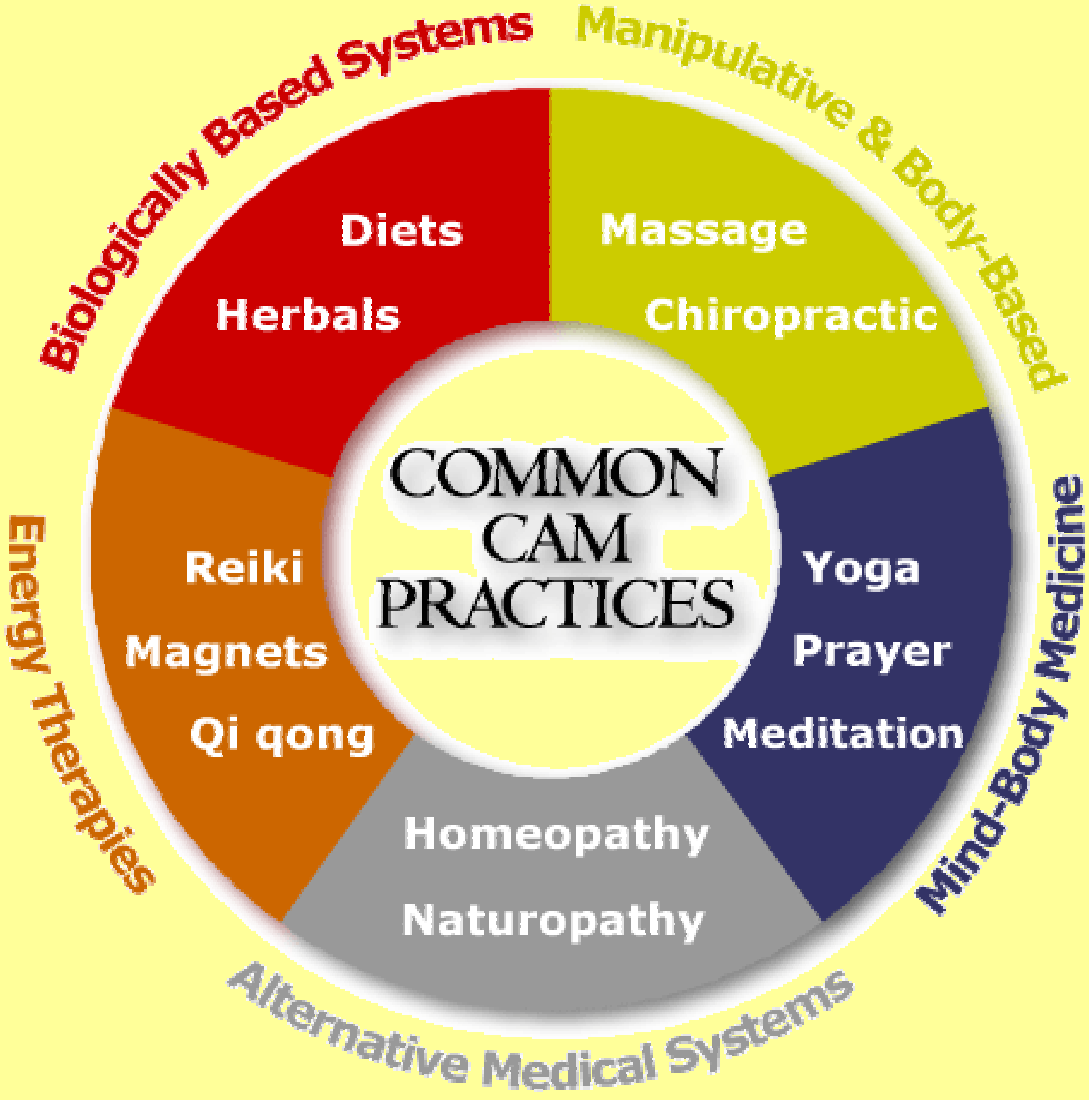
Botanical Agents in 2005:

National Center for Complementary and Alternative Medicine
NIH, DHHS

SBR Nov 2005

The CAM Domains



Botanical Agents

- The FDA characterizes a product primarily based on its intended use.
- A botanical product (vitamin, mineral, herb, amino acid), may be intended to be used as:
  - dietary supplement (food)
  - drug.

Herbal vs Conventional Agents

- Herbal agents
  - Complex mixtures
  - First used (as dietary supplements), then investigated for safety and efficacy
- Conventional drugs
  - Single agents
  - First investigated for safety and efficacy, then used

Issue #1

- Does the use of Botanical Agents as dietary supplements provide data sufficient to inform the public about the medical benefits of Botanical Agents?

Dietary Supplements

- **FDA regulates dietary supplements under a different set of regulations than drug products (prescription and Over-the-Counter).**
- **Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed.**
- **Generally, manufacturers do not need to register with FDA nor get FDA approval before producing or selling dietary supplements.**

- FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market.

Dietary Supplements GMP Benefits

Table 13: Summary of annual benefits

	$ Million
Fewer illnesses (from table 8)	$39
Fewer illnesses (from table 10)	$66
Fewer product recalls (from table 9)	$3
Reduced consumer search (from table 12)	$109
Total Benefits	$218

Dietary Supplements GMP

[FDA Document of 7 Mar 03]

Requirements for:

(1) personnel
(2) the physical plant and environment
(3) equipment and utensils
(4) production and process controls
(5) holding and distributing
(6) consumer complaints related to CGMPs
(7) records and recordkeeping

Dietary Supplements: GMP Cost

Table 1.--Estimated Annual Recordkeeping Burden

21 CFR Section	Number of recordskeepers	frequency of recordkeeping	Total annual records	Hours per record	Total hours
111.15(b)(3).....	231	12	2,772	0.1	277
111.15(d)(3).....	231	260	60,060	0.25	15,015
111.25(d).....	213	365	77,745	0.5	38,873
111.30(b)(2) and (b)(5).....	707	260	183,820	0.5	91,910
111.35(d).....	10	1	10	10	100
111.35(e).....	367	260	95,420	0.25	23,855
111.35(f).....	367	260	95,420	0.1	9,542
111.35(i)(1).....	367	10	3,670	0.25	918
111.35(j).....	367	260	95,420	.25	23,855
111.35(m).....	367	365	133,955	0.1	13,396
111.37(c).....	286	365	104,390	0.5	52,195
111.40(a)(3), (a)(4), (b)(2),	449	365	163,885	0.1	16,389
111.45(a) \2\ and (b) \2\.....	200	1	200	30	6,000
111.60(b)(2).....	133	365	48,545	1	48,545
111.60(d) \2\.....	133	1	133	3	399
111.65(c)(7), (c)(10), and	133	365	48,545	0.1	4,855
111.70(b)(5) through (b)(6),	245	260	63,700	0.1	6,370
111.70(g).....	245	260	63,700	0.50	31,850
111.74(a).....	200	12	2,400	0.1	240
111.82(a).....	53	52	2,756	0.1	276
111.85(a).....	53	260	13,780	0.1	1,378
111.85(d) and (e).....	53	260	13,780	0.5	6,890
111.95(e).....	53	75	3,975	0.1	398
111.95(f)(1).....	93	75	6,975	0.5	3,488
111.125.....	220	4	880	0.1	88
Total.....	**.....**	**.....**	**.....**	**.....**	**500,587**

Dietary Supplements GMP Balance

Table 18. Annual Benefits and Costs of Proposed Rule

Benefits	$218 million
Costs	$86 million

Dietary Supplements

- As a result of proposed changes in GMP standards for dietary supplements, manufacturing and control of dietary supplements will approximate that of drugs.

- Safety and efficacy considerations are unaffected by the 2003 proposed changes.

Dietary Supplements

- FDA regulates dietary supplements under a different set of regulations than drug products (prescription and Over-the-Counter).
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- Generally, manufacturers do not need to register with FDA nor get FDA approval before producing or selling dietary supplements.

- **FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market.**

Ephedra: Clinical data

- Efficacy
  - 0.9 kg/month wt loss
  - JAMA 2003;289:1537
- Toxicity
  - 1 dose of metabolife 356 (12 mg ephedra plus 40 mg caffeine) : 8 of 15 have 30 msec QTc prolongation vs 1 of 15 when xover to placebo
  - JAMA 2004; 291:216

Ephedra: Apr 2005

- US District Court Judge in Utah ruled that FDA had not proven that 10 mg ephedra in DS were dangerous.
- Burden of proof is on govt, via intent of Congress in regulating DS as food, to prove danger of DS.

Issue #1

- Does the use of Botanical Agents as dietary supplements provide data sufficient to inform the public about the medical benefits of Botanical Agents?

- Ans: NO

Botanicals used as a Drug: Data needed to Support Clinical Trials

- There are 3 main sections to a dossier submitted to the FDA to support an IND or an NDA:
  - CMC (chemistry-manufacturing-control) data
  - Preclinical / Nonclinical data
  - Clinical data

Botanicals used as a Drug: FDA Guidance Doc June 2004

- "Botanical drug products often have unique features"
  - Complex mixture with lack of a distinct "active ingredient "
  - "substantial prior human use" as a dietary supplement
- In the FDA guidance, CMC, preclinical, and clinical documentation is:
  - greater than that needed for clinical use of a dietary supplement,
  - reduced compared to that needed for synthetic conventional drugs.

Considerations for Botanical drug Clinical Research: Chemistry Manufacturing Control

SUBJECT	DRUG STUDIES	STUDY DETAILS	Data needed to support PHASE I / II	Data needed to support PHASE III
PLANT SUBSTANCE	Starting material	Botanical description Procedure Quantity of active Identity: Chem (IR, MS, NMR, UV, Chiral); biologic Stability	X X	Expanded Expanded X X X.
PLANT PRODUCT	Manufacturing Finished prod Product assay Storage Stability Excipients Impurities Inprocess controls Reference stan Bioavailability Container Microbiology Environmental	Reagents/flow Quantity of active Methods/Specs Identity (chemical) Purity describe Light/heat/time List List/analyze SOPs Standard batch Dissolution rate Label Contamination Assessment	 X X X X X	X X X X X X. X X. X. X X X X X X

Considerations for Botanical drug Clinical Research: Chemistry Manufacturing Control [2005]

- 1. Identification (genus, species, variety-if applicable)
- 2. Study agent supplier. This information should extend back to the raw material harvest, if possible.
- 4. Reference specimen of the source material.
- 5. Pharmacopeial monograph (e.g., U.S. Pharmacopeia)
- 6. Description (macroscopic) of the parts of the plant from which the product is derived.
- 7. Geographic source of the material, time of harvest, plant part
- 8. **Compliance with the WHO Guidelines on Good Agricultural and Collection Practices**
- 9. Extraction procedure
- 10. Formulation of finished product.
- 11. Active and/or other relevant marker compound(s) used for standardization.
- 12. Chemical profile or fingerprint of the agent
- 13. **Process controls**
- 14 Contaminants or adulterants.
- 15. Certificate of Analysis
- 16. **Bioavailability, dissolution**
- 17. Stability.
- 18. Storage conditions
- 19. Batch-to-batch reproducibility.
- 20. Reserve samples

Issue #2:

- How much CMC documentation should be required for Botanical agents used for Preclinical studies, Initial (Phase I / II) clinical trials, and Pivotal (phase III) clinical trials?

Botanicals used as a Drug: FDA Guidance Doc June 2004

- Many botanical products are legally available in the United States as dietary supplements. Given the wide availability of such products outside of clinical trials, it is important to assess effectiveness…

- **To support initial clinical trials, the nonclinical pharmacology and toxicology information that must be provided …may be markedly reduced compared to that for new drugs for which there is no prior human experience.**

- **In most cases, additional toxicology and CMC data will not be required for such initial trials.**

Considerations for Botanical Drug Clinical Research: Non-Clinical

SUBJECT	DRUG STUDIES	STUDY DETAILS	Data needed to support PHASE I / II	Data needed to support PHASE III
Efficacy	In vitro In vivo animal	Mechanisms 2 species	[literature review]	
Toxicity	Single dose Multiple dose Reproduction Mutagenicity Carcinogenicity Cardiovascular tox Special target tox	2 species 2 species Segment 1, seg 2 In vitro, in vivo Mice, rats Dog As needed	[literature review]	(may need) (may need) (may need) (may need) (may need)
Pharmacokinetics (ADME)	Metabolite synthesis Assay methods In vitro metabolism In vivo metabolism In vivo kinetics Distribution Toxicokinetics Efficacy kinetics	In fungus In vitro, in vivo Metab, drug-drug Metab, drug-drug Absorption, excretion Radiolabel, protein 2 species In vivo models		

Botanicals used as a Drug: FDA Guidance Doc June 2004

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Considerations for Botanical drug Clinical Research: Clinical Considerations

SUBJECT	DRUG STUDIES	STUDY DETAILS	Data needed to support PHASE I / II	Data needed to support PHASE III
PHASE I	Toxicity Pharmacok`inetics Toxicokinetics	Single **dose** **Multiple dose** Impaired pops (renal, hepatic) Fed/fasted, drug-drug Compare to toxicity, Compare to animals	**X**	X (desireable) (desireable) (desireable)
PHASE II	Efficacy	**Multiple dose** Increased pt # s		**X**
PHASE III	Efficacy,Toxicity, PK	Pivotal Trials: Adults Other trials; children renal/hepatic general pop		

Issue #3:

- How much preclinical efficacy and toxicity data needs to be provided to support clinical trials of Botanical Agents?

Considerations for Botanical Drug Clinical Research:

ADDITIONAL NCCAM

CLINICAL REQUIREMENTS RE:

dose escalation

placebo effect

St John's Wort: results on HAM D score

[response]	SJW	Placebo	Sertraline
	N=113	N=116	N=109
Any	43 (**38%)**	50 (**43%)**	53 (**49%)**
Full	27 (24%)	37 (32%)	27 (25%)
Partial	16 (14%)	12 (11%)	26 (24%)

Considerations for Botanical Drug Clinical Research:
Need for Phase 2 trials

- The purpose of a clinical trial is to evaluate an intervention for a clinical condition with the longer-range goal of improving human health and clinical practice.

- Positive (or negative) data can lead to a recommendation to use (or not to use) the treatment.

- **Use of a suboptimal dose that is safe but ineffective does not serve the needs of the community. Although the trial indicates only that the tested dose of the intervention was ineffective, the community may conclude that all doses of the intervention are ineffective, and patients will be denied possible benefit from the intervention.**

Issues #4 and #5:

- Are placebo controls needed in clinical trials of Botanical agents?
- Ans: YES
- Should the Initial Clinical trial be dose-escalation phase I / II
- Ans: YES

Issue # 6: dose-escalation requires Revisit of preclinical issue

- Higher than “customary” doses will be used in the clinical trial
- Substantial human use of those higher doses will not be present
- Need for animal toxicity data to support those higher than customary clinical doses
- **Need for optimal Phase 3 dose**
  - **drives phase 2 dose escalation study design,**
  - **which drives need for animal safety data**

DS / BOTANICAL AGENTS USED AS DRUGS

- **DO PUBLISHED STUDIES SHOW EFFICACY?**
- **ARE THE STUDIES CONCLUSIVE ON THE BASIS OF OUR PRESENT CLINICAL TRIAL DESIGN REQUIREMENTS?**

Dietary supplements: nutrients

- **Diarrhea-prevent**
  - Children undernourished
  - Zinc: 5-20 mg/d x 12-54 wks
  - Diarrhea incidence:Odds Ratio =0.82 (0.72-0.93)
- **Diarrhea-treat**
  - Children undernourished
  - Zinc: 20 mg/day
  - >7d diarrhea: relative risk = 0.61(0.39-0.93)

Botanical phase 3 Trials: Effective? Conclusive?

- Soy isoflavones for cognition [JAMA 2004; 292:65]
  - 25 g soy protein +[52 mg genistein-41 mg daidzein- 6 mg glycitein]: daily for 12 months

	Soy	Placebo	P
Memory	+5.5	+4.7	0.36
Attention	-2.5	-3.5	0.76
Verbal	+0.3	+0.2	0.85
MMSE	-0.4	-0.1	0.47

Not effective. Yes conclusive.

Echinacea to prevent colds

NEJM 2005;353:341

NOT effective; NOT conclusive

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Effect of Various Extracts of *E. angustifolia* Root on Rhinovirus Infection and Common-Cold Illnesses.*

Treatment Day −7 to 0	Treatment Day 0 to 5	No. of Subjects	No. Infected (%)†	95% CI for Difference in Infection Rate vs. Placebo‡	P Value for Difference in Infection Rate vs. Placebo	No. of Clinical Colds in Infected Subjects (%)	Mean Total Symptom Score§
CO_2 extract	CO_2 extract	45	40 (89)	−0.07 to 0.15	0.57	25 (62)	15.45±2.34
60% extract	60% extract	52	42 (81)	−0.09 to 0.17	0.46	24 (57)	13.21±1.91
20% extract	20% extract	52	48 (92)	−0.03 to 0.17	0.22	24 (50)	12.06±1.74
Placebo	CO_2 extract	48	43 (90)	−0.06 to 0.16	0.48	27 (63)	14.60±1.70
Placebo	60% extract	48	44 (92)	−0.03 to 0.17	0.28	33 (75)	19.20±2.28
Placebo	20% extract	51	44 (86)	−0.11 to 0.13	0.89	28 (64)	15.64±1.97
Placebo	Placebo	103	88 (85)	Reference group	—	58 (66)	15.05±1.43

* Plus–minus values are means ±SE. CI denotes confidence interval, and CO_2 supercritical carbon dioxide.
† The P value for homogeneity for the infection rates is 0.58.
‡ Negative numbers indicate a higher infection rate for placebo, and positive numbers a higher rate for echinacea treatment.
§ The total mean symptom score is the sum of symptom scores on days 1 to 5. Higher scores indicate more severe symptoms.

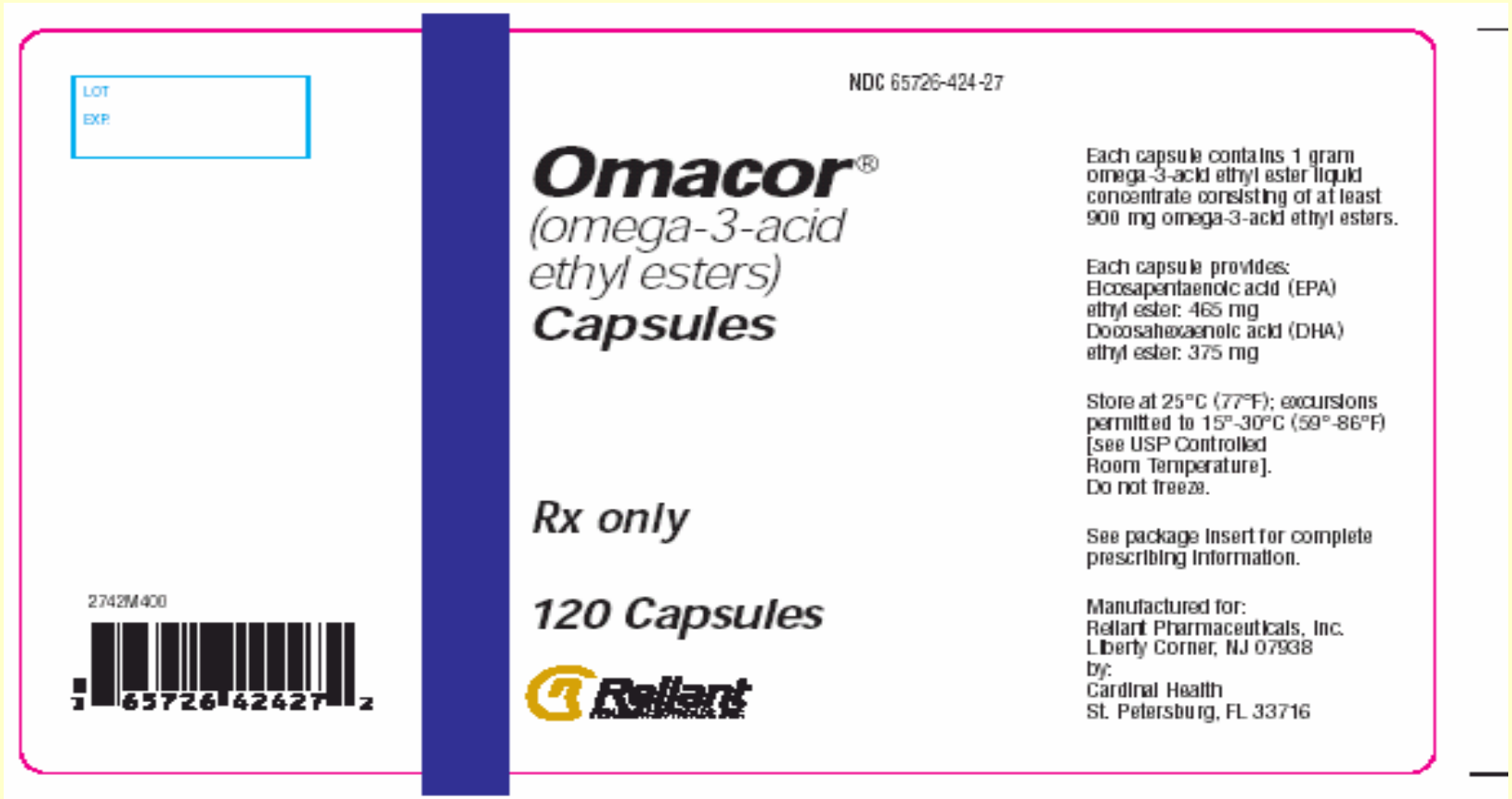
NCAM

GAIT: Response for mod-severe and mild pain . Data = % pts with 20% improvement in pain at 24 weeks.

	All patients	WOMAC Pain 301-400mm	WOMAC Pain 125-300mm
P	60%	54%	62%
CE	70%**	69%¶	70%*
G	64%	66%	64%
CS	65%	61%	67%
G+CS	67%$^{+}$	79%#	63%
	** p= 0.008 CE vs. P $^{+}$ p= 0.09 G+CS vs. P	¶p = 0.06 CE vs. P # p = 0.002 G+CS vs. P	* p= 0.04 CE vs. P

CONCLUSIONS: Combination G+CS is effective in treating moderate to severe knee pain due to OA.

Omacor: a complex biologic agent approved as a drug



NCAM

NCCAM BOTANICAL CLINICAL TRIAL PROGRAM: 2005

- Phase I / II studies
- Phase III studies (older)
- Product Development programs
  - Phase I / II
  - If successful, phase III

NCCAM PHASE I / II BOTANICAL TRIALS

- Echinacea vs placebo for cold
- Black cohost for post menopausal anxiety
- Pycnogenol for lympedema
- Ginger for chemotherapy-nausea
- PUFA for depression
- a-lipoic acid for HIV neuropathy
- Chromium and glucose tolerance
- Oyster mushrooms to decrease lipidemia
- Marine/botanical oils fo rhematoid arthritis

NCCAM PHASE I / II BOTANICAL TRIALS

- IV minerals for fibromyalgia
- Creatine for Huntington's disease
- Melatonin for insomnia
- Valerian for insomnia
- Diet (high carb/low fat vs low carb/high fat)
- Kudzu for alcohol abuse
- Taurine and diabetic neuropathy

NCCAM PHASE III BOTANICAL TRIALS

- GAIT: Glucosamine/chondroitin for knee arthritis
- GEM:Ginkgo Bilboa prevent Alzheimers
- TACT: EDTA/Vitamins prevent 2nd MI
- Phytoestrogens and artherosclerosis
- [Creatine and ALS]
- [SAMe and Depression]

NCCAM PHASE III BOTANICAL PRODUCT DEVELOPMENT PROGRAMS

- Cranberry [Ocean Spray]
  - Prophylaxis for UTI
- Saw palmetto (Indena) and Pygeum africanum [Fournier]
  - Treatment for Benign Prostatic Hypertrophy
- Silymarin [Madaus]
  - Treatment for liver disease due to Hepatitis C or NASH