HISTORY - ANTIMICROBIAL EFFECTIVENESS TEST

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Antimicrobial Effectiveness Test

Nicolas Appert Antione Lavoisier

19th Century
Microbiology is born: Koch and Pasteur
Spoilage and disease
Chemotherapeutics as model preservatives
Mercurials and Salvarsan
Tinctures standardized – USP 1830
Listerine 1879 and Lysol 1892
P&G 1837
Lever Bros. 1885
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**Early 20th Century**
- Pure Foods Act (1906) → FD&C Act (1938)
- L’Oreal and California Perfume Company - 1909
- Cosmetics to middle and working classes:
  - Post crash expansion – Revlon, Avon, Almay, Clairol, Shulton
- Drug & Cosmetic Industry published (t’il 1994)
- Benzoic acid as food preservative
- Parabens introduced 1923

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**20th Century – the 40’s and 50’s**
- WWII actualized US women, post-war demand
- Mass production of products
- Preservation: quats, parabens, formaldehyde, mercurials
- Organized as an industry
  - The Chemistry & Manufacture of Cosmetics – de Navarre, 1941
  - Toilet Goods Assoc. (now PCPC) - 1943
  - SCC and CTPA – 1945; JCIA - 1959

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**20th Century – the 50’s and 60’s**
- USP – concept 1st described
- Expanding cosmetic market – exposed vulnerabilities
- CTFA micro committee org’d 1967
- Increased concern for cosmetic micro safety
  - Kalling report: Euro cosmetic contamination
  - FDA ‘69 NY study – 25% contaminated
20th Century – the 70’s

USP <51> - USP XVIII, 1970

Global organized technical AET efforts: Tenenbaum, Curry, Mulson, Yablonski, Wallhauser, Ishizeki

CTFA broadened challenge to include environmental plant isolates (Halleck, 1970)

FDA requested more clinical isolates (Bruch, 1972)

CTFA Methods established

20th Century – the 70’s

In-Use Contamination


20th Century – the 70’s

“Regrowth”


Strains of Pseudomonas cepacia, …from packages of nasal spray preserved with thimerosal, showed a high degree of resistance to the organomercurial, …

99.9% of the inoculated cells were killed rapidly, but after a lag time of 7-12 days, the few survivors began to increase in numbers and eventually attained high cell concentrations.
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**20th Century – the 70's - 80's**

FDA studies: Ahearn, Aly, Farrington, Tran, Hitchins

FDA's Diminished concern for cosmetic micro

"Microbial contamination of cosmetics during manufacture was a major issue during the 1960's and early 1970's. Since then, significant progress has been made by the cosmetic industry. However, ... adequacy of preservation of cosmetics to prevent contamination during consumer use continues to be of concern..., particularly with respect to cosmetics coming into contact with the eye."

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**20th Century – 80's and 90's**

CTFA micro committee guideline publication

Preservatives: Parabens, Formaldehyde-releasers, Organic alcohols/acid, Isothiazolinones, EDTA

Validation to consumer use - Brannan et al., Lindstrom

FDA's concerns diminished - recalls - avg. ~12 / year

Industry condensed – extending quality concepts

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**21st Century**

Domestic – limited FDA concerns (few to no recalls)

Globalization

>80% share served by major marketers

Developing world product are contaminated

40-70% - Middle East, Africa, Eastern Europe, China

Staph aureus, E. coli, Serratia marcescens, Pseudomonads, C. diphtheriae
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21st Century
Public Relations/Regulatory concerns
BSE, PAO
Pressure on all preservatives
Thimerosal and autism (Wakefield)
Formaldehyde-releasers (Japan, China, Minnesota)
Parabens and breast cancer (Darbre)
Natural preservatives

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Pharmacopeia – Drug AET
USP <51>: concept 1st described by Squibb scientist (Levin, 1962) based on Abbott Lab’s protocol from the 50’s
adopted PMA - Biological Section 1967
established in USP XVIII, 1970
template for others

Antimicrobial Effectiveness Test

USP <51>
Basis: Intuitive - not validated, regulatory significance.
Design:
Prescriptive
Inoculated with ~ millions
Survival monitored over 28 days
Pass/fail - kill rates over time – categorized by product type, anticipated risk
Concept sustained
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**Microbes – USP <51> - In-Use**

- *Staphylococcus aureus ATCC 6538*<sup>TM</sup>
  - late ’30s/early ’40s - FDA - clinical lesion
- *Escherichia coli ATCC 8739*<sup>TM</sup>
  - 1949 - feces - I.C. Gunsalus (GUM)
- *Pseudomonas aeruginosa ATCC 9027*<sup>TM</sup>
  - 1943 - outer ear - C.P. Hegarty (UI)
- *Candida albicans ATCC 10231*<sup>TM</sup>
  - 1950 - bronchomycosis - Chester Emmons (NIH)
- *Aspergillus brasiliensis ATCC 16404*<sup>TM</sup>
  - 1965 - blueberry - S.M. Ringel (WL)

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**USP <51> As Evolving Concept**

- USP Categories
- European Pharmacopeia – A and B criteria
- Pressure on preservatives (esp. Thimerosal)
- “Preservative-Free” – packaging-based
- FDA and USP <51>
  - Recalls based on USP failure
  - Proactive use if AET in risk assessment

**Antimicrobial Effectiveness Test**

**Cosmetic AET – Early Methods**

- **J&J (Marinaro, 1966):** 2 pools, 8 weeks, neat and 5 fold aq. dilutions, < 20/ml
- **Colgate - Palmolive (Owen, 1969):** 3 pools, 2 weeks, 100% kill (product streak) by day 7
- **ICI Pharmaceuticals (Barnes et al., 1969):** 5 pools, product neat, 15 inoculations through 5 weeks, neg. culture of loopful on agar
- **Revlon (Lanzet, 1972):** 4 pools, 13 weeks, rechallenge @ week 6, <0.2% survival
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**Cosmetic AET**

Method — D-Value

Decimal (90%) reduction of inoculum

Championed in cosmetics by Don Orth

- ATCC strains only — max ~ 28 hours
- if bug is in plant — remove it

Use is probably better for screening than qualification

“Tailing” with product isolates is biggest concern

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**Cosmetic AET - D Value**

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**Cosmetic AET - CTFA Methodology**

Additional challenge organisms vs. USP

- *Staphylococcus epidermidis*
- *Enterobacter gergoviae* and *cloacae*
- *Klebsiella pneumoniae*
- *Burkholderia cepacia*
- *Acinetobacter baumanii*
- *Serratia marcescens*
- *Pseudomonas fluorescens* and *putida*

Single or pooled inocula, rechallenge considered

More stringent criteria
**Cosmetic AET - Validation**

**Definitions: Method and Formula**

**Method** – relevance to consumer use protection

**Formula** – in-use testing correlates to efficacy

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**Cosmetic AET - Validation in Execution**


Broad US cosmetic industry participation

Accuracy and precision addressed

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**Cosmetic AET - FDA**

"Formerly, there were no validated tests for cosmetic preservative efficacy, although the test for pharmaceutical preservative efficacy in the U.S. Pharmacopeia or the cosmetic test in the technical guidelines of the… CTFA were used. Recently, the CTFA test has been AOAC validated for use with liquid cosmetics."
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**Cosmetic AET as Evolving Concept**
John Yablonski - “Atypical” products – not suited to simple aqueous-based inoculum testing.
Steve Schnittger: water-in-silicone oil emulsions
Peter Gilbert - Extrinsic v. intrinsic contamination

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Water in silicone oil emulsions

unpublished, courtesy Steve Schnittger, Estee Lauder

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**AET as Evolving Concept**
Cosmetic AET
Based on 80’s manufacturing and consumer use
Classic pass/fail gate approach problematic
Drivers:
Loss of conventional preservation capabilities
Parabens, Formaldehyde-releasers, EDTA,
Organic alcohols/ acids, Isothiazolinones,
Product evolution (e.g. atypical)
Efficiency and speed to market
Antimicrobial Effectiveness Test

AET as Evolving Concept

Cosmetic AET
- Based on 80's manufacturing and consumer use
- Classic pass/fail gate approach problematic

Facilitators:
- Process control
- Evolved GMP/manufacturing controls
- Advanced product understanding
- Passive/active package protection
- In-use Testing

Status of GMP/EM status
Packaging/consumer - in-use data
Contributing elements
- Efficacy - e.g. Aw
- Formula effects
- Analytical understanding