DHHS/NIH Office of Dietary Supplements
March 24-25, 2005
Affects of Bioactives in Foods
Lisner Hall, Bethesda, Maryland

Approaches for Evaluating the Health Effects of Botanicals & Natural Products

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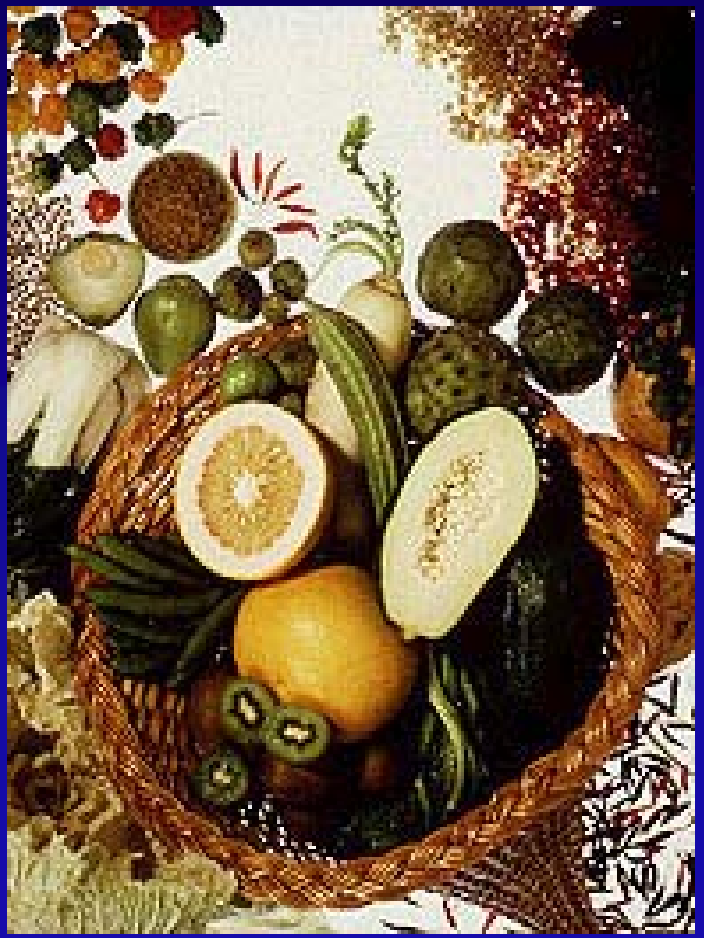
What are
Botanicals & Natural Health Products?



Heterogeneous products derived

from natural sources,

as a

finished product.

What they are not

- fermentation products (yeast, bacteria)
- highly purified or chemically modified substances derived from natural sources (paclitaxel)
- homeopathic drugs or elixirs

Natural Health Products

- From botanicals:
  - ginseng extracts, primrose oil, ginger root, “bee pollen”

- From animals:
  - fish oils, glandular materials
  - shark cartilage; elk antlers “velvet”
  - colostrum

Regulatory Impact on Scientific Assessment of Bioactives

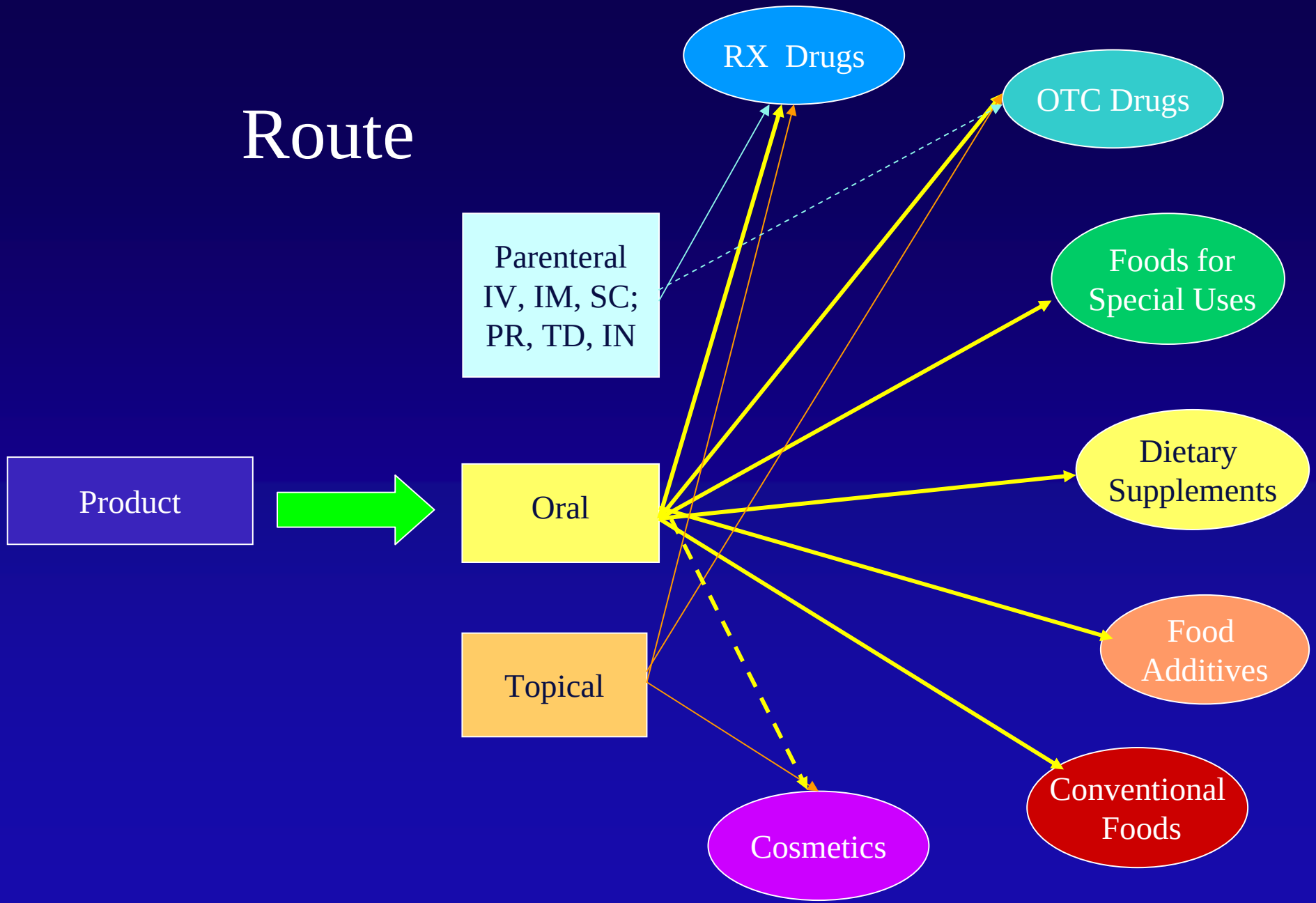
How products are regulated in the United States affects the scientific assessment of Bioactives, as well as what can be done with the results of scientific assessment.

Principles of US Regulation

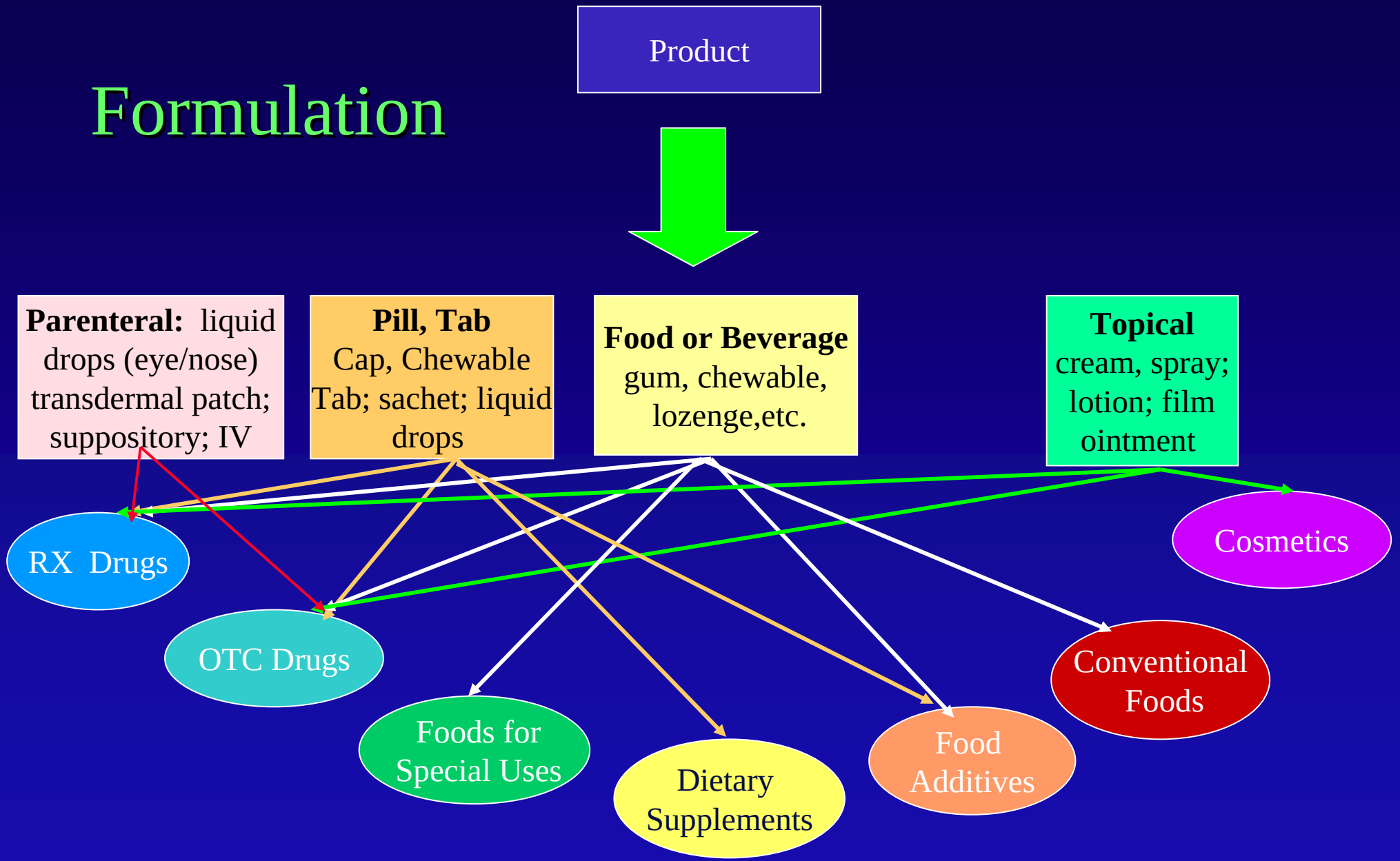
Products are regulated by their:

- Route
- Formulation
- Safety
- “Intended use”

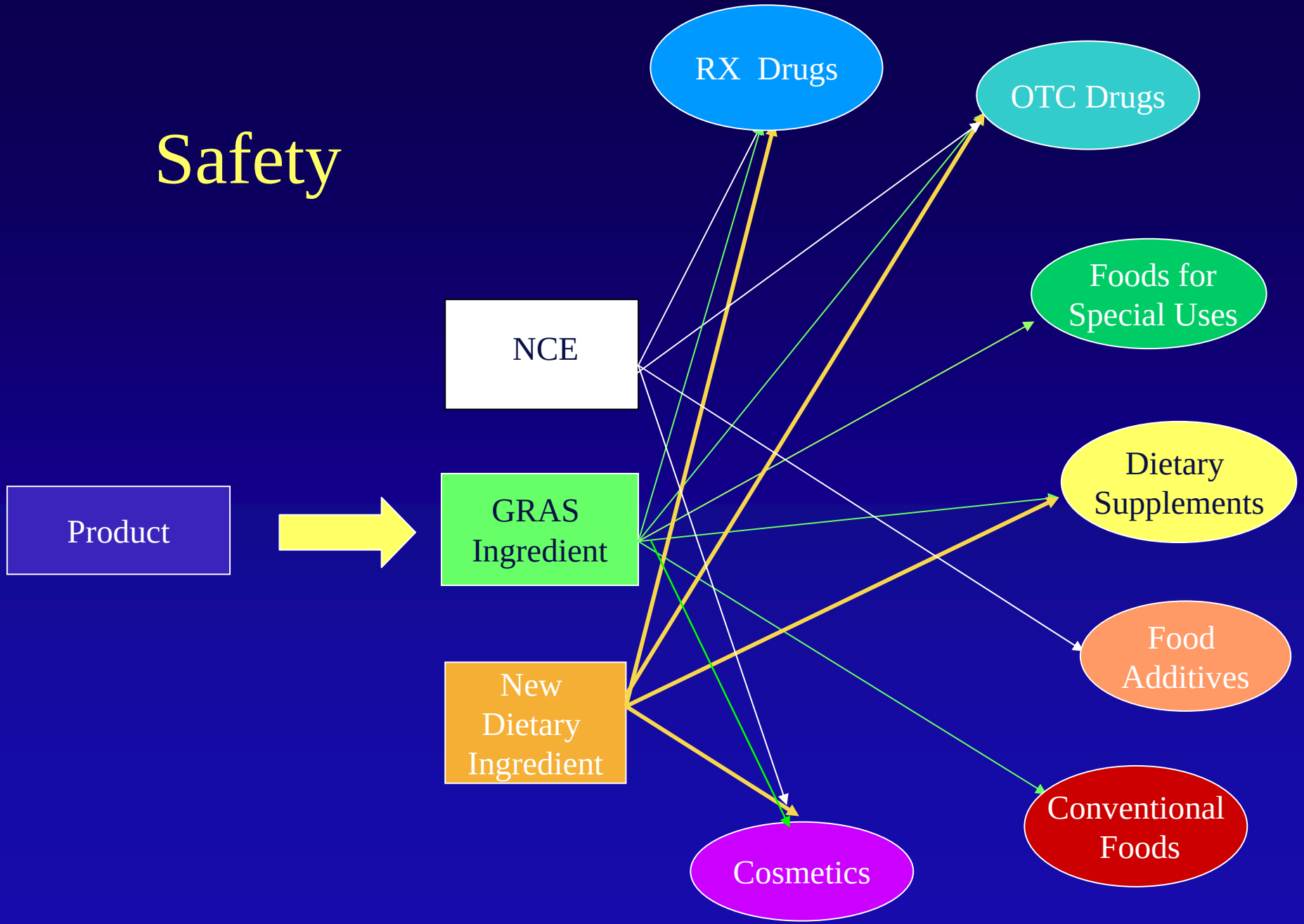
Route



Formulation



Safety



NHPs are Ingredients:

regulated by their "Intended Use"

as defined by their

"Labeling"

Many "faces" of Soy

Principles of US Regulation:

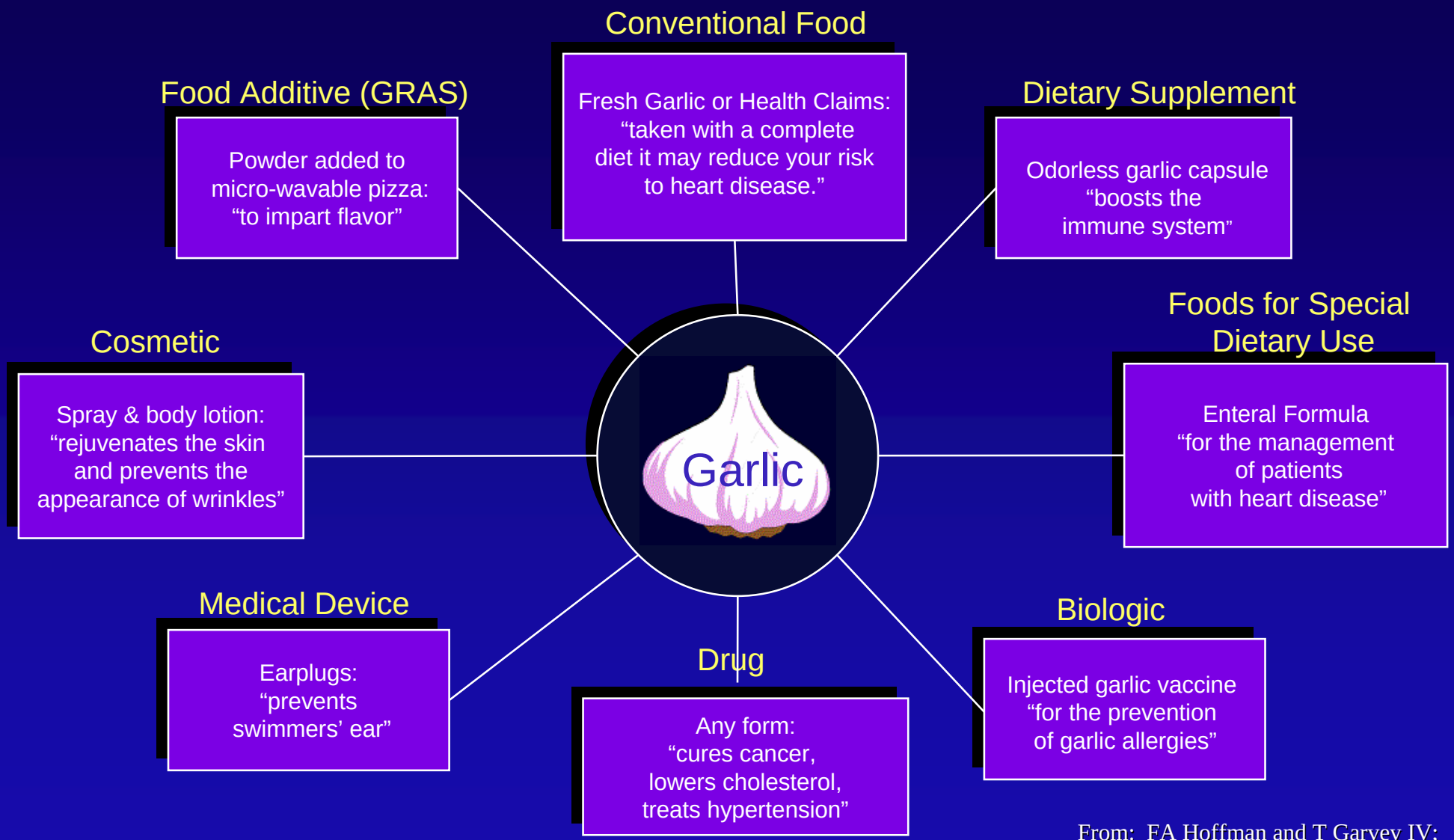
Labeling

includes:

- product container label or packaging
- package insert (if required)
- advertising and promotion (including video, spoken, internet, etc.)
- all other written, printed or graphic material *accompanying the product.*

see FD&C Act Sec. 201(m)

"Intended Use"



From: FA Hoffman and T Garvey IV; Textbook of Legal Medicine, 5th ed/ 2001

"Intended Use"

Types of Labeling Claims

- Nutrient content claims
- Statements of nutritional support
- Health claims (risk reduction)
- Symptom relief
- Disease claims (*to diagnose, treat, prevent, mitigate or cure*)
- **Structure or function claims**

“Structure/Function” Claims

Dietary supplements
are intended to supplement the diet and/or
“Effect the Structure/Function of the Body”
(DSHEA -1994)

“Structure/Function” Claims

Drugs

are intended for to treat, prevent, diagnose, mitigate or cure disease,

OR

“Effect the Structure/Function of the Body”

SAFETY

Foods <<<< >>>> Drugs

Opposing Legal Premises

Legal Assumption:

Foods

"generally recognized as safe"

OR

contain ingredients with

"a history of use or other evidence of safety"

which

"will reasonably be expected to be safe….."

Legal Assumption:

Drugs

not generally recognized as safe & effective

under the conditions prescribed, recommended or suggested in the labeling

[Definition of "new" drug: **Section 201p FD&C Act]**

Legal Assumptions: Risk

Dietary supplements
are intended to supplement the diet of
healthy (normal) individuals for which no risk is tolerable.

Drugs
are intended for use by a population for which the
benefit has been proven to outweigh the risk.

Impact of US Regulation on Bioactives:
Foods vs Drugs?

Foods

- taste, aroma, flavor, nutritional supplementation
- for general population
- documented safety
- no risk: safety is absolute
- consistency not crucial
- manufacturing is not reviewed by FDA

Drugs

- safe/effective to treat, prevent, diagnose, mitigate, cure
- for target population
- documented safety/efficacy
- risk:benefit: safety is relative
- consistency very crucial
- manufacturing is vetted by FDA

Health Effects: *What you can say*

Joints: Study Objectives, Product Claims

- Disease Claim (drug):
  - "treat/prevent [symptoms of] arthritis"
- Structure/Function Claim (drug):
  - "reduce the inflammation associated w/ arthritis"
- Structure/Function Claim (diet. supplmt):
  - "maintain/promote healthy joint range of motion"
- Health Claim (food/diet.supplmt):
  - "may reduce the risk of developing arthritis…"

Health Effects: *Who you should study*

Joints: Subjects

- Drug:
  - patients diagnosed with arthritis
- Dietary Supplement:
  - healthy volunteers
- Food:
  - general public, OR
  - those at high risk to develop arthritis (for FDA-approved “Health Claim”)

Health Effects: *What you must assess*

Joints: Outcome Measurements

- Drug: "perceived (clinical) benefit"
  - clinical improvement of disease parameters, symptoms, quality of life, along w/ improvement of joint space in those who had abnormal studies
- Dietary Supplement/Food: "surrogates"
  - range-of-motion data; maintain normal joint space in "normal" subjects [SF Claim]
  - lack of progression to disease state ("reduce risk") [Health Claim]

Health Effects: *Requirements your "test article" must meet*

Quality Standards

- Drug:
  - "drug" Good Manufacturing Practices (GMPs)
  - focus on lot-to-lot consistency, potency, purity
- Dietary Supplement/Food:
  - dietary supplement or food GMPs
  - focus on filth, adulteration, contamination

Health Effects of Botanicals and Natural Health Products

USDA Historical Photos

Existing Approaches

Existing Approaches:

Pulling the "Bioactive" out of the food:

- Identification of "bioactive"
- Isolation
- Purification
- Synthesis

Beta-carotene from Carrots

Historical approach works well
for vitamins, minerals, and many nutrients

Caffeine in Foods and Drugs

"Botanical Caffeine"

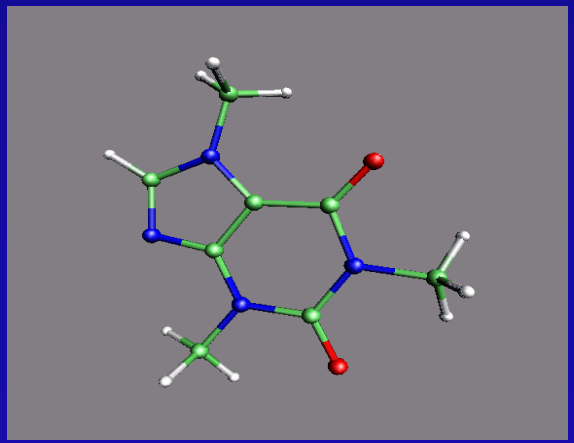
Cup of coffee	90-150mg
Instant coffee	60- 80mg
Tea	30- 70mg
Mate	25-150mg
Cola drink	30- 45mg
Chocolate bar	30mg

FOOD

DRUG

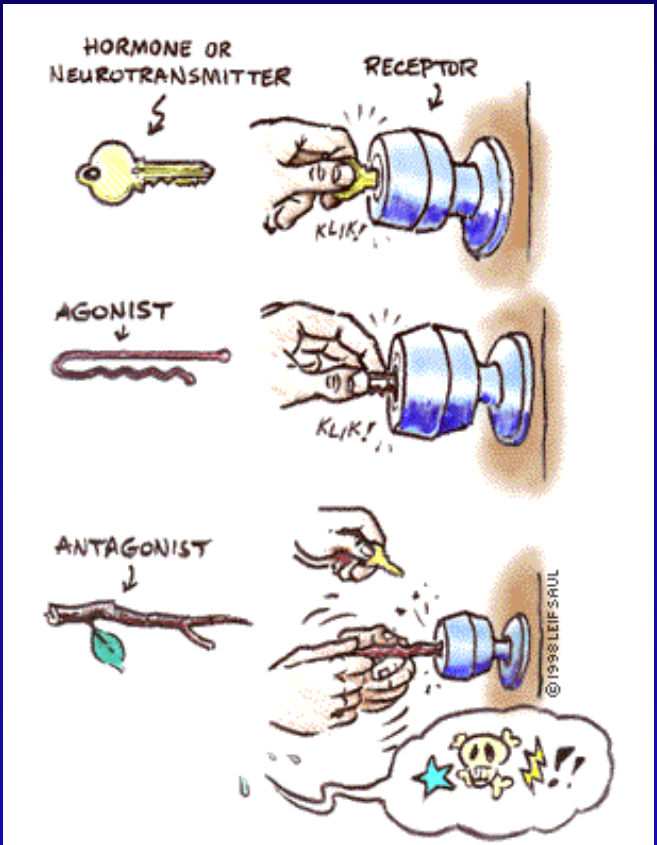
Vivarin	200mg
Stay-awake pill	100mg
Cold relief tablet	30mg
Headache tablet	32mg

"Chemical Caffeine"



Existing Approaches: Chemically Defined Molecules

Preclinical Screens



- Focus on pharmacology of Bioactives & “Mechanisms of Action”
- “Lock & Key” model -
  - Must have the “lock” (molecular targets)
  - If target is unknown, no way to find a ‘new’ active

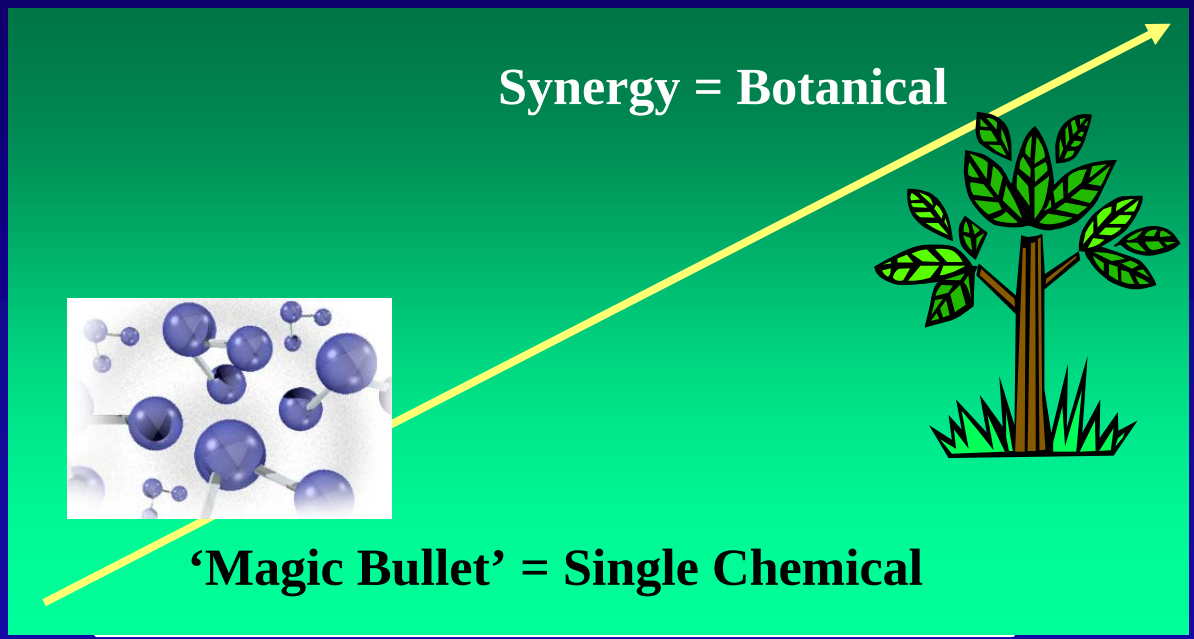
Attributes of Botanical and other "Natural" Bioactives

- Complex mixtures
- True "actives" rarely are known
  - ginkgolides in *Ginkgo biloba* are the exception!!- not the rule
- Major AND minor active(s): what are thought to be "impurities" usually contribute to the biological effect
- "Mechanisms of action" generally unknown
- Product is "process-defined" (not chemically defined)

Single Chemical vs Complex Botanical

Health Benefit "Targets"

Probability of useful Biological Response



Polymorphic Target

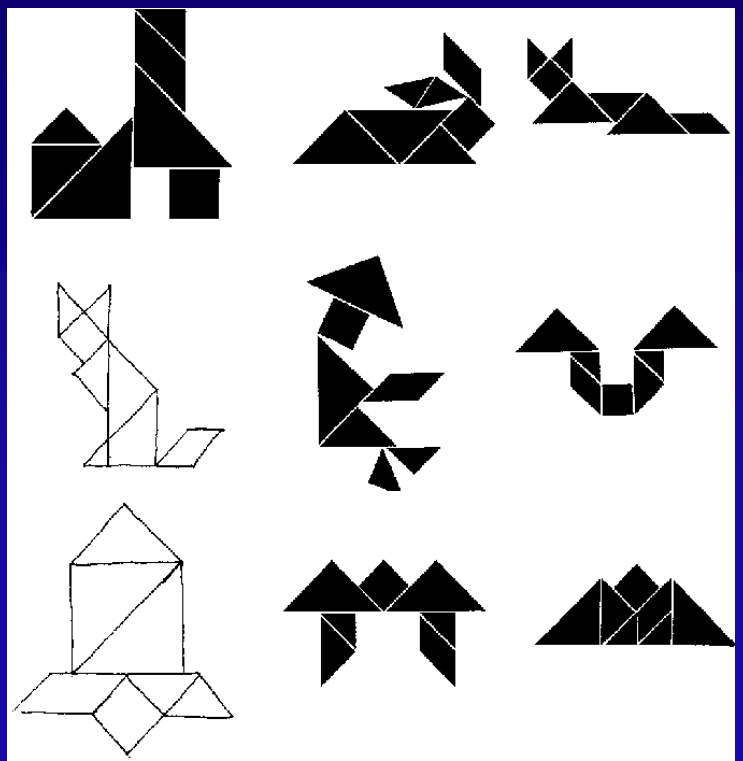
Single Active → Multiple Actives

Health Effects of Botanicals and Natural Health Products

New Paradigm

Why Heterogeneous Products?

When the whole
is greater
than the parts



Focus on Components:
May Miss the "Active"

"Consumption of antioxidant vitamins
may reduce the risk of certain kinds of cancer."

FDA Denies "Health Claim"

- No support for *antioxidant vitamins, alone or in combination..*
- Data "*….did not resolve whether the protective effects of fruit and vegetable consumption….are due to a single or combined effect of the antioxidant vitamins and other nutrients* with antioxidant function… OR

  ….to other nutritive components of such foods…,

  ….to unmeasured components of such diets, …

  ….to displacement of other known risk components… within the total diets."

From: FDA denial of Health Claim for Antioxidant Vitamins & Cancer '93

FDA Allows "Qualified Health Claim"

"FDA has determined that although some scientific evidence suggests that consumption of antioxidant vitamins may reduce the risk of certain forms of cancer, this evidence is limited and not conclusive."

From: FDA Letter – Apr 1, 2003

HeteroGeneity, LLC -2005

GARLIC: *Health Benefits may vary with the product*

- ANTI-INFECTIVE
  - Antibacterial
  - Antifungal
  - Antiviral
- CARDIOVASCULAR
  - Antihypertensive
  - Antiarrhythmic
  - Antithrombotic
  - Antiplatelet
  - Lipid lowering
- ANTICANCER
  - Tumor initiation
  - Immune enhancing
  - Tumor promotion
  - Modification of carcinogenesis

***Allium sativum*, L.**

- ANTI-AGING
  - improved cognitive & spatial memory
  - liver-protection
  - antioxidant

From: R A Nogourney: Jo. of Med Food Vol.1(1):13-28, 1998.

"Throwing out baby with bath-water"

Evaluating "Negative" Results

- *JAMA* article reports a *steam-distilled garlic oil* preparation tableted with beta-cyclodextrin (binder) *"lacks lipid-lowering effect"*
- Formulation: <40% release of oil from tablet binder
- Authors failed to address bioavailability AND dismissed 17 (out of 20) studies that were positive for the health effect!
- But press reported all garlic products were "ineffective"

From: V. Tyler The Scientific Review of Alt Med. 4(2):17-21, 2000.

*"It's often not what you **know** – but what you **don't know** that counts"*

Garlic (*Allium sativum*, L.)

- >100 compounds identified in garlic
- "Process defines the product:"
  - Fresh Garlic, garlic juice, volatile garlic oil, garlic oil macerates, dried garlic powder, aged garlic extracts
- Standardized extracts may not always be the "answer:"
  - Some products are standardized on *Allicin*
  - But health benefits were observed using products containing no *Allicin* (e.g., cooked, steamed, aged garlic extract)

Compounds other than Allicin are responsible for some health benefits of garlic

"Don't believe everything you read…"

Deficiencies in the Scientific Literature

"[Clinical investigators]…are apparently unaware that no standards of quality exist for herbal products…

Accustomed to working with drugs that must conform to official specifications, [investigators] often fail to define adequately the botanicals employed [in studies]…"
---*Varo Tyler*

From: The Scientific Review of Alternative Medicine. 4(2):17-21, 2000.

Botanical Product Forms

each form contains
varying levels of bioactive compounds

Photo by Peggy Greb.

- Powders – dry, crushed, minimally processed
- Infusions - near-boiling water poured over botanical, steeped (e.g., tea)
- Decoction - botanical placed in water, boiled; strained liquid (e.g., coffee)
- Tincture - botanical in solvent, steeped days/wks
- Fluid extract - similar to tincture, but product concentrated through distillation process
- Solid extract - solvent evaporated off, leaving solid residue
- "Standardized" extract - guaranteed amounts of constituents; given as % total weight of extract

New Paradigm: Heterogeneous Products

"Identification"

- Taxonomy/nomenclature not internationally harmonized
- Identification must use a variety of approaches (organoleptic, gross & microscopic, DNA, etc.)

Heterogeneous Products

"Screening"

- By history:
  - prior human use, traditional use, historical use
- Bioassay
  - Study the whole product, not the components
  - Test in a "matrix" (*in vivo* or *in vitro* – using entire systems) because effect may be indirect, i.e., through complex metabolic pathways, cellular recruitment, etc.

New Paradigm: Heterogeneous Products

"Methodology"

- Manufacturers do not use comparable assays to quantify actives
- No high quality, pure standards are available
- Even the term "standardized" -- is not standardized!

New Paradigm: Heterogeneous Products

"Testing"

- Quality standards will rely on a combination of tests and controls
- Toxicology
- But standard pharmacology is not feasible for complex bioactives

Heterogeneous Products (Botanicals)

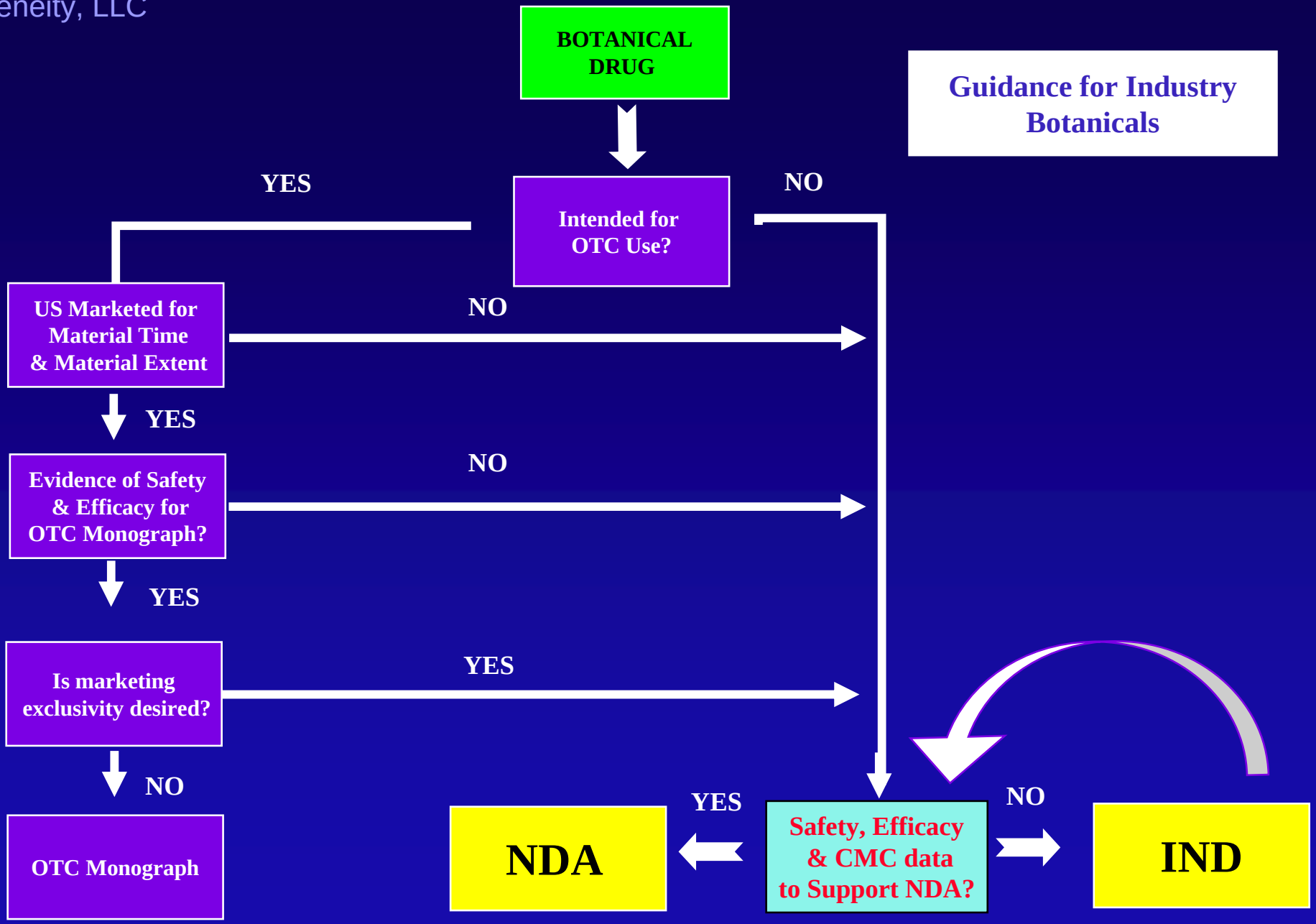
Evolving Regulatory Milieu

- OTC Drug Monographs: Allowing Foreign Marketing Experience (Jan. 2002)
- FDA Guidance for Industry: Development of Botanical Drugs (June 2004)

New Class of Drugs

- Synthetic, small molecular weight
- Recombinant, large molecular weight
- Natural products, multi-component *(including botanicals)*

HeteroGeneity, LLC

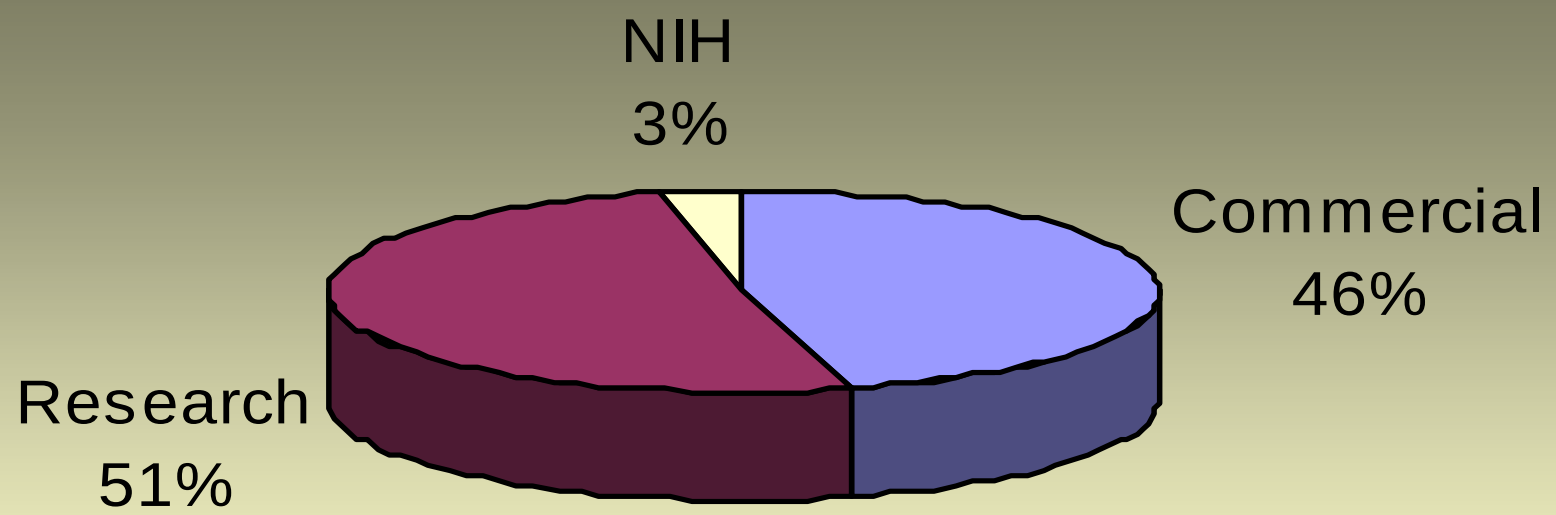


Botanicals as Future Drugs:

Number of Pre-IND & IND Applications submitted to the US FDA

- 1990 - 1998 50
- 1999 - 2005 >200
- 2002 - 1 to 3 per month

Botanical Drug IND Sponsors



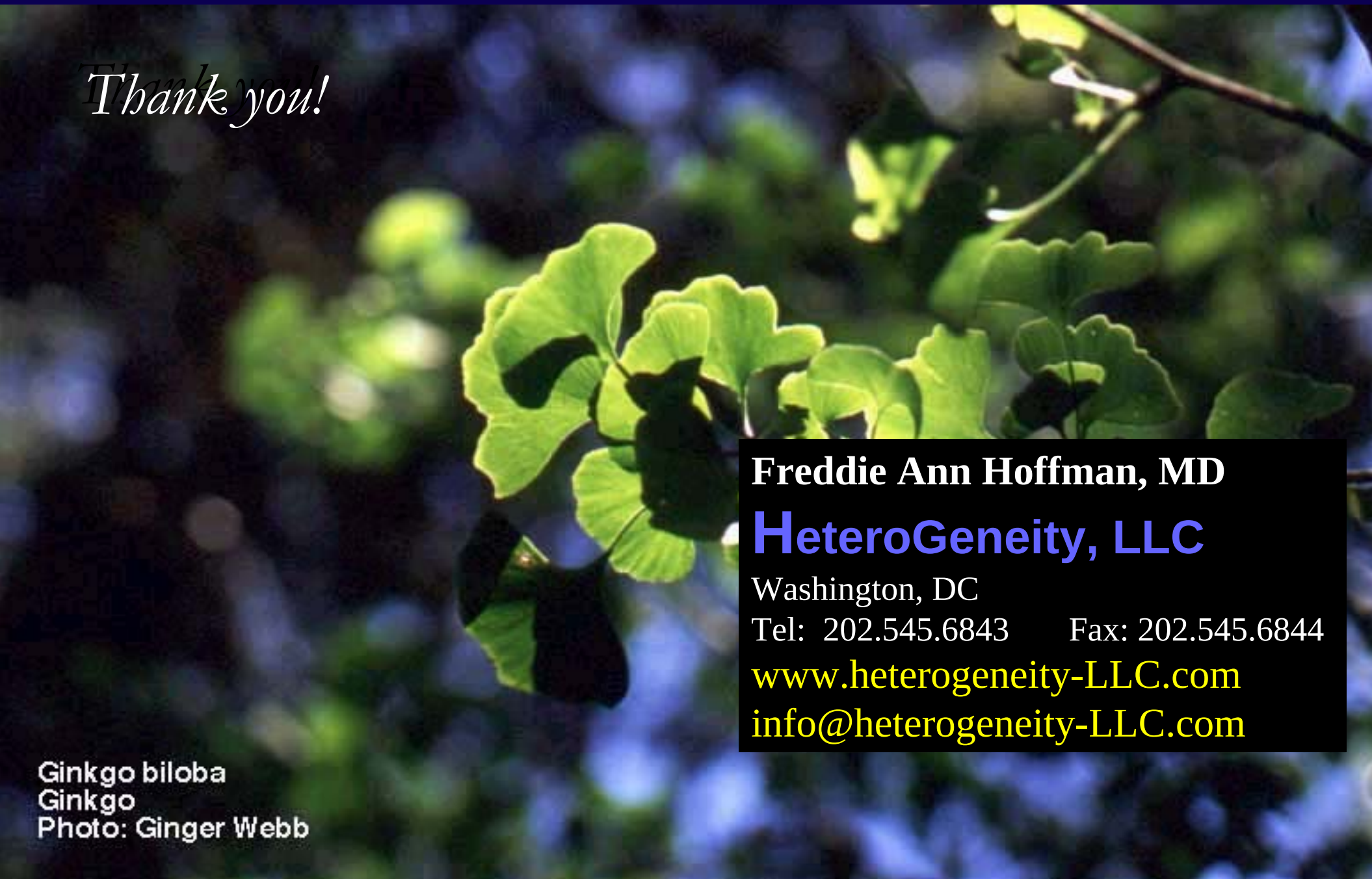
2002

[From S. Chen, CDER-FDA]

Summary

- To assess health benefits, “whole” bioactives should be defined --not just their chemical components.
- Regulatory status of “test articles” can have an impact on scientific investigation and results.
- Complex bioactives may be particularly useful against polymorphic biologic targets.
- Existing approaches for single molecular bioactives may be inappropriate for heterogeneous bioactives.
- Recent changes in US regulatory policies open new avenues for developing beneficial complex bioactives from natural sources.

Thank you!



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Ginkgo biloba
Ginkgo
Photo: Ginger Webb