ENTHALPY ANALYTICAL

The Impact of FDA Regulation, a CRO's Perspective on Changes in the Industry.

Gene Gillman, PhD

Disclaimer

Enthalpy Analytical does not advocate for tobacco product regulations including:

- Compounds of interest
- Number of replicates to be tested
- Schedule and scope of testing

- Enthalpy Analytical performs testing for a range of customers including:
  - Manufacturers and resellers of tobacco products
  - State and Federal agencies
  - Nonprofit organizations and researchers

What are CROs

- Contract Research Organization (CROs)
  - Provides support in the form of research services outsourced on a contract basis. Both internal (FTE) and external (fee for service) models are in use in the industry.
- Tobacco Industry CROs (fee for service)
  - Provides routine analytical testing services to tobacco product manufacturers.
  - Provides routine analytical testing services to government agencies.
  - Provides an independent organization that can validate methods and verify results.

Why are CROs a Stakeholder

- Provide Analytical Testing Services For Compliance With TCA Requirements
  - 904: Testing and reporting HPHCs and constituents in tobacco products
  - 905 & 910: Support for SE and PMTA requirements
  - 911: Support for MRTP Applications
  - 915: Testing and reporting of tobacco constituents, ingredients, additives, and smoke constituents
- Provide Routine Analytical Testing Services to Government Agencies
  - Tobacco and smoke constituents testing projects
- Publication of Original Research in Peer Review Journals
  - Numerous recent publications from a range of CROs
- Participation in Industry Working Groups
  - ISO TC 126, CORESTA Subgroups, TMA and FDA Workshops

The Tobacco Control Act (TCA)

- The Tobacco Control Act (2009) Fundamentally Changed how Tobacco Products are Regulated in the United States
- TCA is a Complex Document that Impacts Many Areas of Deemed Products Including:
  - Product Regulations
    - Registration
    - Labeling
    - Manufacturing Requirements
  - Product Testing Requirements
    - HPHC reporting
    - Pre-market approval

TCA: Testing Requirements

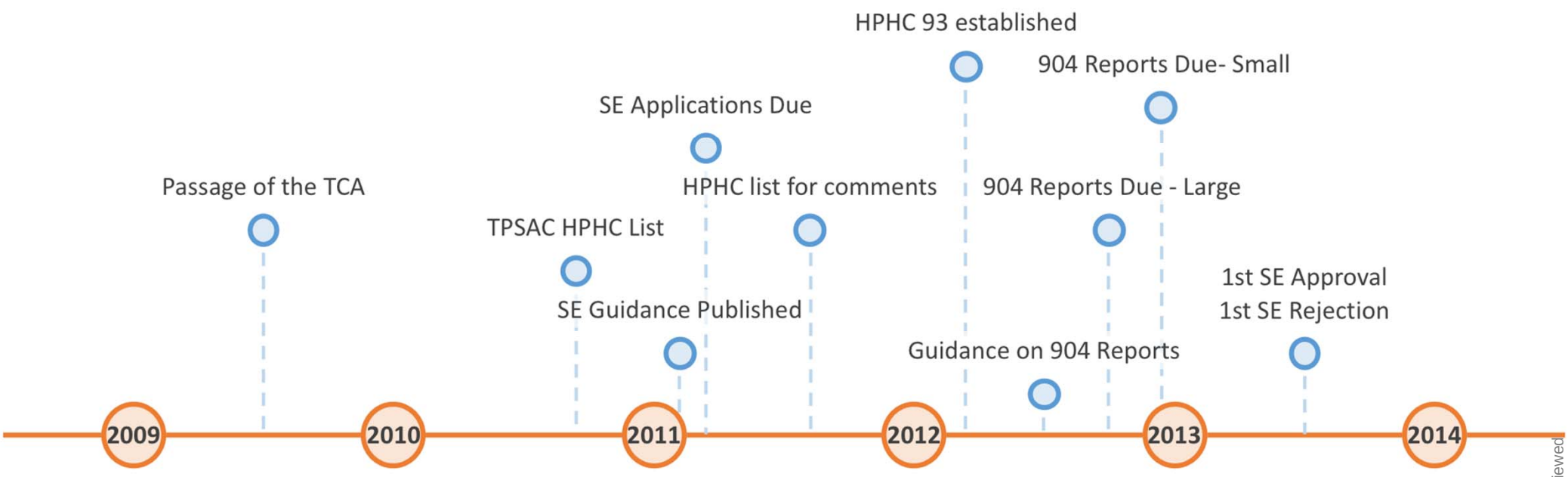
Section 904
"Not later than 24 months after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, the Secretary shall establish, and periodically revise as appropriate, a list of harmful and potentially harmful constituents, including smoke constituents…"

Section 905
Demonstration of substantially equivalent

Section 910
Premarket Review Required
"An order …. for a new tobacco product is required …"

Section 915
"Not later than 36 months after the date of enactment … (The FDA) shall require testing and reporting of tobacco product constituents, ingredients, and additives, including smoke constituents…. (with) Subsequent and Additional Testing and Reporting."

TCA Timeline: 2009-2014



TCA Impact: Enactment

- With the Passage of the TCA, CROs Experienced a Dramatic Shift in Work
  - Decline in product development work
    - Uncertainly of SE and PMTA requirements for new products
  - Expanded capabilities required
    - Expanded list of HPHCs
      - New methods validated and bought online
  - Expanded capacity needed
    - Reporting requirements under section 904, 915 plus SE/PMTA support
      - Expansion to facilities and analytical instrumentation

TCA Impact: 2009-2014

- Post TCA and the CRO industry
  - Decline in revenue post TCA
    - Dropoff in R&D projects related to lack of clarity on SE/PMTA requirements
    - New CROs entered the market
    - Limited review of SE applications
  - Reporting Under Section 904
    - Guidance document released on April 2012 with reports due in September 2012 (Large Manufacturers) and December 2012 (Small Manufacturers)
    - Limited time window to expand capacity for additional product testing
  - Reporting Under Section 915
    - No guidance issued

2012 Section 904 Reporting

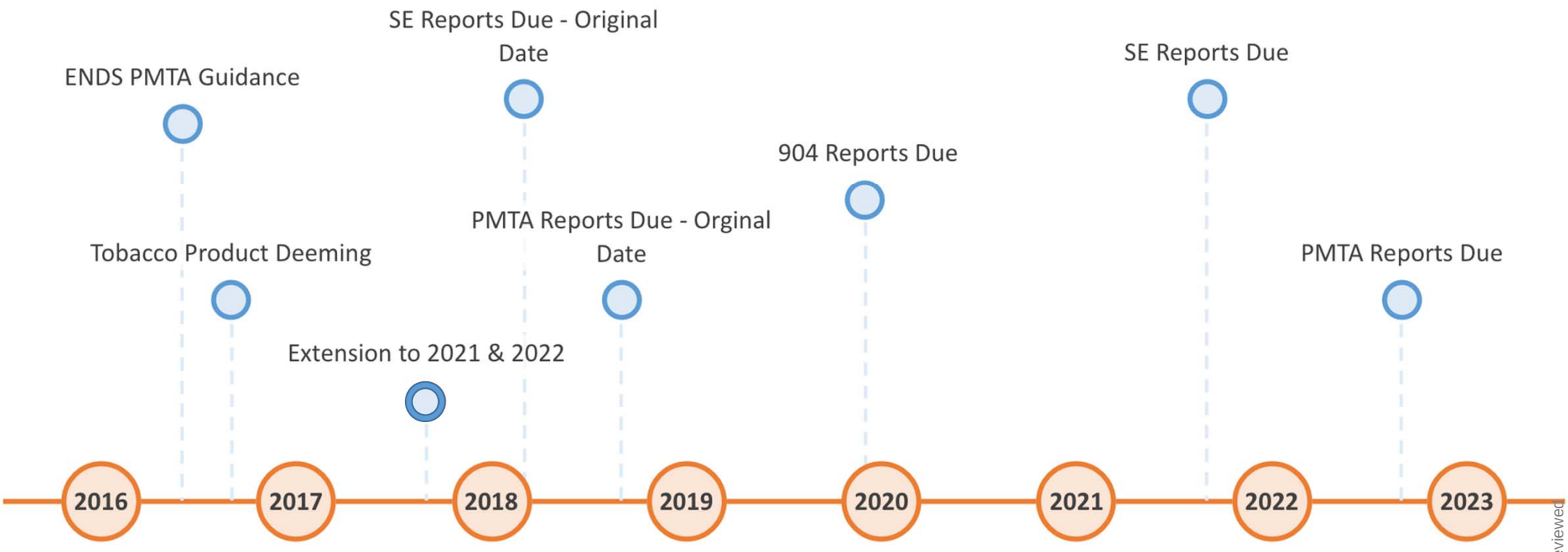
"We recognize that industry will have a short time between the establishment of the HPHC list and June 22, 2012 when the reporting obligations under section 904(a)(3) are effective. We also recognize that manufacturers or importers (particularly small tobacco product manufacturers may not currently have the in-house laboratory capabilities to test for quantities of HPHCs. Consequently, manufacturers or importers may rely on contract laboratories for HPHC testing. Because this will be the first time that tobacco product manufacturers or importers are required to report quantities of HPHCs, **contract laboratories may not be prepared for the large volume of requests for the testing** of quantities of the HPHCs for all brands and subbrands of tobacco products marketed prior to June 22, 2012."

Draft Guidance for Industry: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act: 2012

TCA Impact: 2015

- Limited Guidance from the Agency in 2015
- Active FDA SE Related Projects Underway
  - Cigarettes
  - Smokeless Tobacco
  - RYO products
- ENDS Product Stewardship
  - Batch release testing for nicotine content
  - Selected constituent testing (flavor compounds)
- Reporting Under Section 915
  - No guidance issued

TCA Timeline: 2016-2023



TCA Impact: 2016-2018

- Deeming of ENDS
  - Validation of ENDS HPHC methods
    - Limited projects started to support PMTA
- Deeming of Cigars
  - Validation of methods for cigar testing
    - Limited projects started to support SE Applications
- Extension Granted for Newly Deemed Products
  - Applications now due in 2021/2022
    - Extension led to delay or cancellation of active and planned studies
- Reporting Under Section 915
  - No guidance issued

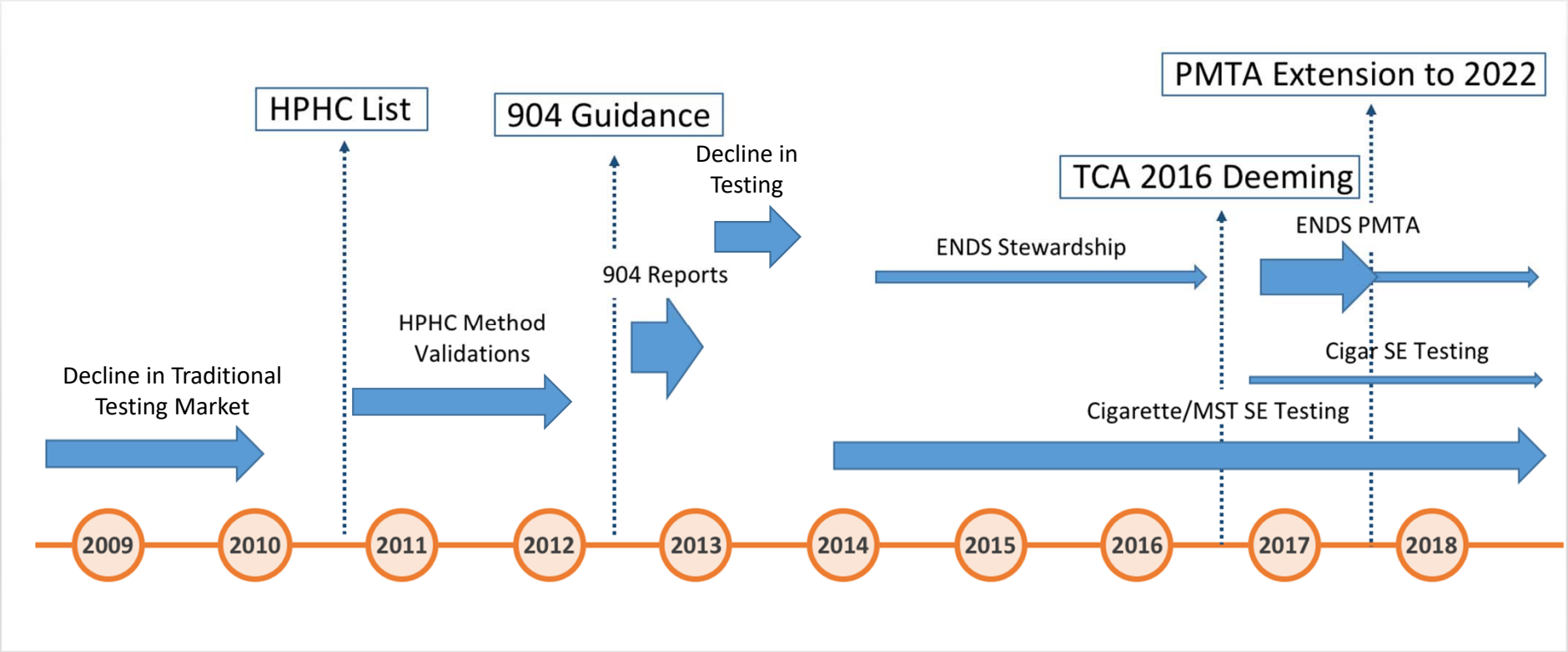
TCA Impact: 2019 and Beyond

- Section 904 Reporting
  - Number of brands is much greater than 2012
    - >10,000 e-liquids and ENDS on the US Market
    - >700 unique cigars brands on the US Market
  - Reporting deadline is approaching
    - November 2019
  - Testing guidance is needed
    - HPHC compounds in tobacco, smoke, e-liquids and aerosol
    - Puffing regime for cigars and ENDS
    - How to test pipe tobacco (traditional versus non-traditional)
    - Number of replicates and reporting units

TCA Impact: 2019 and Beyond

- Section 905 and 910
  - Cigar SE guidance needed
    - Recommended puffing regime
    - Blend considerations: growing region concerns, and curing method
  - ENDS PMTA guidance needed
    - Final PMTA guidance
    - Puffing conditions, HPHCs as appropriate, stability testing etc
- 915 Reporting and Product Standards
    - Timeline
    - What capacity and capabilities will be required

Impact of FDA Rules and Guidance



Unintended Consequences

- Delays in 2012 Guidance on the 904 Testing Requirements Negatively Impacted Industry Readiness and Capacity
  - Perceived lack of stakeholder involvement
- 93 HPHC list Versus Abbreviated HPHC list
  - Uncertainly of future testing requirements will limit capabilities
- Decline in ENDS Product Stewardship Testing after Deeming
  - Product development and stewardship testing declined by 95% (EA)
    - Concern over Section 904 reporting was the main cause
- Two Year Window to File ENDS Pre-Market applications
  - Many small companies did not attempt to meet the deadline
    - Lack of guidance, shortage of qualified consultants, and high cost were given as reasons

Conclusion

- CROs Provide a Valuable Service to Both the Industry and the Agency
- Guidance and Regulations from the Center for Tobacco Products May Have Unintended Downstream Effects
  - Advanced planning allows for appropriate capabilities and capacity to ready as needed
  - Early involvement and consideration of all stakeholder is critical to ensure the health of the broader industry and service providers including CROs, Consultants, Law Firms, other Testing Facilities and Clinical Study Sites

Thank you for your attention