Update on Regulatory Activities Related to Tattoo Inks in the United States

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Overview

- Regulatory Framework
- Prevalence of Tattoos in the U.S.
- Adverse Event Reporting
- Recalls
- Tattoo Ink Survey
- Methods Development
- Outreach
- Gaps

What is a Cosmetic?

- Cosmetics are defined as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance" [FD&C Act, sec. 201(i)]
- Does not affect structure or function of the body and is not intended to diagnosis, cure mitigate, treat or prevent a disease
- Personal care products, cosmeceuticals, natural and organic are not defined in the Act

Color Additives

- Substances that impart color to a food, drug, cosmetic, medical device, or human body
- Must be safe and pre-approved (listed in regulation)
- Individual color additives may only be used as allowed by regulation
- Certain color additives require FDA Laboratory Batch Certification to ensure specifications are met

In this presentation we use the terms color additive (CA) and pigment interchangeably. CA is a regulatory term defined in law.

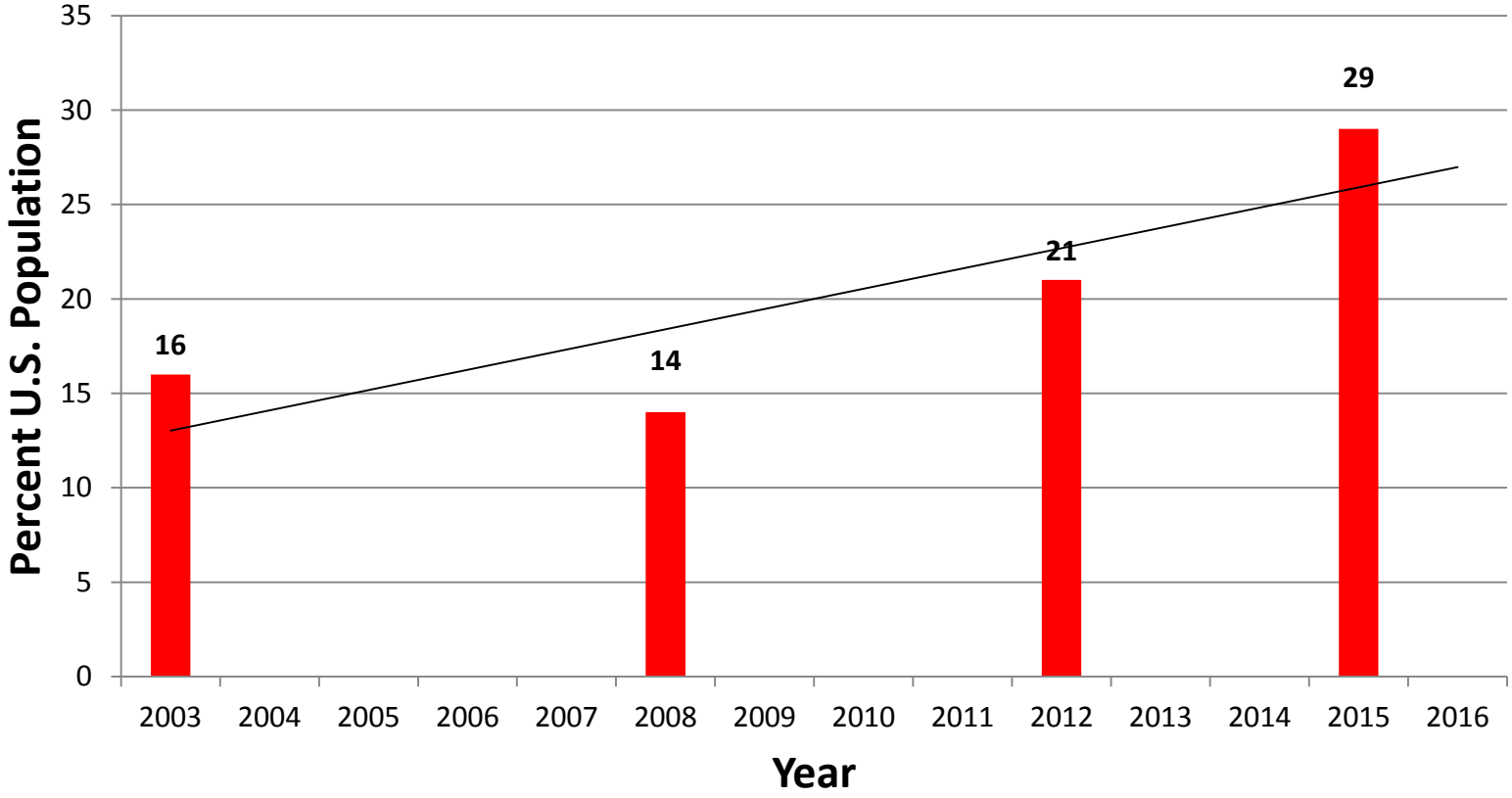
FDA Authority Over Cosmetics

- FDA can take action against harmful (adulterated) or mislabed (misbranded) cosmetics on the market
- FDA does not have the authority to approve cosmetics before they go on the market
- The manufacturer is responsible for making sure cosmetics are safe; may do testing or use available data for similar products
- FDA does not have the authority to require firms to report their test data and does not set standards for that testing
- Color additives used in cosmetics must be pre-approved by FDA
  - 21 CFR Parts 70, 71, 73, 74, 80, 81, and 82
  - Other applicable regulations

Tattoo Ink Regulatory Status
Policies & Jurisdiction

- **Tattoo inks** are a mixture of color additives and diluents (other ingredients, including water) intended for injection into the skin
- **No** color additives (tattoo pigments) have been listed for injectable use for cosmetic purposes
- FDA traditionally has not exercised its regulatory authority over color additives used in tattoos
- The **practice** of tattooing is regulated by state and local jurisdictions
- Other safety issues, such as microbial contamination, have been handled on a case-by-case basis

U.S. Population Bearing One or More Tattoos,[1,2] Harris Polls, (%)

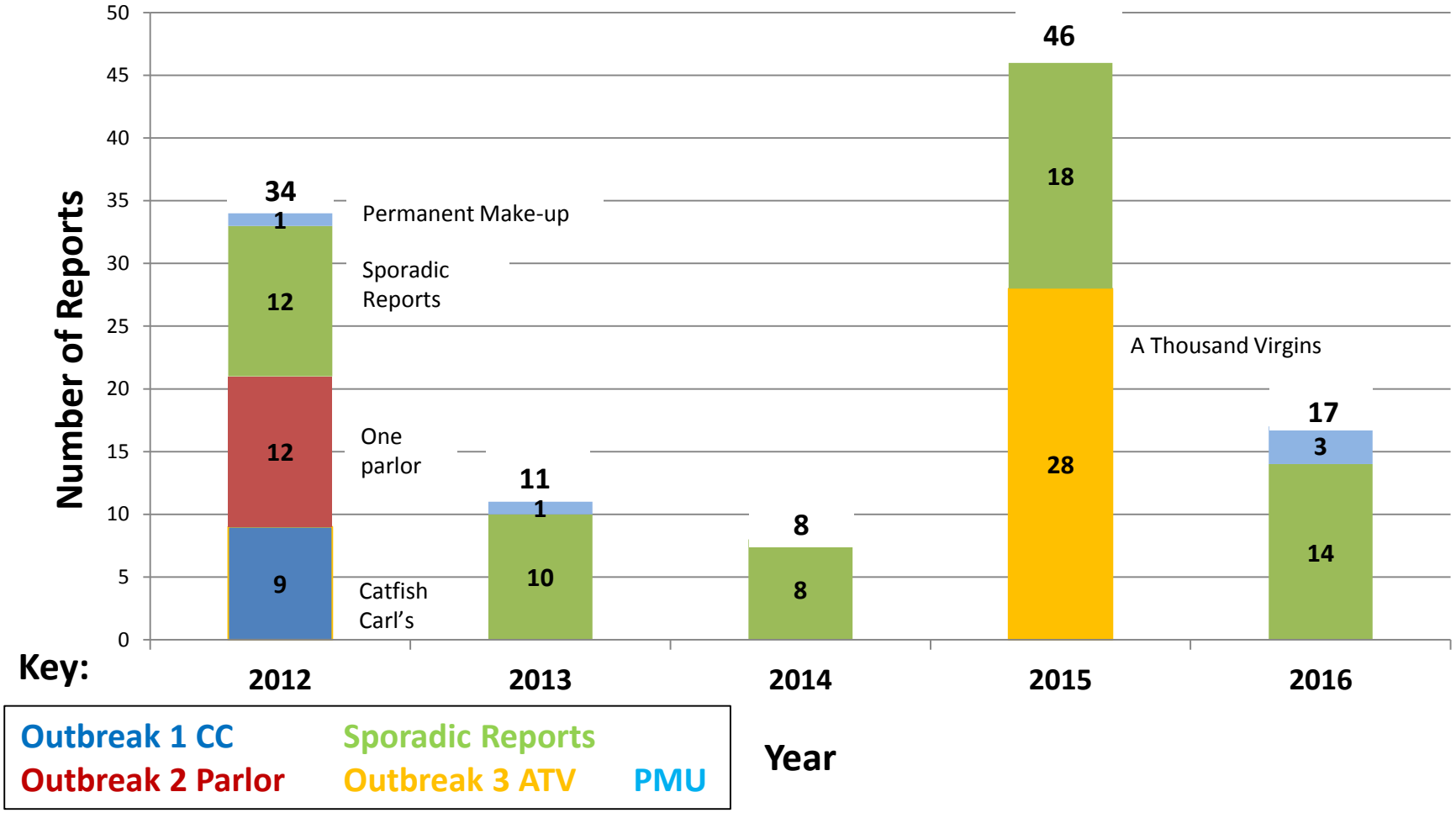


1. 2003, 2008, 2012 & 2015 statistics from the Harris Interactive Poll on 4/10/2014 at http://www.harrisinteractive.com/NewsRoom/HarrisPolls/tabid/447/mid/1508/articleId/970/ctl/ReadCustom%20Default/Default.aspx; and
2. 10/14-19/2015 at http://www.theharrispoll.com/health-and-life/Tattoo_Takeover.html

Cosmetics Adverse Events & Reports

- An adverse event is an undesirable reaction submitted by a reporter via MedWatch or Consumer Complaint Coordinator
  - Such as a rash, redness, burn, hair loss, headache, infection, illness, disfiguring or any other unexpected reaction, whether or not it required medical treatment
- Types of adverse events reported to FDA
  - Serious events average - 30% annually (SERIOUS include: hospitalization, death, disfigurement, life threatening & disability, congenital abnormalities)
  - Non-serious events average - 70% annually
- Product types most often reported;
  - Talc
  - Hair straightening treatments (formaldehyde)
  - Deodorants
  - Men's hair (lead acetate) and beard dyes (PPD or coal tar dyes)
  - Hair dyes (PPD) & Temporary (Black Henna) Tattoos
  - Hair cleansing, detangling, conditioners
  - Tattoos
  - Anti-aging creams (retinol)
  - Baby wipes

Tattoo Related Adverse Event Reports, 2012-2016



Tattoo Related Adverse Events: Reported Symptoms

- Infections and inflammatory reactions
- Swelling, cracking, peeling, blistering, scarring
- Granulomas, keloids, and systemic sarcoidosis
- Allergic reactions (acute/delayed) and cross-reactivity to pigments, their metabolic by-products and other components of inks
- Pruritis, local or generalized, acute or chronic
- Photosensitivity in tattooed areas
- Disfigurement
- Others: medical complications interference with diagnostic testing (MRI, histopathology, etc.)

Adverse Event Investigation

- Adverse event reporting is sporadic
- Increasing numbers of recalls, partly due to:
  - Increased awareness of consumers, healthcare providers and artists
  - Improvements in analytical methods
- Attribution of the source of contamination can be difficult to establish, i.e., parlor practice, the equipment, manufacturing or the container
- FDA needs to know more to educate industry and consumers about safety issues and their most effective solutions

Tattoo Ink Adverse Events & Recalls

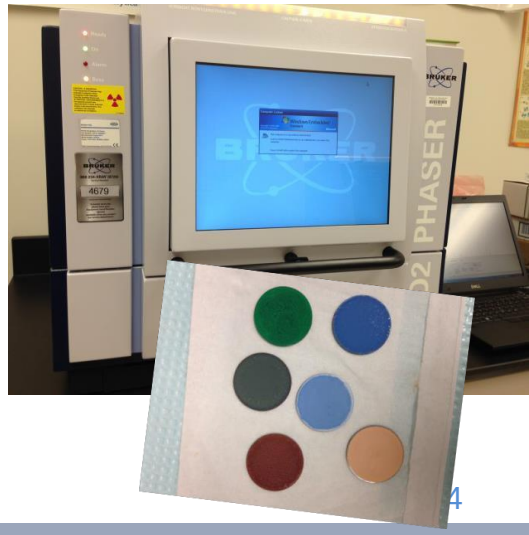
- In 2003, Premier Pigment Permanent Make-up cluster, upwards of 150 cases: an allergic reaction was suspected…
- 2004 Starbrite tattoo ink was recalled – due to microbial contamination
- In 2011, there were several outbreaks in U.S. possibly linked to bottled tattoo ink*
  - Catfish Carl's: 14 confirmed of 19 cases matched to pathogen in sealed ink
  - Kingpin One: 35 reports of adverse events
- Since 2011, three additional recalls for microbial contamination of ink
  - Blacker ink: one report initiated an investigation, recovered *Nocardia farcinica*
  - Blue & White Lion : one report initiated an investigation recovered *Bacillus spp. and others*
  - A Thousand Virgins : parlor diluted inks with tap water, multiple NTM spp., 28 reported cases, sealed ink contained *M. chelonae*, *Microbacterium spp.,* and molds
- Pathogens, other than NTM, have been isolated from sealed containers of ink

*Kennedy, BS, Bedard B, Younge M, et al. Outbreak of Mycobacterium chelonae Infection Associated with Tattoo Ink. N ENGL J MED 2012; 367:1020-1024 September 13, 2012

Tattoo Inks: Methods Development & Challenges

FDA Research Aims

- To identify microbiological contaminants and the sources of contamination in inks
  - Market survey for microbial contamination
  - Develop validated regulatory methods for the microbiological testing of tattoo inks
- To develop validated regulatory methods for pigment identification
  - Identify and create standard references (spectra) for color additives in inks
  - Identify and quantitate ink contaminants of concern
- To understand the potential toxicity of injected pigments/inks
  - Methods Development: Mouse model as human surrogate
  - Methods Development: Color additive extraction & quantification from skin
  - Stability of injected pigments, and impact of light
  - Physiologic response of the body to pigments
  - Toxicology and variability by color additive or ink composition
- Fill other research gaps



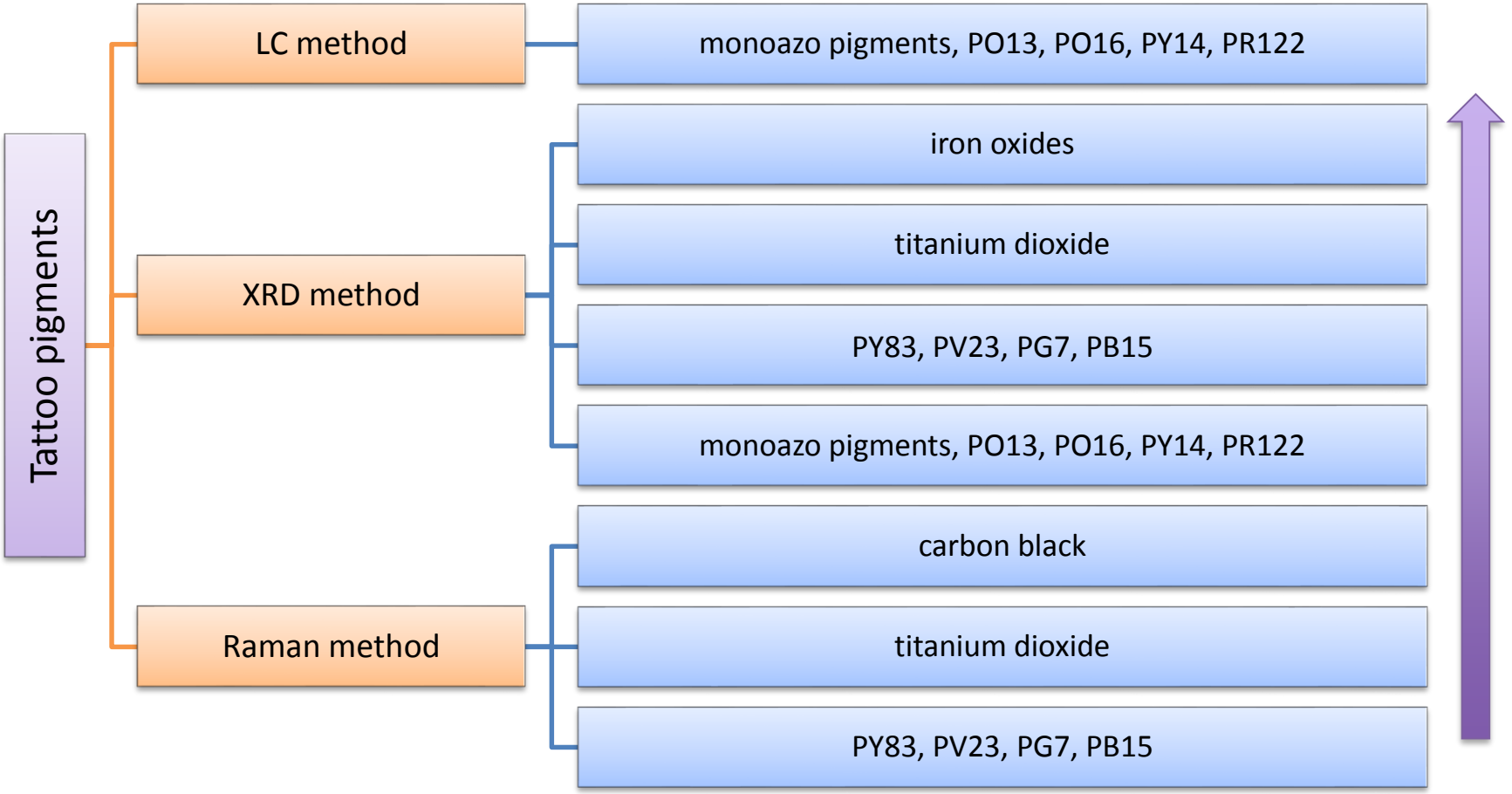
Tattoo Pigments

- Tattoo pigments must be **insoluble** in tattoo inks to prevent **migration** from the skin
- Organic pigments:
  - High tinting strength (**intense colors**)
  - Wide range of shades/colors
  - May contain potentially harmful compounds (e.g., amines)
- Inorganic pigments:
  - Natural sources may also contain clay, silica, etc.
  - Synthetic sources are more pure
  - Shade/color may fade over time
  - May contain heavy metals

Challenges of Methods Development
Pigment Characterization

- Identification of pigments in tattoo inks is **difficult** because of factors such as:
  - Low solubility of the pigments
  - Interferences from additional tattoo ink components (e.g., witch hazel, resins)
  - Low amounts of a pigment in some tattoo inks
  - Limited access to pigment standards

Summary: Methods for Pigment Identification



Wide Research Gaps Still Exist

- Composition of tattoo inks is largely unknown
  - Knowledge of pigment identity, likely contaminants, relative usage and processing methods to reduce potentially hazardous constituents
  - Effects of pigment/ink processing or manufacturing methods are unknown
  - Milling of pigments to create pre-dispersed inks may create nano particle pigments which are bioactive and change ink safety profile
  - Gamma irradiation intended to reduce microbial loads may result in increased PAHs, PAAs or other hazardous constituents in inks
- Safety of tattoo ink ingredients, including pigments and diluents is unknown
  - Risk assessment data related to identification, quantification and distribution of injected pigments, chemicals, and contaminants
- Health effects of long-term exposure to ink ingredients, pigments and diluents, are unknown
  - Development of approaches/methods for detection of long-term outcomes
- Validated regulatory methods development

Outreach

- Educate consumers to;
  - Obtain and save information on inks used to make a tattoo
  - Recognize health effects post-tattooing
  - To report adverse events with ink data to improve product-report linkage
  - To involve a healthcare professional in submitting medical information
- Determine best approaches for improving the quality of reports

Conclusion

- Tattoo inks are regulated under the FD&CA. No Color additives are listed for injection
- Tattoos are increasingly popular in the U.S.
- Adverse event reporting is voluntary for industry, healthcare providers and consumers, the quality of reports needs to be improved
- FDA uses adverse event reports to aid in the identification of cosmetic problems
- When a problem is identified, recalls remove hazardous product from the marketplace, are voluntary and increasing for inks
- Validated regulatory methods are in development
- Toxicity of color additives and contaminants has yet to be well defined
- Outreach to educate consumers and improve adverse event reporting may aid in potential toxicities and problem identification