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ANDAs, OTCs, Orphans and Cosmetics – Key Issues

SDRAN RAC Exam Review Course

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- These slides are intended to provide general educational information and are not intended to convey legal advice.

Our Topics Today

- Generic Drugs
- OTC Drugs
- Orphan Drugs
- Cosmetics

What We Will Cover on Generics

- Basics
- User Fees
- Power
- Addressing Abuses – by Rule & Statute
- Biosimilars – Basics of New Law

PART I – The Basics

- **In the beginning, there were no legal generics…**
- **The 1906 Act and Drug Law**
  - Misbranding
  - Adulteration
  - No new drug application provisions
- **The 1938 Act**
  - Added new drug provisions

Basics …

- **1938 Act …**
  - Did not directly address generics
- **Marketplace reality**
  - "Not new drug" rulings – early '40's
  - "Me too's" entered market
- **1962 Act**
  - Efficacy added
  - D.E.S.I created

D.E.S.I.

- **Laid foundation for first approved generics**
- **By 1970, the ANDA created**
- **Problem**
  - Only applied to pre-'62 drug found effective under DESI
- **Solution??? -- the "Paper NDA" -- 1978**

1984 …

- Not just a cool novel
- Birth of the modern generic industry
- Compromise – smoke-filled room legislation
- "Drug Price Competition and Patent Term Restoration Act of 1984"
- Enacted – September 24, 1984

Waxman-Hatch Basics

- **Any person could file an ANDA for a drug approved under § 505(b) of the Federal Food, Drug, and Cosmetic Act**
- **Requirements**
  - Same active ingredient
  - Same conditions of use (labeling)
  - Same dosage form
  - Same strength
  - Same route of admin.
  - Bioequivalent
  - Patent Certification

Basics …

- **ANDA Suitability Petitions – for some changes**
- **Listing of patents and approved drugs – the "Orange Book"**
- **Patent term restoration –**
  - On new chemical entities – maximum is five years
  - Formula = 50% development time + 100% review time (less any non-diligent time) up to 5 years with a maximum length after extension of 14 years

Basics …

- **Exclusivity**
  - 5-year – NCE
  - 3-year – new uses for previously approved drugs
    - New clinical investigations
    - Conducted or sponsored
    - By applicant
    - Essential to approval

Basics …

- **Patent listings**
  - 30 days of new approval
  - 30 days of issuance if drug already approved
- **Patent Certifications**
  - I – no information filed
  - II – filed patent has expired
  - III – will await patent expire
  - IV – won't infringe or patent invalid – requires notice to patent holder with detailed statement of law and fact for why patent should not block ANDA

Basics …

- **Repealed *Roche v. Bolar***
- **Not an act of infringement if solely related to filing of information under drug laws**
  - Note – also applies to devices – Medtronic v. Lilly
  - Applies to clinical testing of intermediates – Intermedics v. Ventritex -- 1991

"Roche v. Bolar Exception" …

- **Merck KGA v. Integra; USSC # 03-1237 (argued on 4/20/05)**
  - **QUESTION PRESENTED – "**… Did the Federal Circuit err in concluding that this drug-research safe harbor does not protect animal studies of the sort that are essential to the development of new drugs, where the research will be presented to the FDA, and where barring the research until expiration of the patent could mean years of delay in the availability of life-saving new drugs?"
  - **ANSWER** – Yes – June 13, 2005 – Supreme Ct. unanimously reversed the decision

"Roche v. Bolar Exception" …

- **<u>Merck KGA v. Integra</u> – Holding:**
  - "The use of patented compounds in preclinical studies is protected under §271(e)(1) at least as long as there is a reasonable basis to believe that the compound tested could be the subject of an FDA submission and the experiments will produce the types of information relevant to an IND or NDA."
  - "…§271(e)(1) provides a wide berth for the use of patented drugs in activities related to the federal regulatory process, including uses reasonably related to the development and submission of any information under the FDCA."
  - Made clear that the protection of §271(e)(1):
    - Applies "… even when the patented compounds do not themselves become the subject of an FDA submission"
    - Applies even if the experiments do NOT get included in an ultimate submission
    - Is not limited to the generic drug process

Another Waxman-Hatch Creation – The 505(b)(2) NDA

- Not a completely new product (usually)
- Not a generic
- A product with some differences from a previously approved product
- Approval requires (usually) clinical data, but the studies may have been conducted by others.

How is 505(b)(2) Different?

- The applicant and FDA may rely on prior FDA safety and efficacy determinations, based on studies conducted by someone else even though the applicant does not have a right of reference to the data. 21 U.S.C. § 355(b)(2)
- Safety and efficacy can also be supported by published reports

Types of 505(b)(2) NDAs

- **New Chemical Entity (rarely)**
- **Changes to a Previously Approved Drug**
  - New dosage form, dosing regimen, strength, or route of administration
  - New indication
  - New active ingredient
  - New inactive ingredient that requires studies beyond limited confirmatory studies
  - Rx → OTC switch (Claritin)
- **Duplicates of approved drugs that cannot be approved under an ANDA**

Patent and Exclusivity Issues of 505(b)(2) Applications

- 505(b)(2) NDA must include patent certification(s).
- 505(b)(2) NDA must also *list* any relevant patent(s).
- Same Paragraph IV challenge system as ANDAs, *EXCEPT*, no 180-day exclusivity period.
- A 505(b)(2) product may itself qualify for 3 or 5 years of new drug exclusivity

Part II

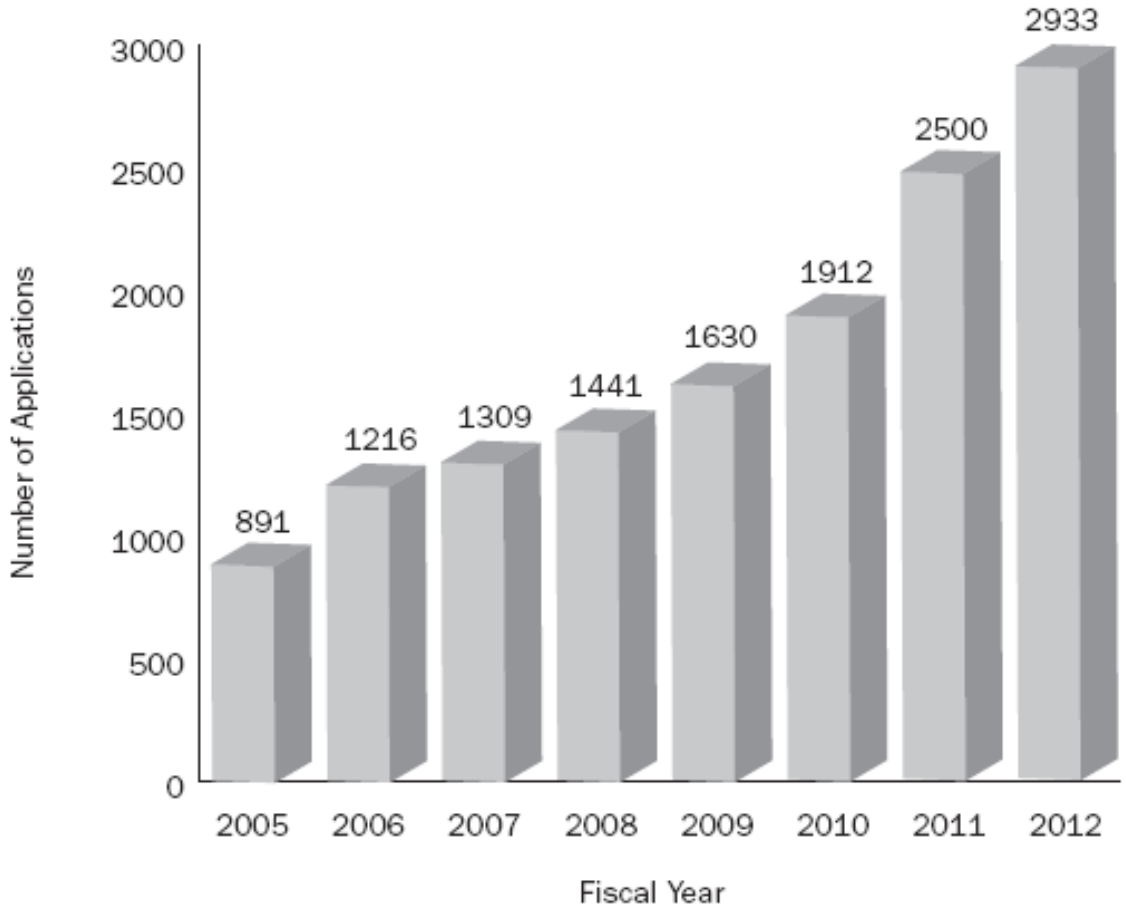
Whence GDUFA – The Backlog

The Backlog Builds

Calendar Year	ANDAs Received	ANDAs Approved
2013	315	194 (5/31)
2012	1059	516
2011	946	461
2010	854	433
2009	794	472
2008	835	480
TOTAL	**4,803**	**2,556**

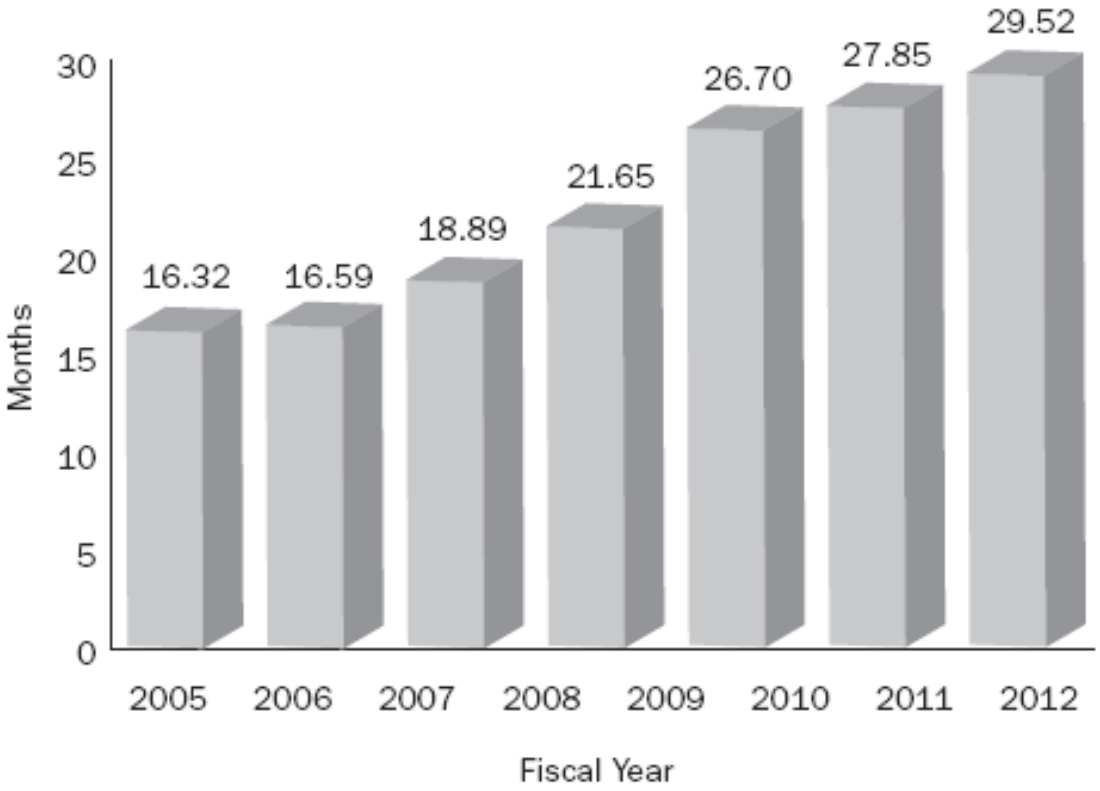
Source: "Update on the Office of Generic Drugs," by Robert Pollock, Senior Advisor and Outside Director, Lachman Consultants, at Orange County Regulatory Affairs Annual Conference, June 13, 2013.

The Backlog – Pending ANDAs



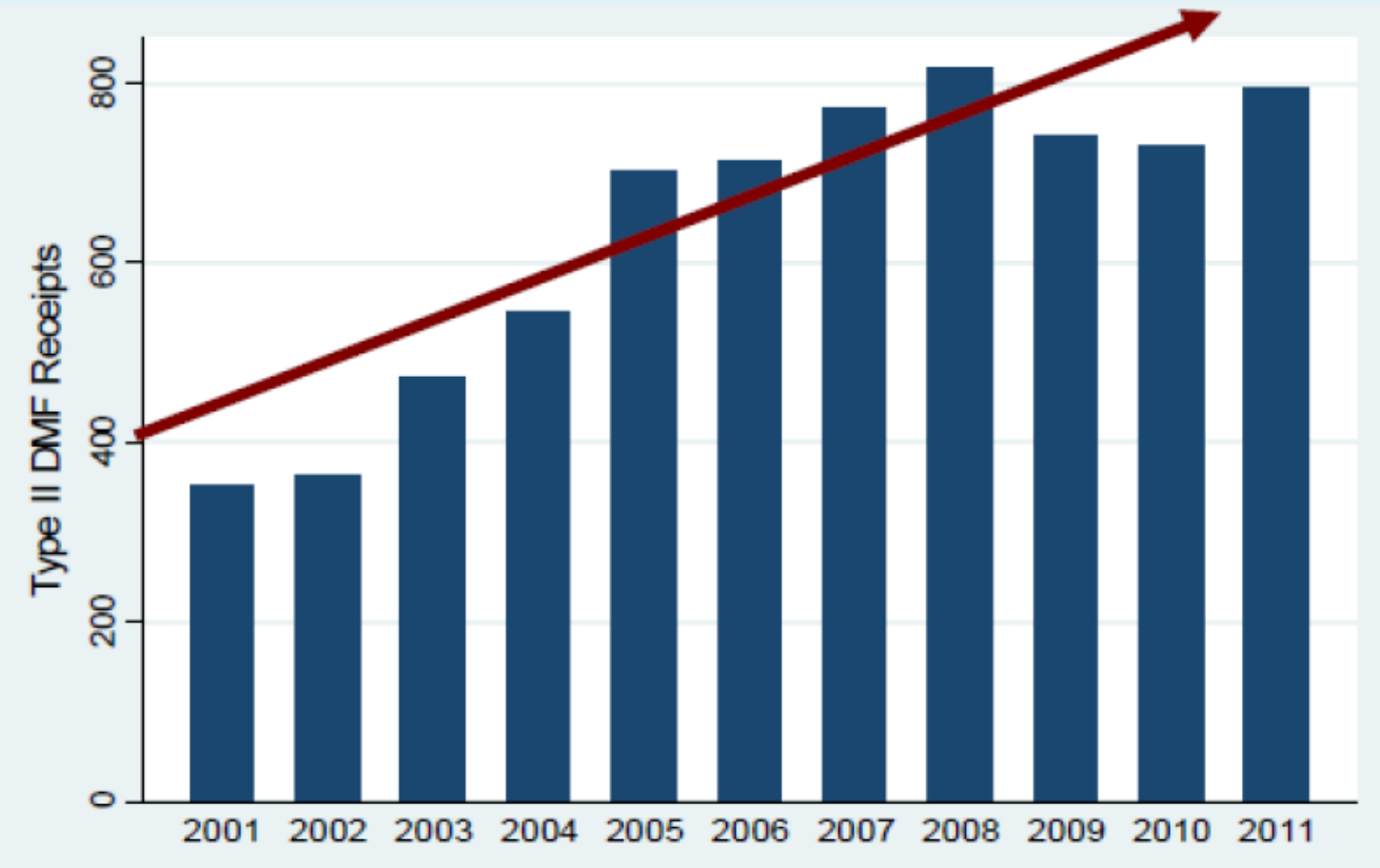
Source: "Generic Drug Submissions," by Michael Swit, in ***Fundamentals of US Regulatory Affairs***, 8th Ed., Chapter 13, Regulatory Affairs Professionals Society. 2013.

The Backlog – Median Approval Times



Source: "Generic Drug Submissions," by Michael Swit, in ***Fundamentals of US Regulatory Affairs***, 8th Ed., Chapter 13, Regulatory Affairs Professionals Society. 2013.

The Backlog – DMF Filings

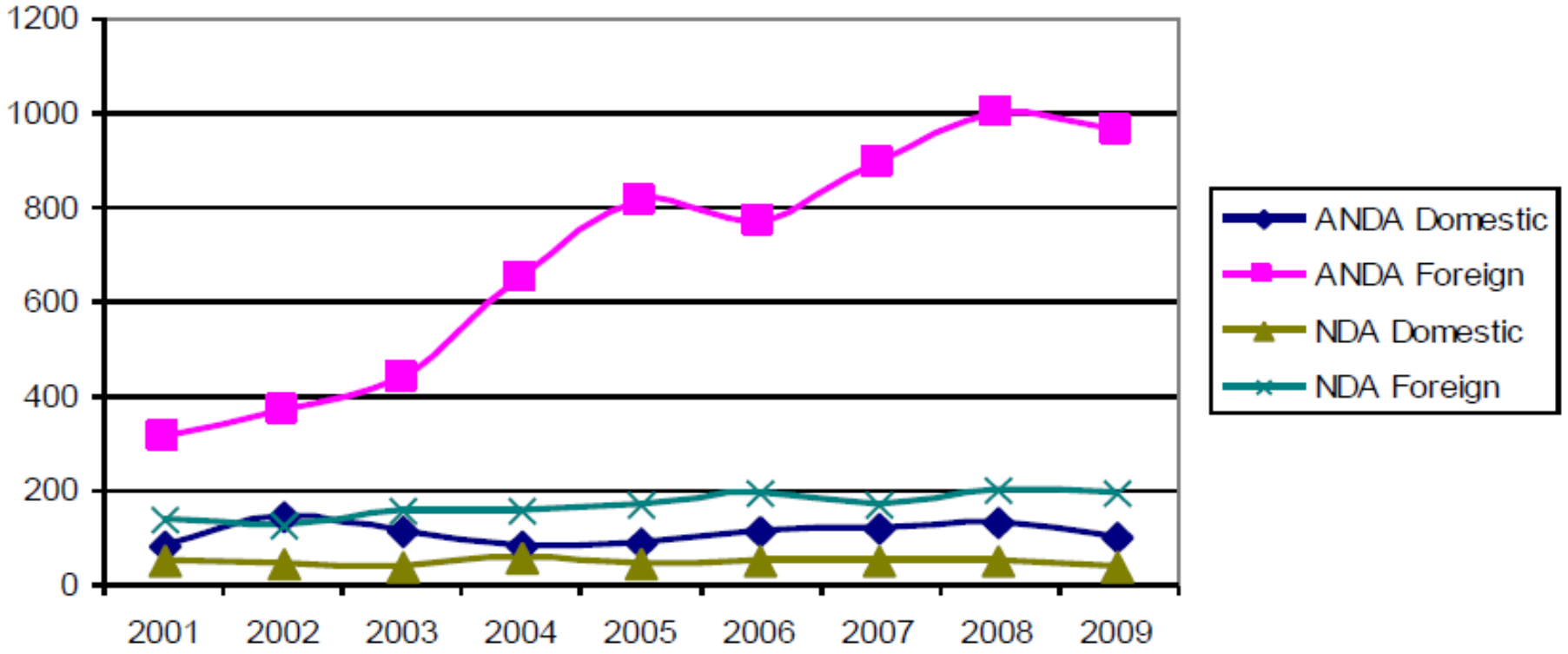


Source: "Overview of GDUFA and Applications Under GDUFA," by Thomas Hinchliffe, Pharm.D., Special Assistant to Director, Office of Generic Drugs, at FDA GDUFA and You Conference, June 12-13, 2013.

Inspections – Finished Dosage Form

Source: "Overview of GDUFA and Applications Under GDUFA," by Thomas Hinchliffe, Pharm.D., Special Assistant to Director, Office of Generic Drugs, at FDA GDUFA and You Conference, June 12-13, 2013.

Inspections -- API



Source: "Overview of GDUFA and Applications Under GDUFA," by Thomas Hinchliffe, Pharm.D., Special Assistant to Director, Office of Generic Drugs, at FDA GDUFA and You Conference, June 12-13, 2013.

GDUFA -- The Solution?

Goals of GDUFA

- **Timely access to generic drugs**
  - faster reviews
  - better guidance
  - greater predictability
- **Maintain affordability of generic drugs**
- **Increase transparency**
  - at FDA
  - within industry -- self-identification
- **Small companies – seen as benefitting via increased certainty and decreased review times**

Goals of GDUFA

- **Ensure industry complies with quality standards –** inspected biennially, on a risk-based approach with domestic and foreign parity
- **Address globalization**
- **Advance regulatory science at FDA**
- **Stabilize financial footing of FDA Generic Drug review program --** increase funding
- **Better Review Management**
- **Better Review Staffing – hiring**
- **Details – in *Commitment Letter*** *(link)*

FDA: Scope, Assumptions & Aspirations

- **Fourteen detailed – some key ones**
  - $299 million/year (inflation adjusted)
  - Number of filings – 750 ANDAs; 750 PAS; 350 newly-referenced DMFs; 2,000 facilities (no major change in number of facilities)
  - FDA to have streamlined hiring authority
  - Basic OGD appropriations will stay at least at 2009 FY levels
  - 2017 – program will be renewed

VII.) FDA will aspire to the extent possible to maintain levels of productivity at least similar to pre-GDUFA levels, while hiring and training incremental staff necessary to achieve the program performance goals, building necessary systems and implementing outlined program changes in years 1 and 2 of the program (see goals for years 3-5 metrics).

FDA: Scope, Assumptions & Aspirations …

- Complete review standard approach; first-cycle deficiency teleconferences; telephone info requests by FDA on easily correctable deficiencies
- If ANDA has only minor admin. amendments pending, FDA will aspire to complete reviews before any patent or exclusivity expiration dates regardless of actual goal dates
- FDA will prioritize inspections involving ANDAs that are otherwise approvable and facilities that have never been inspected before; flexibility in relying on prior inspections
- "Day 1 Para. IV" ANDAs – FDA will try to review within 30 months to avoid possible 180-day exclusivity forfeiture
- Appeals – respond in 30 days; but no formal goal

The User Fees

- **The Four Types**
  - Backlog -- only applies in FY 2013 -- $50 million allocated to it
  - DMF
  - ANDA/Prior Approval Supplement (PAS)
  - Facility
- **How Fees Split -- $299 million per year (infl. adj'd)**
  - ***30% -- submissions***
    - ANDA/PAS -- 24%
    - DMF – 6%
  - ***70% -- from facilities***
    - Finished Dosage Form (FDF) – 56%
    - API – 14%

Backlog Fee – No longer applicable

- **Amount -- $17,434 --** was due on or before November 26, 2012.
- **Eligible ANDAs --** each original ANDA that was pending on October 1, 2012 and that had not been tentatively approved on that date
- **Pending --** any original ANDA that has not been withdrawn, tentatively approved, or approved by September 28, 2012
- **One-time for FY 2013** -- means that the other user fees logically would increase in 2014

ANDA/PAS Fee

- **Amount --** $58,730/$29,370 (FY 2015)
- **Due –** on date of submission of application
- **Failure to pay –** have 20 days from submission date; if not paid, app. will not be received; thus, also not "substantially complete" until fee paid
- **APIs made by ANDA applicant described in an ANDA** – i.e., not subject to a DMF – assessed fee equal to number of APIs and facilities in the ANDA x DMF fee – "***(a)(3)(F) fee***"
- **CBE Supplement** – if rejected by FDA as requiring a PAS, will need to pay PAS fee upon conversion
- **Refund if ANDA not "received"** – 75% -- upon resubmission, have to pay full fee again

Facility Fees

- **Vary per type of facility:**
  - Domestic FDF facility: $247,717
  - Foreign FDF facility: $262,717
  - Domestic API facility: $41,926
  - Foreign API facility: $56,926
    - Note: law allows a $15G to $30G delta between domestic and foreign facility fees
- **"Dual use" facility –** FDF and API – pays two fees
- **Failure to pay –**
  - ANDA based on facility – not received unless paid in 20 days
  - All drugs made in facility deemed misbranded under 502(aa) of FFDCA – added by GDUFA

DMF Fees

- **Amount: $26,720**
- **Covered DMFs --** each person that owns a ***Type II API*** DMF (DMF holder) that is referenced on or after October 1, 2012, in a ***generic drug submission*** by any ***initial*** *(i.e., one time fee)* letter of authorization
- **Generic drug submission --** refers to an ANDA, an amendment to an ANDA, or a PAS to an ANDA.
- **Due** – on date of submission (thus, need to know); ANDA Applicant can pay; if not paid, ANDA "not received"
- **Initial completeness assessment** – required before DMF "available for reference" – ***FDA List*** *(link)* – 1,250 submitted since 10/1/2012 – FDA priority on DMF reviews – those in ANDAs entitled to "expedited review"

Self-Identification

- **Goal –** transparency
- **Annual Process** – by June 1 of federal FY – be submitted, updated or reconfirmed
- **Who must self-identify:**
  - FDF and API makers
  - Other entities identified in generic drug submissions:
    - bioanalytical study sites
    - clinical research organization
    - contract analytical testing labs
    - contract repackager sites

Major Program Targets

- **Application metrics –** Cohort 5 (FY 2017) – FDA to review & act on 90% of submitted ***electronic*** ANDAs within 10 months; DMF metrics also linked to e-DMFs
- **Backlog metrics --** 90% of all ANDA, PAS, and Amendments pending on 10/1/2012 by EOFY 2017 (regardless of type of submission – e-, paper, hybrid)
- **CGMP Inspection metrics** – FDA to conduct "risk-adjusted biennial CGMP surveillance inspection of API and FDF mfrs. with goal of achieving domestic/foreign parity in FY 2017

Major Program Targets

- **Regulatory science** – continue and start R.S. initiatives on 10/1/2012; with additional projects to be identified in conjunction with an industry working group. Some are:
  - Continue developing new bioequivalence methods for orally inhaled, topical dermatological and gastro-intestinal drugs
  - Continue developing science-based recommendations for product development, and post-marketing assessments of generic drug products.
  - Commitment Letter – 13 topics in all
- **Efficiency enhancements –** various detailed in Commitment Letter -- to be implemented on 10/1/2012 – ***some specifics folo …***

Efficiency Enhancement Tactics

- **Complete response letters (CRL) –** to reflect division-level deficiency reviews from all disciplines – ANDAs and DMFs – ***Your reply*** – must also be complete
- **Rolling reviews –** mentioned, but not elaborated on
- **Telephone information requests –** for easily correctable deficiencies in ANDAs and DMFs
- **30-minute First Cycle teleconference meetings –** ANDA applicant or DMF holder can request within 10 business days of getting first cycle CRL – limited to letter
  - no targets for first 2 FY's under GDUFA; then:
    - FY 2015: 200; FY 2016: 250; FY 2017: 300

Efficiency Enhancement Tactics

- **Enhanced Refuse-to-Receive (RTR) Standards –** due by end of FY 2013
- **DMFs –** No Further Comments Letter – after ANDA appr'l
- **Paragraph IV ANDAs –** get expedited review in FY 2013 and 2014 if submitted on NCE-1 Date
  - same for ANDAs that become eligible for approval due to exclusivity or patent expirations, or end of applicable stays
- **Inspections**
  - public database of findings to be developed
  - work on possible reliance on foreign gov't inspections
- **Electronic submissions standards –** to be developed

Other GDUFA Targets

- **Regulatory Science Working group –** to be convened to develop an annual list of initiatives for review by CDER Dir.
- **Hiring**
  - FY 2013 – 25%
  - FY 2014 – 50%
  - FY 2015 – "strive to complete"
- **Original ANDA Cohort Targets** – start Year 3 – FY 2014
  - Year 3 – 60% within 15 months
  - Year 4 – 75% within 15 months
  - Year 5 – 90% within 10 month

Note: similar percentage targets for PAS not needing inspections; but all within 6 months; 10 mos. if inspection needed

Accomplishments – Posted by FDA on 7/9

- **Backlog --** completed scientific review of over 30 percent of backlogged applications
- **Improved quality of communications between FDA and industry during the review process --** including issuing complete response letters reflecting full division-level review of deficiencies from all relevant review disciplines.
- **Conducted completeness assessments for over 900 DMFs**
- **Organized and led a public meeting to discuss regulatory science priorities --** to expand the availability and quality of generic drugs and solicit input from stakeholders.

Accomplishments – FDA -- on 7/9 …

- **Streamlined hiring process --** to recruit new scientific reviewers, project managers, investigators, and support staff. FDA expects to meet its "ambitious year one hiring goal" by bringing on board at least 25 percent of GDUFA hires by October 1.
- **Facilitated development of the most comprehensive list of generic drug industry participants --** more than 2,200 manufacturing and testing facilities submitted self-identification information to FDA -- enhancing quality and transparency of the generics industry.
- **"Unprecedented outreach efforts" --** to educate industry participants and other stakeholders about provisions of the Act.
- **Collected --** over $255 million in first year user fees

The Future?

- **Stay tuned**
- **Some factors impacting OGD speed:**
  - Geba resignation & moving chemistry divisions out of OGD to OPQ – but, when will that occur?
  - Can FDA train fast enough and implement heightened review consistency?
  - OGD – physically to move to White Oak in 2014; DBE just moved near OGD in June
- **For more FDA information, main FDA GDUFA webpage is at:**

  http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

PART III – Power

Protecting and Preserving A Drug Franchise Under Waxman-Hatch – Exclusivity and the 30-month Stay

Market Protections Available

- **Patents (and extensions)**
  - Traditional enforcement
  - Listing patents in FDA's "Orange Book"
- **Statutory exclusivities/extensions under Waxman-Hatch**
- **Other strategies**

Listing Patents in FDA's "Orange Book"

- Requires patent certification by generic competitors
- If approval sought pre-expiration, generic must notify sponsor of bases for alleged invalidity or non-infringement.
- Sponsor may sue for infringement and impose 30-month stay of generic approval.

Statutory Exclusivities Under Waxman-Hatch

- **New Chemical Entity (NCE) Exclusivity**
  - Prohibits the *filing* of an ANDA (or 505(b)(2) NDA) for a product that contains the NCE for 5 years after approval of the first NDA.
    - (4 years if ANDA includes a Paragraph IV challenge to listed patent)
  - NCE: "a drug that contains no active moiety that has been approved by FDA in any other [NDA]."

Statutory Exclusivities …

- **3-Year Exclusivity**
  - Available for NDAs which contain:
    - Reports of "new" "clinical trials"
    - That were "essential to approval" of the NDA
    - Conducted or sponsored by the applicant
  - FDA may not ***approve*** (but can submit) an ANDA or 505(b)(2) NDA for 3 years after approval
  - Applies for new indications, Rx → OTC switch, new dosing regimen, and some other labeling changes.

Statutory Exclusivities -- Other

- **Orphan Drug Exclusivity**
  - 7 year exclusivity
  - Drugs for rare conditions (<200,000 people in U.S.)
- **Pediatric Exclusivity**
  - 6-month extension of existing patent or Waxman-Hatch exclusivity
- **180-day generic (ANDA) exclusivity**

Patent and Exclusivity Issues

- **Waxman-Hatch Exclusivities block ANDAs and 505(b)(2) NDAs, but cannot block a "full" NDA.**
- **3-year exclusivity blocks other pending 505(b)(2)s, regardless of filing date; creates race to approval.**
  - Only the first 505(b)(2) for a change can receive exclusivity. Studies for later applications deemed not essential for approval – because an ANDA would be possible
- **5-year exclusivity does not block other 505(b)(2)s that were filed before first approval.**

"180-Day" or "ANDA" Exclusivity

- **Basics:**
  - First person to file an ANDA with a Paragraph IV certification gets 180 days during which no other ANDA can be approved for that drug
  - Must either (a) not be sued by brand co. in 45-day period or (b) prevail in litigation (or get favorable settlement)
  - 180 days starts from earlier of:
    - Date of first commercial marketing (changed in 2003; used to peg to a court decision as well)

"180-Day" or "ANDA" Exclusivity

- **Advantage –** ideally, incentive to pick apart patents, thus getting generics to market earlier
- **Problems:**
  - Complicated by FDA interpretations later ruled wrong by courts – e.g., must be sued to get it
  - Subject to abuse -- if first to file (and, thus, eligible for ANDA Exclusivity) stays off market, but there is no court decision (e.g., via settlement with brand name) –means no other generic can get approved as 180-day period is never triggered – *addressed by 2003 legislation*

Anti-Generic Strategies

- **Patent listing, litigation**
  - Development of follow-on/ancillary patents
    - Strategy now impacted by Title XI – Access to Affordable Pharmaceuticals Act – part of 2003 Medicare Reform
- **Amendments seeking 3-year exclusivity**
  - New indication for original product (limited utility)
  - Changed dosage form
  - New dosing regimen
  - New strength(s)

Part IV– Regulatory and Statutory Solutions to Power Problems

A. FDA June 18, 2003 Final Rule

B. Title XI of The Medicare Improvement Act of 2003 -- *ACCESS TO AFFORDABLE PHARMACEUTICALS ACT*

FDA 30-Month Rule

- **No need to give notice to a patent that claims a use for which ANDA applicant is *not* seeking approval**
- **More specifically defines those patents that should be listed by brand name companies**
  - Drug substance – must be same as that which is subject to a pending or approved NDA

FDA 30-Month Rule

- Drug product patents – must be subject to a pending or approved NDA
- Method of Use patents – only those indications or "conditions of use" that are in a pending or approved NDA

- **"Patent Declaration" required by brand names relative to patents to be listed**

FDA Rule -- Orange Book Listing

- Patents that "claim the drug for which the application was approved," or
- Patents that claim an approved method of use,
- Must be submitted to FDA within 30 days of NDA approval, or 30-days of issuance (if issued post-approval)

FDA Rule -- 30-Month Stay Limitation

- **The 30-month stay of Paragraph IV ANDA approval may only be imposed with respect to patents listed at time of initial NDA approval, not post-approval patents –** *designed to preclude multiple certifications by generic applicants – i.e. "EVERGREENING" by the brand name co.*

FDA Rule -- Claim-by-Claim ¶-IV Certifications

- **For patents that**
  - Include both product claim and method of use claim(s), or
  - Contain multiple method of use claims,
- **Paragraph IV Certifications and "viii statements" must be claim-specific.**

Title XI -- *ACCESS TO AFFORDABLE PHARMACEUTICALS ACT*

Title XI of Public Law 108-173

H.R. 1

Medicare Prescription Drug, Improvement and Modernization Act of 2003

Title XI – What It Does

- **A number of very substantive and technical changes to the ANDA statutory regime**
- **Key provisions:**
  - Statutorily implements **"single 30-month stay"** rule
  - **Lifting 30-month stay** – makes clear that a court decision is of "district court" – not just one that could not be appealed

Title XI – What It Does

- **Key provisions:**
  - **Declaratory judgment** action by ANDA applicant – have to wait until 45-day period over and not sued
  - **"Delisting" Counterclaim to Infringement Action --** [505(j)(5)(C)(ii)]
    - Not an independent cause of action
  - **180-day Exclusivity**
    - Can be forfeited
    - Pegged solely to commercial marketing – thus, implicitly allow "authorized generics" – by any "first applicant"

The Future is Here – "Biosimilars!"

- **Previously – no legal mechanism can be used to support approval of a "generic" biologic**
- **Why?**
  - Legally, biologics licensed under Public Health Service Act, not Waxman-Hatch
  - Difficulty in characterization

“Generic” “Biologics”

"One cannot completely characterize the biological product and that in itself is an issue, and quite frankly with biological products you really don’t have a homogeneous product, you have a defined range of biological components for which you find consistency in a particular clinical outcome. The challenges of analytical technology are still very great for characterizing biologics."

-- Katherine Zoon, CBER

Biosimilars Under 505(b)(2)

- **For Biologics originally approved under an NDA, FDA will accept a 505(b)(2) for a generic or biosimilar version**
  - Examples include naturally-derived active ingredients (from animal or botanical sources) or those derived from recombinant technology (e.g., insulin, HGH)
  - None have a TE rating
  - Lovenox® – (LMWH) -- approved in July 2010 and arguably a biologic – approved as an ANDA
- **For BLA-approved products, no "generic" or abbreviated approval pathway existed**

The 2010 Law

- **Creates an "abbreviated" pathway for Biosimilars**
- **"Biosimilar" defined**
  - that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
  - there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.
  - ***Contrast to small molecule*** – ANDA – drug must be same
  - ***Reason*** – so difficult to characterize and process

Basics

- **To show biosimilarity, application must contain:**
  - analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
  - animal studies (including the assessment of toxicity); and
  - a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.
- **FDA can waive any of those**

Basics …

- **The biological product and reference product must utilize the *same mechanism or mechanisms of action* for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product;**
- **The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product;**

Basics …

- The route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product
- The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.

Interchangeability

- **Not required, but allowed**
  - The term ***'interchangeable'*** or ***'interchangeability,'*** in reference to a biological product -- means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.
- **However, to prove interchangeability, FDA has said:**
  - To establish that two protein products would be therapeutically equivalent (interchangeable), a sponsor of the follow-on protein product would need to demonstrate, among other things that repeated switches from the follow-on protein product to the referenced product, and vice versa, would have no negative effect on the safety and effectiveness of the products.

Exclusivity

- **Innovator –12 years from date of first licensure**
  - Retroactive – captures BLAs approved before statute's enactment in March 2010
  - Can also qualify for pediatric exclusivity extension
  - First four years – abbreviated app. can NOT be submitted

Exclusivity …

- **First Interchangeable Biosimilar**
  - Applicant gets period of time where no other interchangeable for same Reference Product (i.e., innovator) can be approved
  - Length varies depending on a variety of factors; earliest of:
    - One year of first commercial marketing
    - 18 months of favorable final court decision in patent litigation
    - 42 months of approval if First Interchangeable tied up in patent litigation
    - 18 months of First Interchangeable if no law suit

Until late last month …

- No 351(k) BLA had been filed.
- Sandoz/Novartis – announced on July 24 -- had submitted for a biosimilar version of filgrastim – Amgen's Neupogen®

OVER-THE-COUNTER -- "OTC" -- DRUGS

OTC's – Three Routes

- **OTC Review – monograph system**
  - Covers bulk of marketed OTCs
  - Lacks exclusivity
- **Rx – OTC Switches**
  - May enjoy patent protection
  - May enjoy Waxman-Hatch Exclusivity
    - Yes – most
    - No -- Minoxidil
- **Direct-to-OTC**
  - Very, very rare
  - Only ones I know are both local –
    - Avanir's *Abreva®;*
    - SalonPas® -- Hisamatsu

Why Switch?

- **Preserve franchise in face of impending generic competition on the Rx**
- **Boost sales**
- **<u>Downside</u>**
  - Usually not reimbursed by insurance

OTC's – Key Issues

- ***Wellpoint Petition*** **– sought to "force" Claritin OTC**
- **Will FDA file its own petitions?**
- ***T.E.A. Rule*** **– foreign data can now be used to support an OTC Switch**
- **What studies are sufficient to support Waxman-Hatch Exclusivity?**
  - Make sure they're essential – Minoxidil
  - More than one similar product can get exclusivity

FDA – Reassessing OTC Process

- Held a public hearing in March 2014 to "improve the current OTC monograph process"
- Stay tuned – too early to tell where this is going
- For more info:

  http://www.fda.gov/drugs/newsevents/ucm380446.htm

ORPHAN DRUGS

ADOPTING ORPHANS – The Orphan Drug Act

- **Enacted –** 1983
- **Goal** -- create incentives for pharmaceutical companies to adopt "orphan" drugs for uses for rare disorders.
- **"Orphan"** -- many drugs were known as potentially effective for rare diseases, but had been orphaned -- abandoned for developmental purposes -- by the pharmaceutical industry due lack of profitability associated with small patient population (aka "buyers")

Orphans . . .

- **Orphan Drug Act -- created four key incentives to facilitate drug development for rare diseases:**
  - ***Seven years marketing exclusivity*** during which time no other company can secure approval for the same drug for the orphan indication
  - ***Protocol assistance***
  - ***Tax credits***
  - ***Research Grants***

How Does a Drug Become an Adoptable Orphan?

- **To qualify for benefits under the Orphan Drug Act, a drug must serve a patient population:**
  - < 200,000 people in the United States or
  - if > 200,000, orphan drug applicant must show it cannot reasonably recoup its commercial investment in the research and development of the product –
    - *rarely used (to the best of my knowledge, never been used).*
- **Key question for orphan drug status is patient population --**
  - the indication sought must be "medically plausible"
  - not just a "salami sliced" indication of a greater patient population that might be otherwise over 200,000.

Orphan Designation

- **To get orphan drug benefits, a sponsor must apply for orphan drug designation.**
- **Process -- sponsor-specific**
- **21 CFR 316.20 requires that, among other things, the sponsor show:**
  - patient population proposed -- less than 200,000 people per year.
  - is a confidential process with the designation application not being one subject to public disclosure until after it is approved, if it is approved.
- **Once approved, the designation will appear in a quarterly cumulative list that the Agency publishes and makes available on its website.**
- **Several guidances available**

Designation Issues – or Can Identical Twins Be Adopted by Two Different Families?

- **Clinical superiority –** FDA may regard – for Orphan Drug Act purposes -- as different, drugs that are chemically the same and identically labeled if the second drug is clinically superior to the first drug.
  - Skirts Orphan Drug Act's restrictions on approving same drug by ruling second drug is clinically superior and, therefore, essentially is not the same drug as that one which enjoys exclusivity.
- ***"Molecular differentiation"*** (my term) -- in other cases, FDA has gone to some length to differentiate a product on the basis of how its molecular structure differs from an approved orphan drug.

Recent Designation Issue

- **Orphan Indications where drug also can treat non-rare condition:**
  - FDA will no longer approve as an orphan – even if there is a unique rare disease – if the drug also would be effective against a very similar indication that is not rare

You have requested orphan designation status for in the treatment of related Vitamin deficiency. While it is medically plausible that might be useful in that condition, you have not provided a rationale for limiting therapy to that population; indeed you have provided us with information that demonstrates appropriate use of in persons with certain hematologic illnesses. In order to meet the prevalence criterion for Orphan Drug designation, you will have to make an argument to show that the population of persons with vitamin deficiency from any cause is fewer than 200,000 persons in the USA.

Timing Considerations

- **When viewed relative to ODA exclusivity provisions, timing of designation process is KEY…**
  - Remember -- process is confidential until drug designated; then published in FED REG.
- **Consider not seeking the OD designation until you have done one or more of the following:**
  - Confirmed the stability of your proposed formulation;
  - Validated that the formulation can be produced on a commercial scale-up basis; or
  - Filed to study the product pursuant to an IND.
- **Why – once in FED REG, anyone else can seek same OD Designation and then … you have the race to approval … to get …** ➲➲➲➲

Orphan Drug Exclusivity

- Protects the orphan drug for the orphan indication
- 7 years
- Good thing – can't "remake wheel" (distinguish Waxman-Hatch exclusivity which does not bar a full NDA for a drug with W-H exclusivity)
- Beware – less incentive to study approved drugs for orphan uses – generics may come in and be used off-label

Tax Credits

- Only helpful to a company that is actually enjoying taxable income that needs to be offset.
- For startups, this may not occur any time in the short term when the needs of the tax cut might be most useful.
- See a tax professional -- may be able to give you more advice as to whether any losses can be carried forward and for how long so as to be able to take advantage of the tax cut provisions
- Most observers -- low utility

Protocol Assistance

- Orphan Drug sponsors are as eligible for significant additional assistance from FDA in the design of its clinical study protocols (caveat: nature of that aid is not stated very clearly anywhere)
- LINK any assistance to a clear *written* agreement with the Agency as to the nature of the clinical studies to be performed

Research Grants

- Awarded by FDA to qualified applicants pursuant to criteria being articulated by the Agency.
- While the grants can be somewhat substantial, they are dependent upon the Agency receiving appropriate funding by Congress for the grants.
- Fairly constant struggle for FDA -- historically the gross amount of grants available in a single year rarely exceeds $2 million and individual grants normally range from $50,000 to $200,000.
- Qualifying for a grant involves a number of hurdles

COSMETICS

Definition

- **Dictionary:**
  - [a toiletry designed to beautify the body
  - [adj] serving an aesthetic purpose in beautifying the body; "cosmetic surgery"; "enhansive makeup"
  - [adj] serving an esthetic rather than a useful purpose; "cosmetic fenders on cars"

Source: **hyperdictionary.** *http://www.hyperdictionary.com/dictionary/cosmetic*

Definition

- **Federal Food, Drug, and Cosmetic Act:**

  (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap.

  [Section 201(i)]

Definition - Case Law

- "Old days": many of today's claims might be unapproved new drug claims
  - ***Sudden Change (1969)* –**
    - Product: lotion of bovine albumen & distilled water
    - Label/Ad Claim: "Face Life without Surgery"
    - Decision: while some may say is puffery, this implies will "affect the structure … of the body" = DRUG
  - ***Line Away* (1969) –**
    - Product: lotion of bovine albumen & distilled water
    - Label/Ad Claim: made in a "pharmaceutical laboratory" under "aseptic conditions" and was for "discouraging new wrinkles from forming"
    - Decision: claims strongly reinforce this is a therapeutic product = DRUG
  - ***Magic Secret (1971)***
    - Product: wrinkle remover
    - Label/Ad Claim: "pure protein" that causes an "astringent sensation"
    - Decision: did not rise to the level of *Sudden Change* = COSMETIC

Definition - Case Law

- **Recent years: not much overt regulatory activity**
- **One recent example – January 2004 – *University Medical Products* – got Warning Letter from L.A. District Office**
  - ***Products:*** FACE LIFT Collagen 5 products, including Cell Regeneration Cream, Intensive Wrinkle Reducing Cream, and Intensive Lifting Complex; FACE LIFT Daytime Advanced Retinol-A, Nighttime Advanced Retinol-A, Advanced Under Eye Therapy, Vitamin C Anti-Wrinkle Patch, and Overnight Moisturizer; and BODY LIFT Anti-Cellulite Thigh Cream, Weight Reducing Cream, and Anti-Water Retention Lotion
  - ***Alleged Objectionable Claims*:** Cell Regeneration Cream (red text) and Anti-Cellulite Thigh Cream (blue text)
    - Helps boost collagen production
    - Reduces deep wrinkles up to 70%
    - Visibly Reduces Deep Wrinkles plus Fine Lines
    - Significantly Reduces...Thigh Circumference
    - Stimulate the beta receptors in cells to release stored fat.
    - Clinically proven to...reduce thigh circumference.
  - ***Status*** – not sure

What do you think …?

- ***Repairwear Intensive Night Lotion***
  - *Claim:* Block and mend fine lines and wrinkles at night; build natural collagen and replenish antioxidants.

vs.

- ***Anti-Gravity Firming Eye Lift Cream***
  - *Claim:* Densely hydrating cream lifts, brightens, and firms around the eyes. Helps erase the look of lines.

Regulatory Regime

- **Limited Duties –** see regulations – next slide and FDA Cosmetics webpage --
  http://www.cfsan.fda.gov/~dms/cos-toc.html
- **Cosmetics regulation is based in FDA's Foods Center –** *Office of Cosmetics and* ***Colors***
- **No preclearance – except color additives**
- **GMPS – no mandatory – Guidelines --**
  http://www.cfsan.fda.gov/~dms/cos-gmp.html
- **Listing – voluntary**
- **Registration -- voluntary**
- **Adverse events -- voluntary**

FDA Regulations Impacting Cosmetics

- 21 CFR Part 1 General enforcement regulations
- 21 CFR Part 2 General administrative rulings and decisions
- 21 CFR Part 20 Public information
- 21 CFR Part 250 Section 250.250 Requirements for drugs and cosmetics -- hexachlorophene
- 21 CFR Part 700 Subpart A (Section 700.3) Cosmetics -- General provisions
- 21 CFR Part 700 Subpart B (Sections 700.11 through 700.35) Requirements for specific cosmetic products
- 21 CFR Part 701 Subpart A (Sections 701.1 through 701.9) Cosmetic labeling -- General provisions
- 21 CFR Part 701 Subpart B (Sections 701.10 through 701.19) Package form
- 21 CFR Part 701 Subpart C (Sections 701.20 through 701.30) Labeling of specific ingredients
- 21 CFR Part 710 Voluntary registration of cosmetic product establishments
- 21 CFR Part 720 Voluntary filing of cosmetic product ingredient and cosmetic raw material composition statements
- 21 CFR Part 740 Cosmetic product warning statements

Additional Cosmetics Glosses

- **"Cosmeceutical"** – no such creature under FDA law or regulation; if a product is both a drug and a cosmetic, must meet both
- **Imported products** – must meet all rules – e.g., Dial® Soap – import alert on foreign-made Dial® due to unapproved colors

Questions?

- ***Call, e-mail or fax:***

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