Overview of Cosmetics Research at FDA

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Outline

• Cosmetics regulations in the US
• Role of FDA research in the regulation of cosmetics
• Examples of OCAC research

Strategic planning for future OCAC research

Cosmetics – Scope

• Used by most consumers every day
• Examples:
  – Moisturizers, other skin preparations
  – Hair care, hair dyes, hair straighteners
  – Makeup, nail polishes
  – Shaving preparations
  – Perfumes and colognes
  – Toothpastes, mouthwashes
  – Face and body cleansers, deodorants
  – Tattoos

• Multi-billion dollar industry
• Increasingly global industry
Cosmetic

- Defined in the Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 201 (i)

- Articles intended for:
  - Cleansing
  - Beautifying
  - Promoting attractiveness
  - Altering the appearance

** Excludes “Soap” (alkali salt of fatty acid - CPSC)

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Drug

- Defined in FD&C Act, Section 201 (g)

- Articles intended
  - For use in the diagnosis, cure, mitigation, treatment, or prevention of disease
  - To affect the structure or any function of the body of man or other animals

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Cosmetics – FDA’s Authority

- Cosmetics must not be adulterated or misbranded

- The law does NOT provide for FDA pre-market approval

- FDA’s authority is post-market only
OTC Drug vs. Cosmetic

- **OTC Drug**
  - Monograph or product-specific pre-market approval required
  - Pre-market evaluation of safety & efficacy
  - GMP regulations
  - Establishments & products must be registered
  - Serious adverse events must be reported

- **Cosmetic**
  - Pre-market approval not required
  - No pre-market clearance of safety or efficacy
  - GMP guidelines only
  - Establishments & products not required to be registered
  - Adverse events not required to be reported

Requirements for Market

- **FDA Authority Over Cosmetics**
  - Under the FD&C Act, cosmetics must not be *adulterated* (601) or *misbranded* (602)
  - No pre-market approval of cosmetics, with the exception of color additives
  - Manufacturer bears responsibility for *safety* of marketed products
  - Manufacturer or distributors should have obtained *all data and information* needed to substantiate the safety of the product before marketing

Cosmetics - Challenges

- Limited legal authorities
- Competing agency priorities

- Significant changes in past 5-7 years
  - Manufacturing more global
  - Alternatives to animal testing
  - Increasingly sophisticated technology and complex ingredients
    - Nanotechnology
    - "Active" ingredients
    - Botanicals
Examples of Current Areas of Emphasis

- Safety Evaluation of ingredients
- Adverse Events evaluation and analysis
- Compliance activities
- Development of Guidance and Policies
- Research

Importance of research in OCAC

- Because cosmetics do not have premarket review, FDA depends on the following to carry out its mission:
  - Published research
  - Published position papers from international regulators
  - Industry publications
  - Adverse events reports
  - Enforcement actions

Cosmetics Research at FDA

A look at selected examples
Reasons for doing cosmetics research at FDA

• To evaluate the safety of cosmetic ingredients
  – Scientific interest/innovation/controversy
  – Adverse events analysis
  – Enforcement actions
• In response to inquiries:
  – Citizen Petitions
  – Stakeholders expectations
  – Media interest
• In order to align with international regulators

Ultimately……

• FDA does cosmetics research to support policy development and regulatory mandate:
  – Guidance
  – Regulations
  – Enforcement actions

Mechanisms used for Research

• Laboratory based work:
  – FDA
  – Contract
  – Collaboration
• Literature based work
  – Published papers
  – Databases (internal, commercial)
• Computational/ in silico
Examples of OCAC Research

- Ingredient surveys: analytical work
  - FDA research laboratories
  - FDA field offices
  - Contractors
  - Academia
- Adverse events analysis: epidemiology
- In vitro/in vivo research: toxicology
- In silico research: computational toxicology (QSAR)
- Literature/database research: regulatory

Examples of cosmetic ingredient and contaminant surveys conducted under contract

<table>
<thead>
<tr>
<th>Title</th>
<th>Status</th>
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<tbody>
<tr>
<td>Lead in Lipstick</td>
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<tr>
<td>Heavy Metals in Cosmetics, I</td>
<td>Completed</td>
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<tr>
<td>Heavy Metals in Cosmetics, II</td>
<td>Completed</td>
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<td>Asbestos in Talc</td>
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<td>Eye area Cosmetics for Microbial Contamination (Micro I)</td>
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<td>Assessment of Microbial Contamination of Eye Area Cosmetics Containing Non-Traditional Preservatives (Micro II)</td>
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<td>Tattoo and Permanent Make-Up - Injectable Cosmetics for Microbial Contamination</td>
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</tr>
<tr>
<td>Diethanolamine (DEA) in Cosmetic Products</td>
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</tr>
<tr>
<td>Natural Latex Protein Antigens in Cosmetic Products</td>
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Cosmetic Products Adverse Events

<table>
<thead>
<tr>
<th>CAERS Year</th>
<th>Number of Individual Reports</th>
<th>Number of Suspect Products</th>
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<tbody>
<tr>
<td>2011</td>
<td>291</td>
<td>318</td>
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<tr>
<td>2012</td>
<td>352</td>
<td>418</td>
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<tr>
<td>2013</td>
<td>293</td>
<td>314</td>
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<tr>
<td>2014</td>
<td>344</td>
<td>388</td>
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Adverse events analysis

- Leave on products versus rinse off:
  - Products
  - Reports
- Hair care versus skin care:
  - Products
  - Reports

Leave on versus rinse off-related adverse events
Skin care versus hair care-related adverse events

2014 Product Report Distribution

In Silico research in OCAC

Available (Q)SAR Models for the Mechanism of Action (MOA), Physicochemical Properties, ADME, and Toxicological Endpoints Relevant to the Safety Assessments of Cosmetic Ingredients

SOFTWARE (DEVELOPER) |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>CASE-Ultra (Multicase Inc.)</td>
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<tr>
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<tr>
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● = Commercial (Q)SAR Models
* = In-house (Q)SAR Models
### Table (continued)

#### SOFTWARE (DEVELOPER)

<table>
<thead>
<tr>
<th>SOFTWARE (DEVELOPER)</th>
<th>Skin irritation</th>
<th>Skin sensitization</th>
<th>Skin corrosion</th>
<th>Eye irritation</th>
<th>Eye corrosion</th>
<th>Bacterial mutagen (Ames assay)</th>
<th>Eucaryote mutagen</th>
<th>Eucaryote clastogen</th>
<th>Eucaryote DNA damage</th>
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<th>Kroes TTC decision tree</th>
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</tbody>
</table>

= Commercial (Q)SAR Models

= In house (Q)SAR Models

### (Q)SAR Software Used to evaluate 3 ingredients

- Software programs utilized:
  - ADMET Predictor: Simulations-Plus, Inc. ([www.simulations-plus.com](http://www.simulations-plus.com))
  - Percepta: Advanced Chemistry Development Labs, Inc. ([www.acdlabs.com](http://www.acdlabs.com))
  - CASE-Ultra: MultiCASE Inc. ([www.multicase.com](http://www.multicase.com))
  - Leadscope Model Applier: Leadscope, Inc. ([www.leadscope.com](http://www.leadscope.com))
  - Derek Nexus: Lhasa Ltd. ([www.hapalmtd.org](http://www.hapalmtd.org))
  - Toxtree: Idiaconsult Ltd. ([www.toxtree.sourceforge.net](http://www.toxtree.sourceforge.net))
Abbreviations in QSAR result summary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>+</td>
<td>Predicted positive</td>
</tr>
<tr>
<td>–</td>
<td>Predicted negative</td>
</tr>
<tr>
<td>P</td>
<td>Positive class</td>
</tr>
<tr>
<td>N</td>
<td>Negative class</td>
</tr>
<tr>
<td>O</td>
<td>Outside model's applicability domain</td>
</tr>
<tr>
<td>PA</td>
<td>% Confidence in prediction of skin irritation is based upon 21 QSAR models</td>
</tr>
<tr>
<td>+a</td>
<td>Predicted positive in Mouse Lymphoma</td>
</tr>
<tr>
<td>+p</td>
<td>Predicted positive either in Mouse Lymphoma cell or in vitro test</td>
</tr>
<tr>
<td>*</td>
<td>Log Kp In Vitro Skin Permeability coefficient through human skin</td>
</tr>
<tr>
<td>Eqv</td>
<td>Equivocal</td>
</tr>
<tr>
<td>%</td>
<td>% Confidence in prediction of skin sensitization is based upon only three QSAR models</td>
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SUMMARY: (Q)SAR RESULTS

<table>
<thead>
<tr>
<th>CHEMICAL NAME</th>
<th>SKIN ABSORPTION</th>
<th>GENOTOXICITY</th>
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<tr>
<td></td>
<td>Log Kp (MEDIAN VALUES IN CM/H)</td>
<td>EUCARYOTE MUTAGENESIS (AMES ASSAY)</td>
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<tr>
<td>INGREDIENT - 1</td>
<td>2.65</td>
<td>2.50</td>
</tr>
<tr>
<td>INGREDIENT - 2</td>
<td>2.65</td>
<td>2.25</td>
</tr>
<tr>
<td>INGREDIENT - 3</td>
<td>2.65</td>
<td>2.25</td>
</tr>
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</table>

Examples of FDA analytical research

- Prostaglandin analogs in cosmetic products
- Skin whiteners
- Arbutin stability
In 2008, the US FDA approved the use of Latisse™ as a prescription drug for the treatment of hypotrichosis (inadequate lashes).

The ingredient responsible for eyelash enhancement is the prostaglandin, bimatoprost, which activates prostamide F<sub>2</sub>α receptors found in the hair follicle.

Bimatoprost is also marketed under the trade name, Lumigan®, for the treatment of ocular hypertension/glaucoma.

Prostaglandin analogs traditionally used for treatment of ocular hypertension/glaucoma:

- Side effects include conjunctival hyperemia, excessive tearing, inflammation, coloring of iris, skin pigmentation, and increase in eyelash length, thickness, and darkness
- "Eyelash-enhancing" effects spurred the production of new cosmetic products containing prostaglandins
- A number of new eyelash-enhancing cosmetic products containing other prostaglandin analogs were placed on the market
- Up until now, no analytical method had been reported for the detection and quantitation of prostaglandins in cosmetics

Prescription Prostaglandin Analogs

- Prostaglandin analogs traditionally used for treatment of ocular hypertension/glaucoma

Market Survey Results

- 31 products were analyzed for all 16 prostaglandin analogs (LC-MS/MS)
- 13 of 31 products tested positive and concentrations ranged from 27.4 – 297 µg/g
- Only 4 of the 16 prostaglandin analogs were found in the products surveyed
- Different lots numbers were analyzed and concentrations were consistent between lots
- The concentrations of the prescription products were all calculated to be within 2% of the labeled concentration
- The concentration levels found in the cosmetic products is similar to that found in the prescription drugs

<table>
<thead>
<tr>
<th>Product</th>
<th>Prostaglandin</th>
<th>Calc. Conc. (±RSD) (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product 1</td>
<td>Trav</td>
<td>36.6 (8.05)</td>
</tr>
<tr>
<td>Product 2</td>
<td>Lat</td>
<td>50.3 (7.43)</td>
</tr>
<tr>
<td>Product 3</td>
<td>Bima</td>
<td>290 (4.15)</td>
</tr>
<tr>
<td>Product 4</td>
<td>Bima</td>
<td>206 (46)</td>
</tr>
<tr>
<td>Product 5</td>
<td>Bima</td>
<td>172 (44)</td>
</tr>
<tr>
<td>Product 6</td>
<td>Bima</td>
<td>141 (84)</td>
</tr>
<tr>
<td>Product 7</td>
<td>Bima</td>
<td>133 (11.3)</td>
</tr>
<tr>
<td>Product 8</td>
<td>Bima</td>
<td>126 (10.6)</td>
</tr>
<tr>
<td>Product 9</td>
<td>Bima</td>
<td>91.6 (10.6)</td>
</tr>
<tr>
<td>Product 10</td>
<td>Bima</td>
<td>206 (3.34)</td>
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<tr>
<td>Product 11</td>
<td>Bima</td>
<td>43.5 (1.0)</td>
</tr>
<tr>
<td>Product 12</td>
<td>Bima</td>
<td>65.9 (0.79)</td>
</tr>
<tr>
<td>Product 13</td>
<td>Bima</td>
<td>90.3 (0.69)</td>
</tr>
<tr>
<td>Product 14</td>
<td>Bima</td>
<td>63.6 (0.44)</td>
</tr>
<tr>
<td>Product 15</td>
<td>Bima</td>
<td>27.4 (0.08)</td>
</tr>
<tr>
<td>Product 16</td>
<td>Bima</td>
<td>90.2 (0.99)</td>
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<td>Product 17</td>
<td>Bima</td>
<td>126 (1.07)</td>
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<td>Product 18</td>
<td>Bima</td>
<td>297 (1.16)</td>
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<td>Prescription Product 1</td>
<td>Trav</td>
<td>36.6 (8.05)</td>
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<tr>
<td>Prescription Product 3</td>
<td>Bima</td>
<td>290 (4.15)</td>
</tr>
</tbody>
</table>
Research on Skin Whiteners

- Study objective: to develop an HPLC-UV method to quantitate vitamin C, α-arbutin, β-arbutin, kojic acid, nicotinamide, hydroquinone, resorcinol, 4-methoxyphenol and 4-ethoxyphenol

- 59 different types of skin lightening products were analyzed, including creams, lotions, serums, foams, gels, masks, bar soaps, tablets and capsules

Distribution of individual analytes in skin lightening products

- Distribution shows:
  - Hydroquinone: 17%
  - Nicotinamide: 20%
  - Kojic acid: 14%
  - Vitamin C: 14%
  - β-arbutin: 29%
  - α-arbutin: 17%
  - Resorcinol: 5%
  - Others (N.D.): 24%

Arbutins research

- Arbutin is the glycoside derivative of hydroquinone
  - β-arbutin is commonly found in species of several plant families in nature
  - α-arbutin can be obtained by biotransformation or by chemical routes

- β- and α-arbutin popular skin whitening agents because of ability to interfere with melanin synthesis
- Biological activity is related to inhibition of tyrosinase enzymes in melanocytes
Conclusions of Arbutin research

- Of 33 Skin lightening products claimed to contain arbutin:
  - 52% contained β-arbutin and 30% contained α-arbutin
  - 21% did not contain detectible levels of β-arbutin or α-arbutin
- Both α- and β-arbutin were found stable to mild chemical conditions up to 6 months, while readily hydrolyzing to hydroquinone in extreme conditions of heat and pH
- Both α- and β-arbutin were found unstable in vivo, with a half-life of 8 h in both cases, but the formation of hydroquinone was minimal if not absent within the tested conditions
- No anomerization of either α- or β-arbutin was observed in any of the tested experimental conditions

Safety research

- Testing biologic activity of chemicals yields high concordance with in vivo assays
- Derived from normal (non-cancer, non-transformed) human skin cells
- Highly differentiated to form normal layers of intact epidermis
- Validated for Irritation and Micronucleus Tests
- Metabolically and mitotically active
Assay to measure skin irritation

Micronucleus assay detects clastogens

Comet Assay in NHEK Cells

Comet Assay - Treat primary human skin cells (NHEK) with compounds of interest and detect DNA damage

Control (untreated) Positive Control (H₂O₂)

Comet assay conditions have been optimized, and NHEK primary human skin cells will be exposed to potential chemicals of interest to assess genotoxicity

Laboratory Validation results of Comet Assay in NHEK Cells

NHEK cells treated with H₂O₂ as positive control: DNA damage can be visualized and quantitated in
Future directions for OCAC research

• Development of systematic processes for the analysis of adverse events and for linkage of specific cosmetic ingredients with adverse events

• Risk assessment

Future strategy for OCAC research

• Develop models for specific testing needs
  – Dermal penetration (baby skin versus adult skin)
  – Sensitization/allergenicity
  – In vitro toxicology for various endpoints (e.g. dermal penetration, genotoxicity, eye area toxicity, inhalation toxicity)

• Areas for future focus:
  – Allergens (fragrance allergens, latex, gluten…)
  – Preservatives (parabens, MIT, …)
  – Ingredients of interest (formaldehyde, hydroquinone, …)
  – Botanicals
  – Tattoos
  – Ingredients that are pharmacologically "active"

Safety Research paradigm

• Hypothesis generation from:
  – Adverse events analysis
  – In silico modeling
  – Literature survey/public inquiry

• Testing via:
  – Product surveys (contract, FDA laboratories)
  – Establishing In vitro toxicology models developed for safety assessment of cosmetic ingredients
  – Establishment of collaborations/partnerships
“Quality” research paradigm

- Use results of in-house testing and field operations to ensure:
  - Lack of microbiological contamination
  - Identification and qualification of impurities, degradants, heavy metal, and other contaminants
  - Product consistency through adoption of GMP principles:
    - Manufacturing process controls
    - Stability
    - Microbial/endotoxin contamination
    - Efficacy of preservatives
    - Product/ingredient specifications
- Use data from laboratory surveys to quantitate select ingredients in specific products of interest:
  - Address presence and quantity of select ingredients in product labeling

Ultimate goal of OCAC research

- Impact on policy development:
  - Guidance
  - Rule making/regulations
  - Product labeling
- Propagate research results:
  - Publications
  - Consumer updates on website and social media
- Focus future enforcement actions
  - Inspections
  - Warning letters
  - Seizures

Conclusions

- The goal of OCAC research is for FDA to have:
  - More public confidence in cosmetic product quality AND safety
Looking towards the future

• Prioritize research goals
• Use available resources to meet defined research goals
• Leverage resources with collaborators to maximize impact on public health:
  – Academia
  – Industry

Thank you

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