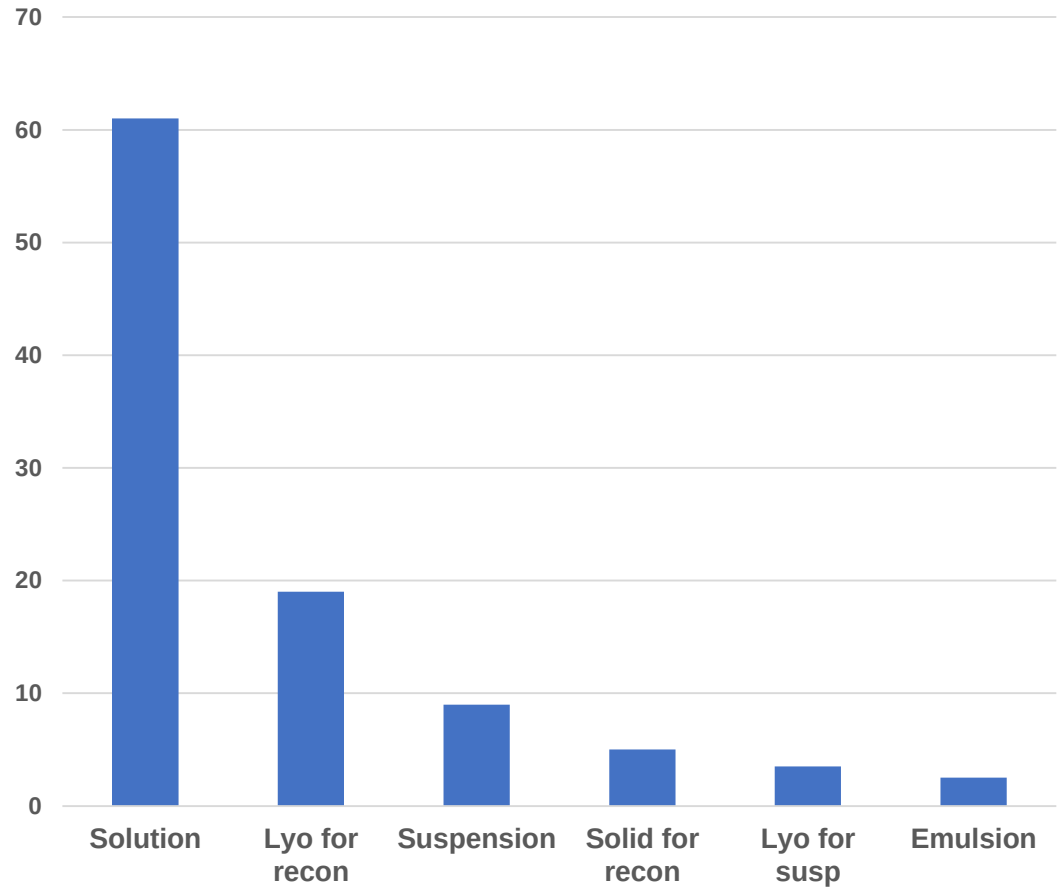
Preservatives in Prescription Products ("drugs@fda".com)				
Preservative	**Oral**	**Topical**	**Ophthalmic**	**Parenteral**
p- hydroxybenzoate esters ("Parabens")	39	14	None	None
Parabens/Na benzoate	4	13	None	None
Na Benzoate	24	2 (antifungals)	None	1
Sorbic acid/Potassium Sorbate	5	2 (one with methyl paraben)	1	None
Benzalkonium Chloride	1	1	31	None
Benzodecinium Bromide	None	None	2	None
Benzyl alcohol	1	9	None	3
Phenylethyl alcohol	None	2	None	None
Phenoxy ethanol	None	4	None	None
m-cresol	None	None	None	1
Stearalkonium Bromide	None	2	None	None
Chlorbutanol	None	None	None	1
Thimoresal	None	None	1	1

Product Forms in US (Y axis = percentage**)**
(Oral and Parenteral only)

Oral dosage



Parenteral dosage



Products requiring Preservation

Product Type	Preservative ?
• Solids for oral dosage eg tablets/capsules	no
• Liquids (aqueous) for oral dosage	
• multidose (incl when constituted from solid on dispensing)	yes
• single dose (eg in a sachet or dispersible/effervescent tablet)	no
• Sterile liquids (aqueous) for infusion/injection	
• multidose	yes
• single-dose	no
• Ophthalmic Preparations aqueous	
• multidose	yes
• single dose	no <u>if sterile</u>
• Topical Products (applied to skin, mucosal surfaces etc)	
• ointments (non-aqueous)	no
• creams/lotions: (aqueous):	
• multidose	yes
• single-dose	no <u>if sterile</u>
• Liquids for nasal inhalation (aqueous, multidose)	yes

Preservatives in Pharmaceuticals

- Preservative must be
  - suitable/appropriate for the mode of dosage/use
  - compatible with the drug and other ingredients
  - effective throughout the shelf life/usage period of the product
    - (preservative stability)
- Inclusion level must be minimal for antimicrobial efficacy
  - Regulatory and pharmacopeial guidelines
    - *" - the minimum concentration be used to give the required level of efficacy" (EMEA)*
    - *" - - below a level that may be toxic to human beings"* (USP)
- A preservative must not be a substitute for "poor GMP"

Exclusion of a Preservative: Justifications

- Active ingredient(s) provide(s) the requisite effect
  - antimicrobial agent(s) in oral, parenteral, topical etc products
    - must provide antibacterial and antifungal effect
      - meet pharmacopeial Antimicrobial Efficacy Test requirements
- Other product component(s) has/have antimicrobial effects
  - sucrose in oral products
  - non-aqueous solvents in topical products
    - glycerol, propylene glycol, ethanol
      - lower the “water activity”

Antimicrobial Efficacy Testing

- Detailed in Pharmacopeias (USP, Ph.Eur, BP J.P'copeia.
  - Test organisms comprise common bacteria and molds/fungi
    - Bacteria *P.aeruginosa and S.aureus (+ E.coli* in USP)
    - Molds/fungi *C.albicans and A.brasiliensis*
    - Additional organisms may be included where appropriate e.g
      - possible contaminants in facility, materials, operators etc
        - *E.coli* in oral products
        - *Z.rouxii* in sucrose-containing products
  - Performance standards include microcidal and/or microstatic activity
    - depending on mode of product use
- Testing procedures are (mostly) common
- Some differences in performance standards
    - USP/JP versus *Ph.Eur/*BP
    - Less stringent requirements for antacid products in USP and JP.

Performance Requirements

Reference	Product Type (aqueous)	Organisms	*	Required Log_{10} Reduction (minimum)					
				6 hours	24 hours	48 hours	7 days	14 days	28-days
Ph.Eur and British P'copeias	Parenteral and Ophthalmic	Bacteria	A	2	3				No recovery
			B		1		3		No increase from day 7
		Fungi	A				2		
			B					1	No increase from day 14
	Oral	Bacteria						3	
		Fungi						1	
	Topical	Bacteria	A			2	3		No increase from day 7
			B					3	No increase from day 14
		Fungi	A					2	
			B					1	
	* "A" is recommended. "B" criteria may be acceptable if adverse reactions are a (justified) issue.								
USP and Japan P'copeias	Parenterals, sterile nasal/ophthalmic products (aqueous)	Bacteria					1	3	No increase from day 14
		Fungi					No increase from initial		
	Oral, except antacids	Bacteria						1	No increase from day 14.
		Fungi						No increase from initial	
	Antacids (aqueous)	Bacteria						No increase from initial	
		Fungi							
	Non-sterile topical, nasal, aural (aqueous)	Bacteria						2	No increase from day 14
		Fungi						No increase from initial	

Preservative Performance Requirements

- Product meets pharmacopeial preservative performance standards
- Is compatible (chemical, physical) with the other product components
- Preservative is effective over the product pH range.
- Effective at the lower limit for preservative content in the product specification
- Effect is sustained throughout product lifetime (including use).
- Solubility in the product is adequate and not compromised by conditions encountered during product manufacture, storage, transport and use.
- Does not adversely affect patient-sensitive quality attributes such as
    - taste, odour, irritation etc at the inclusion level in the product.

Preservative Efficacy and Product pH

Preservative	Active Moiety	pH for optimum activity
p- hydroxybenzoate esters ("parabens")	Ester	pH 4-8
Benzoic acid/salts	Unionised (acid)	<pH 4.5
Benzalkonium Cl	Cation	pH 4-10
Benzyl alcohol		<pH 5.0
Chlorhexidine	Cation	pH 5- 7
Propionic Acid	Unionised (acid)	pH 3.9
Sorbic acid/salts	Unionised (acid)	pH 4.5
Phenylmercuric salts	Cation	pH 5-8
Thimerosal		"acidic pH"

pH, and Ionisation of Organic Acid Preservatives			
pH	% not ionised (unionised)		
	Benzoic acid	Sorbic acid	Propionic acid
pKa	**4.2**	**4.76**	**4.88**
2	99.4	99.8	99.9
3	94.1	98.4	98.7
4	61.3	85.2	88.4
5	13.70	36.5	43.50
5.5	4.78	15.4	19.23
6	1.56	5.4	7.04
6.5	0.50	1.8	2.34
7	0.16	0.6	0.76

Interactions with Excipients/Packaging Components

Preservative	Adsorbent/Substrate
Benzalkonium chloride	Hypromellose
	Filter Membranes
Benzoic acid	Kaolin
Benzyl alcohol	Polyethylene, Natural Rubber
Cetrimide	Bentonite
Chlorbutanol	Polyethylene
Chlorhexidine	Various polymeric excipients eg sodium carboxymethylcellulose
p- hydroxybenzoate esters	Ion Exchange Resins, some plastics
Phenoxy ethanol	PVC, Cellulose-based excipients
Phenylmercuric salts	Various suspending agents
Sorbic acid/sorbates	Polypropylene, PVC, Polyethylene
Thimerosal	Polyethylene, other plastics, rubber

Residues and Additives in Pharmaceutical Excipients	
Excipient	**Residue/Additive**
povidone, crospovidone,	peroxides
fixed oils, lipids	antioxidants
polysorbates	peroxides
benzyl alcohol	benzaldehyde
polyethylene glycol	aldehydes, peroxides, organic acids
microcrystalline cellulose	lignin, hemicelluloses, water
starch	formaldehyde
talc	heavy metals
stearate salts	alkaline residues
hydroxypropylmethyl & ethyl celluloses	glyoxal

Preservatives Susceptible to Adsorption	
Compound	**Adsorbent**
Benzalkonium chloride	PVC, Polyethylene
Benzoic acid	Kaolin
Benzyl alcohol	Polythylene, natural rubber
Chlorhexidine	Polymer-based excipients, Contact lense material
Parabens	Ion exchange resins, some plastics
Phenoxy ethanol	Cellulose-based excipients, PVC.
Phenylmercuric salts	Various suspending agents
Sorbic acid/sorbates	Polypropylene, PVC, Polyethylene
Thimerosal	Polyethylene

Oil/Water Partition Coefficients for Preservatives

Preservative	Oil	Partition Coefficient
Methyl Paraben	Almond Oil	7.5
	Mineral Oil	0.1
	Isopropyl Myristate	18
	Diethyl Adipate	200
Ethyl Paraben	Soya Bean Oil	26
Propyl Paraben		87
Butyl Paraben		280
Benzoic Acid		6.1
Sorbic Acid	Almond Oil	3.3
	Mineral Oil	0.21
Phenol	Arachis Oil	5
	Mineral Oil	0.07

Preservative “Enhancement”

- **Combinations of Preservatives**
- Oral liquids
  - Sucrose, glycerol, propylene glycol, (+ a formal preservative)
- Topicals
  - Propylene glycol, ethanol, EDTA (+ a formal preservative)
- Parenterals
  - EDTA (+ a formal preservative)
- Ophthalmics and (occasionally) intranasal
  - EDTA
    - with benzalkonium chloride (BAC/BKC) at inclusion levels of 0.0075% - 0.02%)

Combinations of Preservatives

Preservative	Preservation Capability	Potential Companion Preservative
Benzalkonium Chloride	More active against g-positive bacteria .	Benzyl alcohol and phenylethanol can enhance anti- Pseudomonas activity. EDTA facilitates reduced inclusion levels to reduce irritancy in ophthalmic products.
Benzoic Acid/Na salt	Suitable for oral liquids with acidic pH values (not bitter). Activity is reduced as pH increases. Antifungal effect less susceptible to pH than antibacterial activity	Combinations with p-aminobenzoates can extend spectrum of activity.
p- hydroxybenzoic acid esters ("Parabens")	Particularly effective against Yeasts and Moulds. Less effective against Gram-negative organisms. Activity increases with increase in alkyl chain length.	Combinations of two esters can overcome solubility constraints. Possible synergies with phenylethanol.
Benzyl alcohol	Effective against gram positive bacteria, yeasts, moulds; less active against gram- negative bacteria.	Enhance the activities of benzalkonium chloride and chlorhexidine against pdeudomonas.
Chlorhexidine	Active against a wide range of bacteria, except for some Pseudomonas. Antifungal activity is limited.	
Phenylethanol	Good anti-Pseudomonas activity so is often used to improve anti-pseudomonas activity of a companion preservative .	Combination with Sorbate can enhance antifungal effect. Anti-Pseudomonas activity improved in combinations with benzalkonium chloride and chlorhexidiene gluconate. Synergistic effects with parabens against Yeasts and Molds.
Phenoxyethanol	Good anti-Pseudomonas activity. Poor antifungal.	

Preservative “Enhancement”

- Combinations of Preservatives
- **Oral liquids**
  - Sucrose, glycerol, propylene glycol, (+ a formal preservative)
- **Topicals**
  - Propylene glycol, ethanol, EDTA (+ a formal preservative)
- **Parenterals**
  - EDTA (+ a formal preservative)
- **Ophthalmics and (occasionally) intranasal**
  - EDTA
    - with benzalkonium chloride (BKC/BAC) at inclusion levels of 0.0075% - 0.02%)

Benzalkonium Chloride (BKC) in Ophthalmic Products

- Wide spectrum of antimicrobial activity
- Effective over wide pH range (pH 4-9).
- May enhance drug penetration to anterior chamber
  - disrupts the hydrophobic barrier of corneal epithelium
- Effective at low inclusion levels
- Low allergenic potential
- but
  - Long term use can cause allergic/inflammatory reactions/corneal damage
- Co-formulation with EDTA helps reduce inclusion levels of BKC

The Future

What might change ?

CAR-T Cell Therapy.

- Now (autologous therapy):
  - patient-specific plasma,
  - separate the T Cells
    - “incorporate the cancer-seeking protein” (CD 19) using gene editing techniques
  - culture the modified cells to increase numbers
  - formulate the product
  - test and ship to Center
  - administer to patient.
- The Future ? ? ? (allogenic therapy)
  - plasma from healthy donors rather than cancer-patient-specific plasma
  - separation, gene-editing, formulation, shipping etc as above
  - “stockpile” material(s) at the Treatment Center ?
  - administer to patient following diagnosis of cancer type