CAN US FDA SUBSTANTIALLY EQUIVALENT PREDICATES BE DEVELOPED WITHOUT KNOWLEDGE OF AND A SAMPLE OF THE PREDICATE PRODUCT?

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Disclaimer – 1

- This is a scientific presentation, not a legal presentation
  - Those considering the use of the ideas presented should seek competent legal advice before proceeding
  - Many of the ideas presented have not been evaluated with laboratory studies
  - Many of the analytical techniques described are for research, not for routine testing and use
    - Require skilled scientists
    - Require expensive instrumentation
    - May not be readily available

Disclaimer – 2

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Current situation (1)

- FDA Substantial Equivalence (SE) rule has created much grief since original guidance issued January 6, 2011
  - Original guidance less than clear
  - FDA has increased amount of data it has requested, especially for predicate product such as specifications, QA data
  - It appears that the FDA has changed the meaning of SE to require a “Substantially exact” match
  - Why the focus on minor changes?
- Is FDA still looking for “smoking gun”?

Current situation (2)

- The SE rules have been difficult for many small manufacturers
  - The grandfather date of February 15, 2007, has been particularly troublesome
    - Some started business after that date, thus no predicate products of their own
    - Many making cigarettes did not use FSC cigarette paper until all states required it
    - Have made quality products, but have not had QA systems of major manufacturers
    - Thus, need to remanufacture 2007 products
- By asking for QA data on 2007 products, is FDA being anticompetitive?

Aren't all similar products really SE?

- Are not most all US-style blend, non-menthol filter cigarettes similar?
  - All have similar construction
  - Many have similar blends and ingredients and use-levels for ingredients
  - Nontobacco materials are very similar
  - All have same adverse health effects
    - All tested give similar results *in vitro* toxicological assays on mainstream smoke (MSS)
    - HPHC levels are similar, especially when adjusted for nicotine delivery
  - Do minor differences (density, PD, vent rate, NRE) among similar products "raise different questions of public health?"

Is this why no product standards?

- If most regulated products of a given type are similar to each other, why aren't there product standards?
  - For example, product standards for KS FF nonmenthol cigarettes would specify:
    - Types/amount of blend components that could be used with limits on TSNAs, metals, alkaloids as well as ingredients, use levels
    - Nontobacco materials and range of allow-able cigarette design parameters, tolerances
  - If made to the standard, would be SE
- Thus, anyone could enter the market as long as products met the standards – no need for predicate products

So you need a predicate

- What to do if you need a predicate
  - Purchase one or more predicates
    - Some companies have stopped making brand-styles on market February 15, 2007, but numerous pitfalls, unless you can get
      - Proof of market presence on February 15, 2007 or grandfather status, if applicable
      - Accurate bill-of-materials and specifications
      - Actual samples of predicate product in-hand
      - Needed tobaccos, ingredients, and nontobacco materials used in 2007 to recreate the predicate
    - Can you manufacture product and not “raise different questions of public health”
  - Have SE's via this route been approved?
  - What if you can't get everything needed?

What to do if still need more data?

- It depends on several factors
  - Commercial and/or scientific deficiencies
    - Show on market on February 15, 2007
      - Newspaper ads (newspaper archives)
      - State attorneys-general listings (some on-line)
      - Commercial information sources
      - Use data from FDA SE marketing orders
    - Missing scientific information
      - Ask (industry experts, vendors, former workers)
      - Search (Google, legacy docs, PubMed, etc.)
      - Published ingredient lists
      - Use data from FDA SE marketing orders
      - Reverse engineering grandfathered products
  - How much money do you have?
  - Can you retain the right attorneys, consultants, and laboratories?

Reverse engineering (1)

- Start with the literature, it is cheap
  - Lab work for reverse engineering is costly
    - Products of a given class (RYO tobacco, light cigarettes, filter tubes) usually similar
      - Often limited number of vendors and products
      - Much in the literature for some products
      - Conventional tobacco products and nontobacco materials have not changed much over time
    - Use literature to narrow down the questions that you need answered by lab work
      - Most tobacco/smoke analytical labs do the basics (FDA HPHC, TNCO (cigarettes) routinely
      - Finding labs that can do the in-depth analyses to show “substantially exact” can be more difficult
    - May need a contract research organization

Reverse engineering (2)

- Decision needed before beginning costly reverse engineering work
  - FDA marketing orders have listed grand-fathered products and the SE products
    - Target one grandfathered or SE product
    - Or show that members of a group are so close to one another that the FDA requirement of a single predicate is scientifically unsupportable
  - Techniques for reverse engineering can be found in legacy documents
    - Extensive multidisciplinary analytical and product development support needed
    - May need new blends and/or processes

Reverse engineering (3)

- Verify finished blend chemistry
  - Differences versus reference products
  - Comparisons with published food-type recipes, ingredient lists, MULs, QNEs
  - If blend is for smoking, HPHC and detailed smoke chemistry needed
    - Prototype, reference and predicate blends
    - Use of MYO with filter tubes, if necessary
- Can make it on a commercial scale and have no differences with target?
  - Routine and detailed tobacco chemistries
  - *In vitro* tox testing should be considered
  - Get sensory testing, if possible

Reverse engineering (4)

- Smoking article fabrication
  - If RYO tobacco, can you match using popular RYO papers and filter tubes?
  - If cigarette tobacco, can you match predicate design and nontobacco materials?
- Commercial cigarette manufacture
  - Prototype, reference, predicate blends
  - Knowledge of, and choice of, nontobacco materials (NTMs) very important
    - Need to avoid differences in FSC banding
    - Need to avoid adhesives with additives not used by major cigarette manufacturers
    - Compliance with 21 CFR 175.105 desirable

Reverse engineering NTMs (1)

- Paper, paper-like materials
  - Cigarette paper including RYO paper and paper in MYO tubes
  - Plugwraps and tipping papers
  - Packaging for other tobacco products
- Adhesives
  - Cigarette, MYO tube sideseam, tipping
  - Filter rod sideseam and anchor line
  - Other adhesives
- Minor ingredients
  - Is vendor giving you an “exact match”?
  - Will a rejected SE give you the answer?

Reverse engineering NTMs (2)

- FDA looking for small differences?
  - Fibers used to make paper
  - Fillers and burn additives
  - Brightness, opacity, color
  - Binders in paper and plugwrap
  - Differences in antimicrobials, minor components in adhesives
- Getting lab work done
  - Paper labs for fiber analysis, color, etc.
  - Tobacco labs for burn additives, filler
  - Getting other analytes likely difficult
    - May require sophisticated analytical work
    - May require research to develop methods

Putting it all together in the lab

- Tobacco blends (smoking, chewing)
  - Use 1989 Colby/Johnson report as guide
  - http://industrydocuments.library.ucsf.edu/tobacco/docs/kmpm0213
    - Blend separations
    - Routine analyses blends and blend fractions
    - GC-MS scan techniques and PY-GC-MS
- Smoking articles (MYO/RYO, cigarettes)
  - MSS TNCO, FDA HPHC (ISO, INT)
  - *In vitro* toxicological assays on MSS
- NTMs (paper, plugwraps, adhesives)
  - Use PY-GC-MS and FT-IR techniques especially if only have finished products

Putting it all together on the SE report

- With luck, you have all data for an SE
  - Data are not actionable information
    - Need to avoid Refuse to Accept (RTA) or NSE
    - Avoid errors shown in NSE reports
    - Need to have complicated test results explained by credentialed experts and their written reports included in your SE reports
- Don't expect a warm welcome at FDA
  - Has anyone used another manufacturer's predicate/grandfathered product for SE?
  - Expect plenty of questions on how you made product versus how predicate or grandfather product was made
- Get legal review of SE reports

What if FDA give you RTA or NSE?

- You and your attorney should have planned for such a rejection
  - Was rejection arbitrary or correctable?
    - Are you missing data that the FDA needs?
    - Are the missing data just not available?
    - Are the issues fixable without legal action?
    - Do you have the funds for legal action?
- Does FDA want to risk SE in court?
  - Would a NSE based on minor changes in NTMs or properties stand up in court?
  - Would a RTA based on use of another manufacturer's stand up in court?
- Attorneys should supply the answers

Summing it up

- FDA SE rules have made it hard for smaller manufacturers to survive
  - Grandfather date of February 15, 2007
  - Increasing data requirement for SE
- Predicates are available
  - Grandfathered products and products FDA has found to be SE
  - Grandfathered products no longer manufactured but details for sale?
- Reverse engineering and reconstruction of predicates doable but costly
- Many legal issues unresolved