Compounded Prescription Drugs: Liability Issues for Healthcare Professionals
Bruce Patsner, M.D., J.D.

Objectives
- To educate everyone about the history of how compounded drugs are regulated
- To review types of general liability issues for physicians, nurses, physician assistants (and compounders) who prescribe drugs, medical devices, and vaccines in general
- To review some specific risk management concerns arising from compounded bio-identical hormone drug therapy

Current Perspective
- October 2012 – New England Compounding Center meningitis disaster: 63 deaths, 749 illnesses, >10,000 patients exposed
- For the last year, the safety and regulation of the compounding pharmacy “industry” has been news
- What has changed since 1996? A little history..

Brief Overview of Compounding Regulation
- 1996 – FDA Commissioner D. Kessler comments on the growing “shadow” industry w/o regulation
- 1997 – FDAMA gives FDA clearer authority to treat them as drugmakers
- 2001 - meningitis deaths from compounded drug pharmacies in Calif and So Carolina
- 2002 - WLF case strikes down ENTIRE statute re: compounding on 1st Amendment groups
- A decade of FDA issues compliance “guidelines” for an industry that could ignore them, and explosive growth in BHRT following WHI
- 2012…the states step up to regulate – how????

An aside
David Kessler, MD, JD
Former FDA Commissioner who in his brief tenure took on...at the same time....
1. The tobacco industry
2. The dietary supplement industry
3. The Pharmacy Compounding industry!
So what's changed?

- More publicity about bad outcomes and risks of compounded prescription drugs
- More litigation at the state level since FDA is clearly doing very little – limited resources, fear over litigation. GAO Report confirms this
- More risks for compounders for sure
- More risks for physicians? Maybe... I’m not sure use of these medications can decrease any liability risks for physicians

GAO Report on August 7 2013

- Government Accountability Office
- Investigatory arm for Congress, though what Congress will do with the info is anyone’s guess...politics
- FDA lacks clear authority and necessary (inspection) resources and data to oversee large-scale drug compounding facilities

Basic Claims Which Can Be Made for Any Product

- Strict Liability Claim against manufacturer – dangerous product in design or production
- Medical negligence
- wrong product prescribed, or wrong dose
- Failure to warn – about side effects
- Failure to offer alternative therapy

What would you have to warn about to get real informed consent for...

- Any prescription drug
- Any vaccine
- Any implantable or prescription medical device

Another way of thinking about this is...

- What’s the physician expected to know? From a legal point of view*....
  1. Everything in the label for the drug, device, vaccine?
  2. The current medical literature?
  3. Clinical guidelines (from ACOG etc.) on the standard of care
  4. special issues arising in the news...example rely tampons and toxic shock
  5. *what you might expect to be asked at trial if you were sued over BHRT and e.g. breast cancer

What do you have to tell the patient if you are a...

- Physician counseling/prescribing?
- PA or RN counseling/prescribing (depending on the state you’re in)?
- A prescription drug compounder?

- The bigger question: with Commercial v Compounding Prescription drugs whose job is it to warn about possible adverse events and safety concerns??
**Possible things to talk to patients about re: BHRT**
- Does it work? Well, yes they do.
- Do they work better? Well..... does it matter if there’s no medical evidence so long at patients state they feel better on BHRT (a PRO)
- Are they safe?
- Are they safer?
- How are they made? How well?

**Unique liability concerns are present for every medical product**
- Prescription commercial drugs or their alternatives such as compounded drugs or CAMs
- Restricted or prescription Medical devices e.g. vaginal mesh
- Vaccines
- Unique biologics e.g. stem cell treatments, gene therapies, “experimental” surgeries – eg fetal

**Unique liability issues for Rx drugs**
- The risk that the label might not be considered adequate in instructions, warnings, etc despite it appearing to be bullet proof to the doc – Wyeth v Levine case as an example
- Off label use – company limited in information is can give to physicians

**The learned intermediary doctrine**
- In 49/50 states shields pharmaceutical industry manufacturers of prescription drugs from failure to adequately warn claims in the label*
- This does not shield you if you are a compounding pharmacy b/c no standard label
- The onus of responsibility is on mds
- *more complicated by the recent US Supreme Court Wyeth v Levine case

**This is one reason why the label is so critical**
- With commercial HRT drugs there is class labeling and the info content as well as warnings are standardized..
- This is a huge advantage for both physicians and patients
- Compounded prescription drugs are made, prescribed, and promoted in the shadow of all of this but the liability for the prescriber is greater

**Unique liability issues for medical devices**
- Lack of long-term safety data
- Limited to none efficacy data depending on route of FDA approval
- Limited to no comparative data to either other devices or older approaches
- “indication” creep
- Lack of a PDR, a label
Unique liability issues for vaccines
- Problems with manufacturing facility
- Problems with potency or super-potency
- May cause the disease
- Surrogate markers (e.g. Gardisil) with no proof of efficacy

Unique liability issues for health profession for compounded BHRT
- No label
- No standardized manufacturing process
- No comparative data, and rarely if ever have met efficacy and safety standards for comparable drugs as in FDA Guidance documents
- False promotional claims
- Lots of bad press and lawsuits now
- Use of expensive lab tests to “tailor” therapy – not often covered

The Problem of the Rx drug Label
- Physicians expected to know what’s in the label, so it’s a double-edged sword – liability for docs, but also valuable info for patients (handing pts a copy of the label won’t help you
- For menopausal commercial drugs there is “class” labeling

The problem of drug safety
- Cancer risks for HRT – endometrium for unopposed estrogen; increased risk of breast cancer for some progesterone products
- True for endogenous and well as manufactured commercial drugs...so how could something identical have less risk???
- But, we normally don’t collect data

FDA and Industry
- Each keep databases
- AE reporting for drugs in the US is voluntary, unlike in England, so the data isn’t as good
- AE recording and evaluation for pharmaceutical companies is required, and a “mini-industry”
- No such equivalent for compounding pharmacies or compounding docs

Importance of the Dietary Supplement (D.S.) Issue
- The absolute low-point for FDA in terms of its ability to regulate a class of products
- A high-point for grassroots political activism: the most mobilized, organized, and sensationalized in modern legislative history
- A classic example of how big medical policy decisions will become politicized and how data is “managed” or viewed by Congress for “promotion of health”
- U.S. consumers the big winners and the big losers
- The classic study for battle lines being drawn for decades with no end in sight.
**History of Dietary Supplements**
- Started with cod liver oil – diets in the U.S. in the 19th century really needed vitamin supplementation: scurvy, beriberi, rickets
- A vigorous industry: during Depression 1929–1939 retail vitamin sales rose from $32 million to $83 million
- 1938: FD&C Act authorizes FDA in section 403(j) to promulgate regulations governing the labeling of “vitamin, mineral, and other dietary properties of food represented for special dietary uses.”
- 1962: labeling of foods for special diet uses is “confusing”
- Vitamin-Mineral Amendments of 1976 defines “special dietary use” to supplement diet
- The term Dietary Supplement is not really defined until the Dietary Supplement Health and Education Act (DSHEA) of 1994
- Enacts new provisions specific to this subcategory of food

**Facts About Dietary Supplement Industry**
- It’s a $20 billion+/year industry
- Based in Utah, New Mexico and New Jersey
- Less regulated than anything else FDA is concerned with. Fighting for >50 years
- More than half of Americans use these products
- 75,000 distinct labels/products, all exempt from safety, efficacy, labeling requirements
- Enormous political power with friends on both sides of the aisle. Hillary Clinton talked openly about the importance of these products for health
- Medical profession slow to recognize their dangers but clearly does so now, and this more than FDA poses a potential problem for the D.S. industry
- Internet has greatly increased reach of products

**Regulatory Classification of a Product Matters**
- Different regulatory requirements
- Different substantiation of efficacy
- Different safety considerations
- Different marketing and advertising approach
- Different manufacturing approach
- Different legal challenges from FDA
- FDA wants to regulate some as drugs; industry wants to keep all as food is the bottom line

**Before DSHEA**
- Dietary supplements regulated as food or drugs depending on intended use and how they were labeled
- Drugs and food additives have pre-market approval requirements as result of 1938 FD&C Act

**Dietary Supplement Health and Education Act (DSHEA)**
- Passed in 1984
- FDA made it worse than it had to be because of Commissioner’s overt hostility, attitude, and tone-deafness to the politics of if. FDA animosity. Teaching point: calling Senators “stupid” doesn’t work unless you want to be the Lone Ranger
- Serious question as to whether the statute went too far
- Every dietary supplement store in the U.S. put up banners telling people government was going to take their vitamins
- 1983: more letters to Congress in one year than in 8 years of the Vietnam War
- A LONG tradition of these products and medical practices they reflect in the U.S. for “promotion of health”
- DSHEA reaffirms the status of D.S. as FOODS, but also as a distinct category unto itself
- A dietary supplement must be intended for ingestion

**Dietary Supplements: DSHEA Definition**
- Product Intended to supplement the diet that bears or contains
- one or more of the following dietary ingredients:
  1. A vitamin, a mineral, an amino acid, an herb or other botanical (not tobacco); a “dietary substance” for use by man to supplement the diet by increasing the total dietary intake; or
  2. Concentrate, metabolite, constituent, extract, or combination of any of above
Dietary Supplements under DSHEA

- A product that is:
  - ingested in a tablet, capsule, liquid, powder, gel-cap, softgel
  - not represented as conventional food
  - not represented as sole item of meal
  - not represented as a total diet
  - labeled as a dietary supplement

The problem with D.S.

- Includes not just old, agreed-upon supplements such as vitamins and minerals viewed as essential by mainstream nutritionists, such as Vitamin A or iron, but
- Other substances FDA personnel often regard as being of either dubious value or useless — rutin, bio-flavinoids, herbs, shark cartilage
- The expanded definition of a D.S. under DSHEA now applies to a wider class of products which include many which FDA nutritionists regard as having NO nutritional value, and some of which might be flat-out harmful

D.S. under DSHEA: Exclusions

- Does not include articles that are:
  1. Approved new drugs, antibiotics or biologics
  2. Authorized investigational new drug, antibiotic, or biologic
- UNLESS first marketed as a dietary supplement
- For INDs authorized, "substantial clinical studies" have been initiated, and "existence...has been made public"

Some side issues re: definition

- P263: text correctly points out how expansive the definition of D.S. is
- Street drug alternatives are not dietary supplements because not intended to supplement the diet
- Vitamin B-12 to be applied inside the nose (p.264) does not qualify because it’s not ingested
- If it was the subject of a previous IND, NDA or BLA prior to its marketing as a D.S. it won’t fly

DSHEA: other provisions

- Manufacturers must inform FDA when they use new dietary ingredients that are vitamins, minerals, herbs, etc.
- Manufacturers do not have to register with FDA
- Manufacturer bears sole responsibility for ensuring that its products contain the ingredients listed on the label. But who checks this anyway? Consumers groups
- No GMP requirements. ? A chance after ephedra

Issues

- Safety: Is the D.S. safe, useless, possibly unsafe, or dangerous?
- This can be true even if the product is not adulterated with lead, etc. Sometimes they actually do have Rx drugs in them (e.g. “male enhancement” products sometimes do have Viagra in them (and for once they are cheaper!)
- Claims: Deceptive marketing practices – pushing the envelope re: claims
V.E. Irons, Inc. v. U.S. 244 F. 2d 34 (1st Circuit 1957)

- text p. 246
- A deceptive marketing practices case that illustrates the problem FDA had with D.S.
- Vit-Ra-Tox introduced into interstate commerce. Claiming special curative powers.
- FDA uses overlapping defs of drug and food to attack products marketed to prevent nutritional deficiencies and other diseases. The next case concerns misbranding of a food product: the label is misleading
- It's easy when they claim every disease is due to a nutritional deficiency one product can treat

Regulation of D.S. under DSHEA

- Caused substantial changes in the way FDA could regulate these products
  1. Creation of a broad, new definition of what a dietary supplement is
  2. Moderation of the regulatory burdens for use of dietary ingredients in dietary supplements, changing both the safety standard for use of an ingredient and the regulatory procedure from one of FDA pre-marketing clearance to one of post-marketing FDA policing
  3. Permitting additional promotional use of information about the nutritional benefits of dietary supplements, both through the use of “statements of nutritional support” on labels or in other labeling, and by enabling sellers to refer customers to books, articles, and other publications that provide health-related information

The new safety standard

- DSHEA replaced the voided food additive provisions with some new safety standards in 2 distinct scenarios:
- In general, DSEHA provides that a D.S. will be deemed to be adulterated if it "presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling under ordinary conditions of use"
- FDA bears the burden of proof

Adulteration

- For a "new dietary ingredient" (those first marketed on or after October 15, 1994), a dietary supplement may be found to be adulterated if it is shown that "there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury."
- It helps FDA's case when young people have died allegedly because of use of a product. Even better if they're athletes

Result of new safety standard

- The FDA-asserted "food additive" requirement for agency pre-clearance of D.S. not believed to be generally regarded as safe (GRAS) have been deleted
- Secretary of HHS HAS been granted substantial police authority to stop immediate distribution of a D.S. if government personnel believe that the D.S. poses "an imminent hazard to public health or safety." Can't be delegated to FDA
- But, there must be an immediate formal hearing at which FDA must present data to "affirm or withdraw the declaration." This is an on-the-record rulemaking proceeding to show that a D.S. is adulterated.

D.S Safety post-DSHEA

- No pre-market registration, review, or approval by FDA
- Exempt from food additive provisions
- "Optional" GMP regulations
- FDA has the burden of proving a dietary supplement is unsafe. Given lack of mandatory reporting, and multiplicity of drugs people take, this is VERY difficult, even for what appears to be easy items like ephedra
- How has the dietary supplement industry changed since DSHEA was passed? Went from $4 billion a year in business to $25 billion in 2007
**Adverse Event Reporting**

- No requirement
- Post-ephedra, industry now not opposed

**Dietary Supplement Claims**

- The issue of deceptive marketing practices is the core here
- Text p. 246 case V.E. Irons v. U.S. 244 F.2d 34 (1st Cir. 1957)
- FDA’s strategy in the past has been to classify all disease prevention claims as drug claims, but as evidence of the important link between diet and disease has mounted, FDA must now re-think its traditional ban on specific prevention claims for food
- FDA’s view on this may be to narrow

**DSHEA Exception to Claims**

- DSHEA specifically crafts a new exception to NELA, and allows dietary supplements to make 4 types of “statements of nutritional support” on labels or in other labeling without obtaining FDA approval.
- These allowed statements are:
  - A statement that “describes general well-being”
  - A statement that “characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function”; and
  - A statement that “describes general well-being from consumption of a nutrient or dietary ingredient.”

**Claim Exceptions cont.**

- A statement that claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the US
- A statement that “describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans”
- FDA’s view on this may be to narrow claims for food
- A statement that “classifies all disease prevention claims as drug claims, but as evidence of the important link between diet and disease has mounted, FDA must now re-think its traditional ban on specific prevention claims for food.
- FDA’s view on this may be to narrow

**DSHEA “splits” the drug definition**

- The disclaimer on the D.S. label, bottle states that the D.S. is not making one type of drug claim (cure, treat, prevent, or mitigate disease)
- But, the D.S. is allowed to make a structure/function claim that normally would also categorize the product as a drug.
- DSHEA provides statutory exception to this drug definition for dietary supplements. They in effect make a type of drug claim without being labeled a new drug.
- This is why, however, some U.S. dietary supplements are regulated as drugs overseas.

In other words, DSHEA allows not health claims per se but “truthful and not misleading” statements as to the relation between a supplement and the structure or function of the human body.

Text p. 246 case V.E. Irons v. U.S. 244 F.2d 34 (1st Cir. 1957)
Labeling of Dietary Supplements
- Like foods, dietary supplements must list ingredients, including ingredients that have established daily values.
- Supplements must also be identified on the bottle as such.
- If derived from a plant, must list that.
- Must also provide number of capsules or pills, the name and address of the manufacturer, and the composition of the product, and the percentage of RDA the quantity of the product represents, if known.

Nutritional Support Statement in the D.S. label
- Manufacturers must notify FDA when they intend to market a supplement with a label that contains a statement that the supplement contributes to health, affects the body's structure or function, or relieves a certain nutritional deficiency.
- Must attest that the statement is "truthful and not misleading".
- Disclaimer is required.

The Required Disclaimer
- “This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.”

FDA’s position
- Many are really drugs and making thinly-disguised drug claims.
- Often outright fraud ripping people off.
- The barrier to intervention – imminently harmful or threat to public safety – is very high, and burden on FDA. But no AE reporting so tough to track data.
- FDA usually finds out after there is publicity about a D.S. e.g. ephedra.
- Why not tax instead of trying to regulate?

Why are D.S. not drugs?
- In other countries many of these products are regulated as drugs, but not here by statute.
- Intended use is not as a drug: not to make claims re: disease prevention, mitigation, prevention, or cure.
- The structure/function claims are worded oddly, though FDA claims they are thinly-veiled prevention claims.

Arguments to leave D.S. alone
- Too popular.
- Too politically powerful, and a total loser battle.
- FDA lacks resources for.
- Americans LOVE this stuff. See New Yorker article.
- Part of "natural medicine/ holistic health/homeopathic/patient empowerment" movements.
- It’s a lifestyle choice; little harm from their use.
- FDA’s attitude is patronizing: people should be allowed to make stupid health decisions.
When CAN FDA intervene?: 2 circumstances

- If a D.S. manufacturer is stupid enough, greedy enough, or arrogant enough to make a drug claim. Even Sen. Hatch won’t defend this.
- Once a company does this they immediately come under FDA direct jurisdiction and subject to all new drug regulations.
- Or, the dietary supplement is an imminent health risk at any dose and cannot be marketed. We talked about this earlier. Companies will fight this. Ephedra is the perfect example.

Enforcement by FDA

- FDA can’t really act until it is sure there is a health risk, or a drug claim has clearly been made, because it WILL be challenged in court. These cases are ALWAYS litigated. And, reform of DSHEA impossible.
- In any enforcement proceeding the court must decide each issue “de novo”, meaning on the basis of the evidence presented in court.
- This precludes the government from relying on an administrative record in judicial proceedings, thereby limiting the court’s scope of review.

DSHEA

- How did we move from 1938→1962 concern over ridiculous formulations→1973 Vitamin Mineral regulations→1994?

History behind DSHEA

- History behind DSHEA 1
  - There is a long history of “natural” remedies going back centuries.
  - There is a history in U.S. medicine of different “schools” – osteopathy, naturopathy, homeopathy.
  - 1962: at time of Kefauver-Harris Amendments there was general dissatisfaction with regulatory scheme and FDA sought to establish “standards of identity” for supplement based on FDA daily requirements and to prohibit “irrational” combinations of nutrients; and prohibit marketing of “shotgun” preparations without evidence of need; and outlaw label-based and other promotional efforts propagating an emergent nutritional mythology.
  - FDA Commissioner Larrick 1965: characterized FDA’s concern and conclusion by stating that D.S. were “the most widespread and expensive type of quackery in the U.S.”

- History Behind DSHEA-2
  - FDA proposed rules for potency levels at 50/150% of RDA and proposed prohibiting the marketing of ingredients not recognized by “competent authorities.”
  - Bad timing for FDA: starting in 1960’s Adele Davis and others are attacking the entire food industry. Rise of anti-establishment, anti-corporate, back to nature 60’s movements.
  - Congress dismisses FDA’s proposals without a hearing!
  - Despite this, in 1966 FDA proposes even more restrictive version of its proposed rules: “Vitamins and minerals are supplied in abundant amounts by the foods we eat. The Food and Nutritional Board of the National Research Council recommends that dietary needs by satisfied by foods. Except for persons with special needs, there is no scientific basis for recommending routine use of dietary supplements.”

First public outcry

- Result: an avalanche of public objections, letters to Congress, industry petition for administrative relief.
- Resultant hearing from 1968-1970 are a forum for acrimonious debate between FDA and the D.S. industry: 162 witnesses, 32,000 pages of testimony.
- 1973: FDA announces final version of amended final regulation to become effective in 1975 which promulgates standards that doses exceeding 150% of RDA make the D.S. a drug. This was not so crazy. Actually melatonin comes in 1, 3, 5, and 10 mg doses in GNC.
- FDA states that “Americans are taking worthless, unnecessary, and sometimes potentially harmful amounts of patent medicines and nonprescription remedies”. Dumping out “vitamin pills, mineral supplements, and laxatives” in particular.
- Industry views this as a potentially crippling move.
- Movement to portray this as a boon to big drug companies making vitamins begins to surface.
Political winds begin to shift

- Industry hires more experts, notes FDA’s “narrow” interpretation of scientific evidence regarding D.S.
- White House Conference on Nutrition and Health condemns restrictive approach, champions emerging food technology and potential for labels to inform consumers.
- But strikes down the statutory conversion of supplements to drugs when exceeds potency maxima, holding that the INTENT of the manufacturer for the product was the proper test to categorize a product.
- Justice Friendly also comments that both sides in the controversy have “an all or nothing attitude” is making resolution of the issue intractable, and that FDA is at fault for “partially ignoring” the “fairly widespread if minority belief” in optimal nutrition through supplementation pRDA.
- This is all part of Kessler’s extensive plans for FDA to
- Promulgation of regulations delayed by White House

The Battle Shifts to the Hill

- After 2nd Circuit decision, even though a “mixed result”, lobbying shifts into high gear.
- Starting in mid-1970s nearly 70 bills are introduced in an effort restrict FDA’s authority to limit potency of vitamins and minerals.
- National Health Federation leads to effort, and corral Sen. Wm Proxmire, a moderate who now opposes FDA efforts. A bad sign. Gets worse when Dole, Goldwater, McGovern and Sam Nunn join in.
- Senate Hearings by Kennedy try to focus on “delicate balance”, but Proxmire just asks whether FDA was “going to play God”; called its regulatory campaign against D.S. backwards, and lambasts FDA as essentially captured by the food and pharmaceutical industries.
- Irish/French political winds begin to shift.
- NELA is the Result in 1990

The Proximire Amendment

- Passes Senate by vote of 81 to 10 in 1974, inserted into a health bill that is certain to pass.
- FDA prohibited from setting maximum limits on potency of any synthetic vitamin or mineral, from restricting combinations or distribution of D.S.
- FDA scales back regulatory efforts, and in the 1980’s begins to use “enforcement discretion” to only go after dietary supplement companies when they make either express drug claims or outrageous declarations.
- Number of supplements on markets explodes in early 1980s as a result.

NELA is the Result in 1990

- FDA regulations published pursuant to the Nutrition Labeling and Education Act (NELA) provide that no health claim may appear on the label or in other labeling (including brochures) of any food products, including dietary supplements, unless the FDA first approves the use of the claim in a final regulation. PREMARKET arena now.
- NELA mandated the now ubiquitous and culturally ingrained nutrition label on the back of food products.
- NELA was interpreted to require “significant scientific agreement” for health claims for both food and supplements alike among “qualified experts.” It was the perfect prop to go after the dietary supplement industry.
- The D.S. people sensed a material threat to their industry, and drew upon the deeply held convictions and suspicions of their consumer base.

The Quiet is Broken by Kellogg

- 1984: cereal manufacturer Kellogg “evades” existing restrictions by using a recommendation from the National Cancer Institute to imply that eating its cereals would help prevent cancer.
- FDA not willing to challenge NCI on this.
- Gets 47% increase in market share.
- FDA unable to block claim, so announces it will develop regulations for permissible health claims for foods but that they would not be applicable to D.S.
- Food industry now upset with FDA.
- 1987: FDA issues regulations for food AND D.S. that would permit “truthful and not misleading” health claims if 6 substantiation criteria met.
- Promulgation of regulations delayed by White House because of broader “Deregulatory Agenda.”
- Result: by 1989 40% of all new food products have a health message of one kind or another. Congress must act.

History of DSHEA - 4

- Ironically, the new FDA Commissioner David Kessler was a former aide to Senator Hatch, and was believed would promote a moderate approach under NELA, but
- 1991 FDA proposes new rules, and newly commissioned 1992 FDA taskforce supports enhanced FDA regulation of D.S. manufacturing and content, and the regulation of amino acid supplements as drugs and other D.S. as “food additives” subject to pre-market review.
- This is all part of Kessler’s extensive plans for FDA to “restore credibility and integrity” in the dietary supplement market, and adopts the paradigm associated with previous regulatory cycles including elevating consumer-fraud concerns over product safety concerns.
GAO report in 1999 finds that FDA data on AEs inadequate

At this point industry, Congress & consumer not in FDA's corner. Industry decides to fight

A bronchodilator, marketed extensively as weight-loss supplement as well as performance enhancer for body builders and other athletes

DSHEA was the end result of this brutal tug of war over the reach and requirements of the Nutrition Labeling and Education Act of 1990 (NLEA)

Intensive lobbying effort, once Newt Gingrich joins in, results in brokered agreement when Waxman agrees to a compromise on health claims and when the D.S. industry agrees to certain disclaimers.

Clinton signs it into law October 25, 1994

DSHEA is passed

A Triumph for Industry

Disclaimers are a joke

No pre-market review for safety or efficacy

A D.S. may bear a statement describing how consumption of the supplement affects structure or function in humans, or their general well-being

DSHEA expands number of things now classified as a D.S.

No pre-market review for safety or efficacy

A significant retreat for FDA. Loses to big tobacco the same year

Until ephedra happens a decade later, its perfect!

Nutritional Health Alliance Forms

Feb. 1992: organized political opposition to FDA reaches its zenith when 70 D.S. industry leaders meet

Strategy is to use 10,000 company storefronts as an infrastructure for organizing a grass-root campaign against the proposed rule

Mantras: freedom of choice, back to nature, anti-government, suspicion of FDA's motives and ties to industry

They stall the proposed regulations for one year while intensive lobbying in Congress reconsider the entire subject of D.S. regulation. Effort to split it off from drugs completely, and separate from conventional foods too

Dietary Supplement Act of 1992 imposes one year moratorium on the subject because the proposed nutrition labeling for D.S. are too close to those for conventional food. In effect, Congress overrules the agency, requires new rulemaking proceeding.

Ephedra: Background

Botanical known by ancient Chinese name of ma huang

A bronchodilator, marketed extensively as weight-loss supplement as well as performance enhancer for body builders and other athletes

Mid 1990s FDA begins to receive reports of AEs and deaths

Task force meetings: 1995, 1996: in 1997 FDA proposed regulations setting dosing limits and requiring specific label warnings about extended use and adverse reactions

At this point industry, Congress & consumer not in FDA's corner. Industry decides to fight

CAG report in 1998 finds that FDA data on AEs inadequate proof of causation under the law to restrict ephedra. Industry operates from favorable political position.


FDA is tone-deaf

Despite the gathering storm, in June 1993 FDA issues an Advanced Notice of Proposed Rulemaking (ANPR) in response to the Dietary Supplement Act which is being put together

Amaznigly, this states that many herbs and amino acids were being marketed as unapproved drugs or an unapproved food additives not generally recognized as safe

Also wants to treat single ingredient food products as food addititives, subject to pre-marketing review

In the background, Sen. Orrin Hatch and Rep. Bill Richardson (NM) begin pushing for a comprehensive legislative package to block the FDA's proposed regulations

Despite lobbying efforts, Rep. Waxman and Sen. Kennedy refused to allow the bill out of respective committees. Lobbying intensifies. Members of Kennedy's committee took rare step of over-riding their chairman by a 12-5 vote and report DSHEA to full Senate.

The Ephedra Debacle

On February 27, 2003 Baltimore Oriole pitcher Steve Becher died of complications following heat stroke during a pre-season workout. The Broward County (FL) medical examiner subsequently concluded that ephedra played a "significant role" in his death. HUGE change in politics

Current status: there is a complete ban on sale of dietary supplements containing ephedra alkaloids

No D.S. with this at ANY dose is safe

FDA ban in effect upheld in court 10th Circuit decisions 8/21/06. Supreme Court denied cert., so it stands

A rare instance where the health risk bar to go over was met. Ephedra was first and only such removal under DSHEA

The difficulty for FDA now comes down to resources: finding people who are still marketing it and taking enforcement actions against them. No room for "enforcement discretion" on this one.
The Politics of Ephedra

- A rare instance of deaths due to a D.S. Most of the time the products are just expensive and worthless. Up to 155 deaths possibly related to it.
- Virtually all other companies wanted this issue to go away and not to fight it. It was bad P.R. for business.
- The fact is it is easy to substitute one D.S. product for another.
- The fact that professional athletes were involved made it a loser for D.S. industry; allowed professional sports to take the higher ground in an arena they have an otherwise terrible track record on. Have more cloud on the ball than even the D.S. industry.
- FDA did not ban ephedra until most major manufacturers had ceased production.

The Medical Profession Now Begins to Look at D.S.

- Peer-review studies publish side effects, adulteration data.
- Efficacy of D.S. now questioned as result of large, peer-review journal studies, the kind that industry never had to perform for approval.
- Aura of invincibility now gone, but will probably try to ride it out anyway.
- Attention turns to how these products are being promoted, which raises the core issue of product labeling.

DSHEA and Promotion of D.S.

- Labeling applies to literature accompanying a regulated item.
- FDA has asserted that books and other literature carried in stores selling D.S. constitute labeling. It is certainly true to drugs.
- DSHEA alters this principle by excluding certain articles and other information about D.S. from the definition of labeling.
- DSHEA permits publications, including articles, chapters in books, and certain scientific literature to be used in connection with the sale of D.S., provided that:
  1. It is not false or misleading
  2. Does not promote a particular manufacturer or brand of D.S.
  3. Presents a balanced view of the available scientific literature
  4. If displayed in a store, is physically separate from the D.S.
  5. Does not have appended to it any information by sticker.

D.S. Industry post-Ephedra: more success in court than Congress

- Government bears burden of proof to establish that an article or book is false or misleading.
- Pearson v. Shalala (D.C. Cir. 1999):
  1. Court of appeals held that FDA's existing requirement of "significant scientific agreement" for health claims imposed a higher standard than permissible under 1st A protection of commercial speech.
  2. "If a health claim is not inherently misleading, the balance tilts in favor of disclaimers rather than supression."

High-water mark in Court for D.S. Industry

- Expanded regulatory space now for health claims for supplements.
- Despite data on disclaimers being essentially worthless.
- FDA changes policy and now comes out with "Qualified Health Claims" for Omega-3 Fatty Acids and Coronary Heart Disease (October 2000)...a more relaxed standard for structure/function claims.

Changes to D.S. Regulation After Ephedra

- FDA hasn't changed its opinion of D.S.
- D.S. industry realizes it has a P.R. disaster and fewer friends on the Hill.
- Takes position similar to that of cosmetics industry: better to propose more oversight than allow Congress to tinker with things.
- Propose Adverse Events Reporting to forestall potentially more severe regulatory requirements.
- Industry now favors GMPs (no downside for the big D.S. manufacturers anyway).
The Qualified Health Claim
- Following a 1999 D.C. Circuit Court of Appeals decision Pearson v. Shalala
- Even when substantial scientific agreement may be lacking, supplement manufacturers (but NOT food manufacturers) are permitted to make statements supported by the "weight of scientific evidence" if these statements are accompanied by a disclaimer or qualification that the evidence is not definitive; that the scientific evidence "in support of the claim outweighs that against it", and that the claim is "consistent with consumer health and safety."

Example of qualified health claim
- This case started after manufacturers rejected FDA's approach toward claims regarding folic acid use for prevention of neural tube defects in pregnancy and for omega-3 fatty acids and the risk of coronary artery disease.
- Supplement manufacturers may now make the following claim: "Consumption of omega-3 fatty acids may reduce the risk of coronary artery disease. FDA evaluated the data and determined that, although there is scientific evidence supporting the claim, the evidence is not conclusive."
- Qualified health claims also permitted for folic acid, vitamin B6 and Vitamin 12 and vascular dis.

FDA Can Reject Qualified Health Claims for a Dietary Supplement
- Continue to be the subject of controversy and litigation
- May 2001 letter: FDA rejected claim for anti-oxidant vitamins (C, E) and reduced risk of certain cancers because "the scientific evidence demonstrates a lack of significant scientific agreement" establishing such a relationship.
- Also rejected claim for Vitamin E and reduced cardiac disease, as well as one for dietary fiber supplements and reduced risk of colon cancer

Advertising and Promotion of Dietary Supplements 2008
- FDA works with Federal Trade Commission, which regulates fraudulent advertising for non-prescription medical products such as D.S.
- Operation Cure-All: FDA and FTC and various state agencies send "cyber letters" to web sites making improper health claims for D.S.
- FDA has Consumer Health Information Website to alert consumers as well – see "fringe autism treatment" handout

Populations vulnerable to bogus health claims by supplements
- Athletes
- Back to nature freaks
- Individuals with sick relatives, children not helped by conventional medical therapies e.g. autistic kids
- Californians
- People who voted for Ralph Nader
- Anyone who listens to Madonna records

Other D.S. related-issues
- "Chinese" medicine – e.g. herbs you can buy in a Chinese apothecary in Chinatown NY – NO regulation at all by anyone as far as I can tell