Legal, ethical and business considerations in developing drugs derived from traditional medicine

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School of Management, Steyr Campus

Drug Design & Development

⇒ Usually involves *design* of small organic molecules

⇒ These usually bind to proteins

⇒ The design is traditionally done by Medicinal Chemists

⇒ It is about helping people – but it is driven by market forces ($)

Brand name	Ingredient	Company	Indication	Sales (growth) [$ billion]
Lipitor®	Atorvastatin	Pfizer	hypoercholesterolemia	7.0 (31%)
Prilosec®	Omeprazole	AstraZeneca	ulcers	6.1 (0%)
Zocor®	Simvastatin	Merck & Co.	hypercholesterolemia	5.3 (25%)
Norvasc®	Amlodipine	Pfizer	hypertension	3.7 (14%)
Prevacid®	Lansoprazole	Takeda/Abbott	ulcers	3.5 (13%)
Zyprexa®	Olanzapine	Eli Lilly	schizophrenia	3.2 (35%)
Celebrex®	Celecoxib	Pharmacia/Pfizer	pain, arthritis	3.1 (32%)
Procrit®	Erythropoietin	J&J/Amgen	anemia	2.9 (35%)
Paxil®	Paroxetine	GlaxoSmithKline	depression	2.8 (19%)
Vioxx®	Rofecoxib	Merck & Co.	pain, arthritis	2.6 (44%)
all 10 products				$ 40 200 000 000

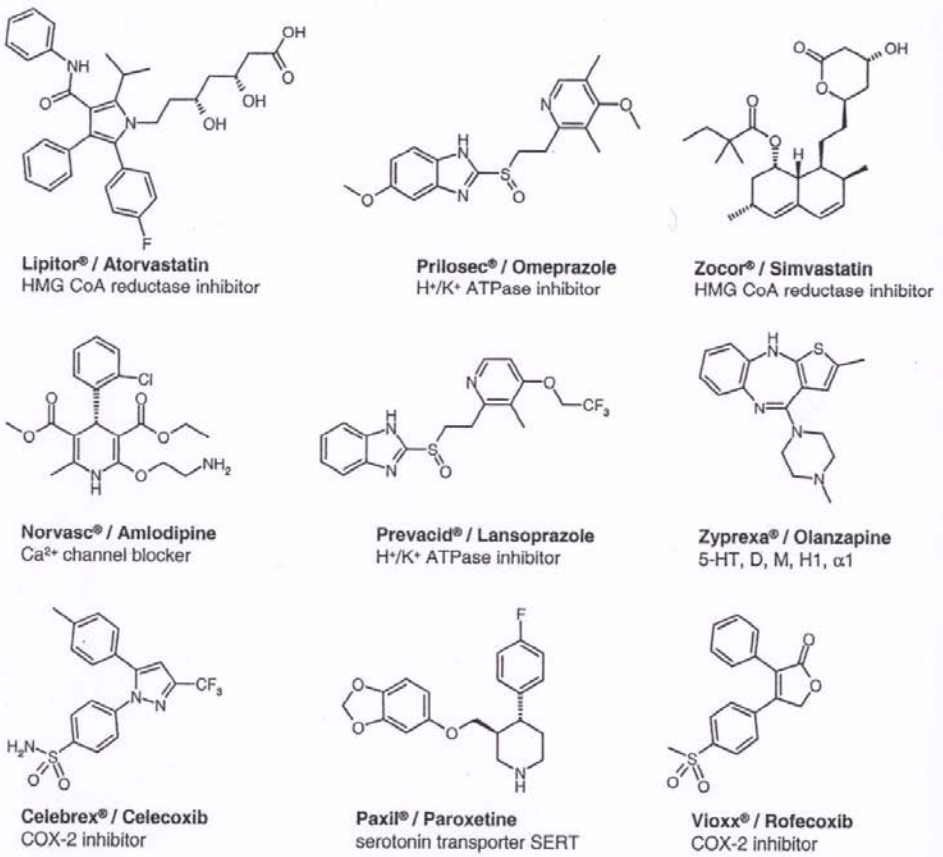


Figure 1.1 Chemical structures of the best-selling drugs of 2001 [4]. Nine of the top ten drugs are low-molecular-weight compounds.

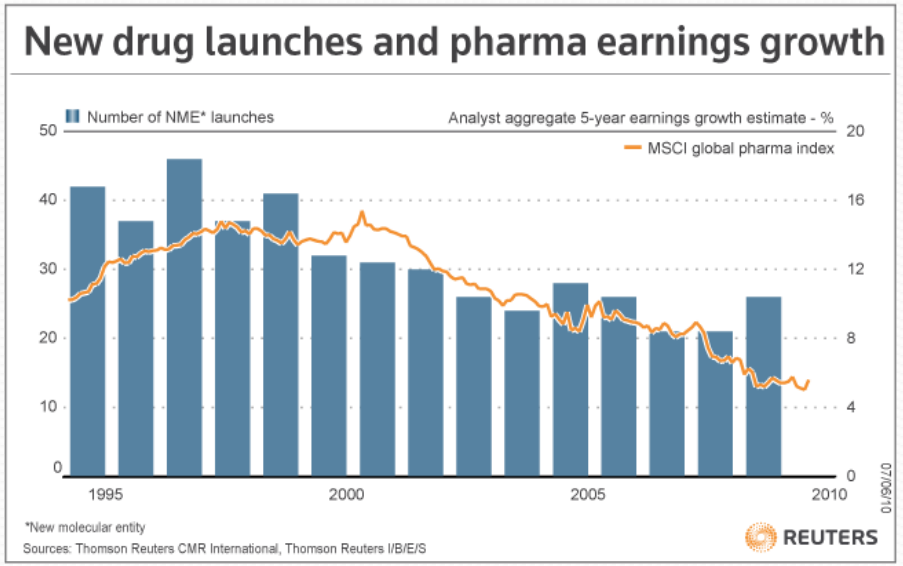
Pharma's Drug Pipeline Problems

- Drug discovery slowing
- "Patent Cliff"

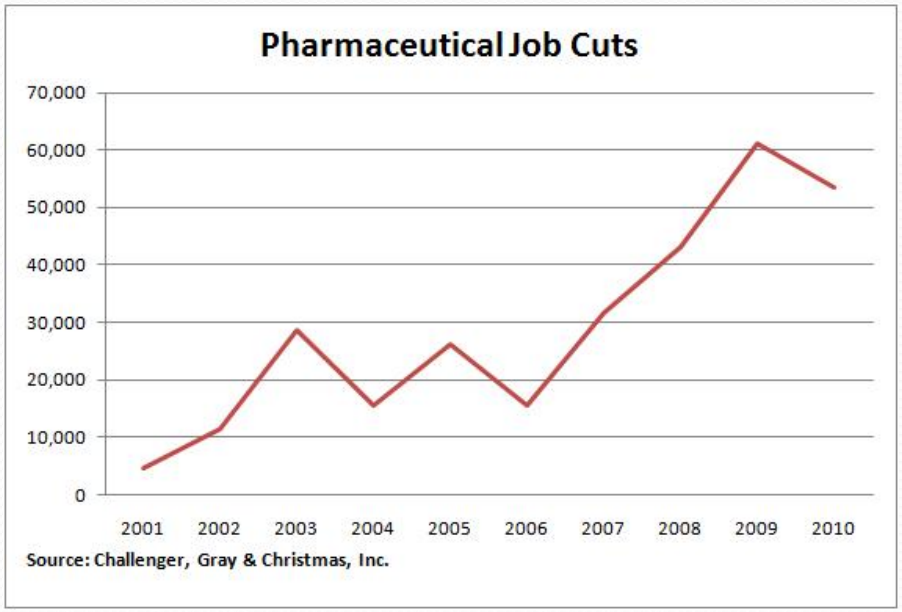
Table 1. Selected Top Brand-Name Drugs With Patent Expirations From 2011 to 2020

Brand	Generic Name	Manufacturer	Expected Availability[a]
Aciphex	Rabeprazole	Eisai	2013
Actos	Pioglitazone	Takeda	2012
Actoplus Met	Pioglitazone/metformin	Takeda	2012
AndroGel 1%	Testosterone	Solvay	2016
Atripla	Efavirenz/emtricitabine/tenofovir disoproxil	Gilead	Uncertain
Avapro	Irbesartan	Bristol-Myers Squibb	Generic available
Avodart	Dutasteride	GlaxoSmithKline	2015
Benicar	Olmesartan	Daiichi Sankyo	2016
Benicar HCT	Olmesartan/hydrochlorothiazide	Daiichi Sankyo	2016
Boniva	Ibandronate	Roche	Generic available
Caduet	Amlodipine/atorvastatin	Pfizer	Generic available
Celebrex	Celecoxib	Pfizer	2014
Combivir	Lamivudine/zidovudine	GlaxoSmithKline	Generic available
Crestor	Rosuvastatin	AstraZeneca	2016
Cymbalta	Duloxetine	Lilly	2013
Detrol	Tolterodine	Pfizer	2012
Diovan	Valsartan	Novartis	2012
Diovan HCT	Valsartan/hydrochlorothiazide	Novartis	2012
Evista	Raloxifene	Lilly	2014
Focalin XR	Dexmethylphenidate ER	Novartis	2012
Geodon	Ziprasidone	Pfizer	Generic available
Gleevec	Imatinib	Novartis	2015
Levaquin	Levofloxacin	Ortho-McNeil-Janssen	Generic available
Lexapro	Escitalopram	Forest	Generic available
Lipitor	Atorvastatin	Pfizer	Generic available
Loestrin 24 Fe	Ethinyl estradiol/norethindrone acetate/ferrous fumerate	Warner Chilcott	2014
Lovaza	Omega-3-acid esters	GlaxoSmithKline	2015
Lunesta	Eszopiclone	Sepracor	2012
Lyrica	Pregabalin	Pfizer	2013
Namenda	Memantine	Forest	2015
Nexium	Esomeprazole	AstraZeneca	2014
Niaspan	Niacin ER	Abbott	2013
Opana ER	Oxymorphone ER	Endo	2013
OxyContin	Oxycodone ER	Purdue Pharma	2013
Plavix	Clopidogrel	Sanofi-Aventis	2012
Protonix	Pantoprazole	Pfizer	Generic available
Reyataz	Atazanavir	Bristol-Myers Squibb	2017
Sensipar	Cinacalcet	Amgen	2016
Seroquel	Quetiapine	AstraZeneca	Generic available
Seroquel XR	Quetiapine ER	AstraZeneca	2017
Singulair	Montelukast	Merck	2012
Strattera	Atomoxetine	Lilly	2017
Tricor	Fenofibrate	Abbott	2012
Viagra	Sildenafil	Pfizer	2020
Vytorin	Ezetimibe/simvastatin	Merck	2014
Zetia	Ezetimibe	Merck	2016
Zyprexa	Olanzapine	Lilly	Generic available

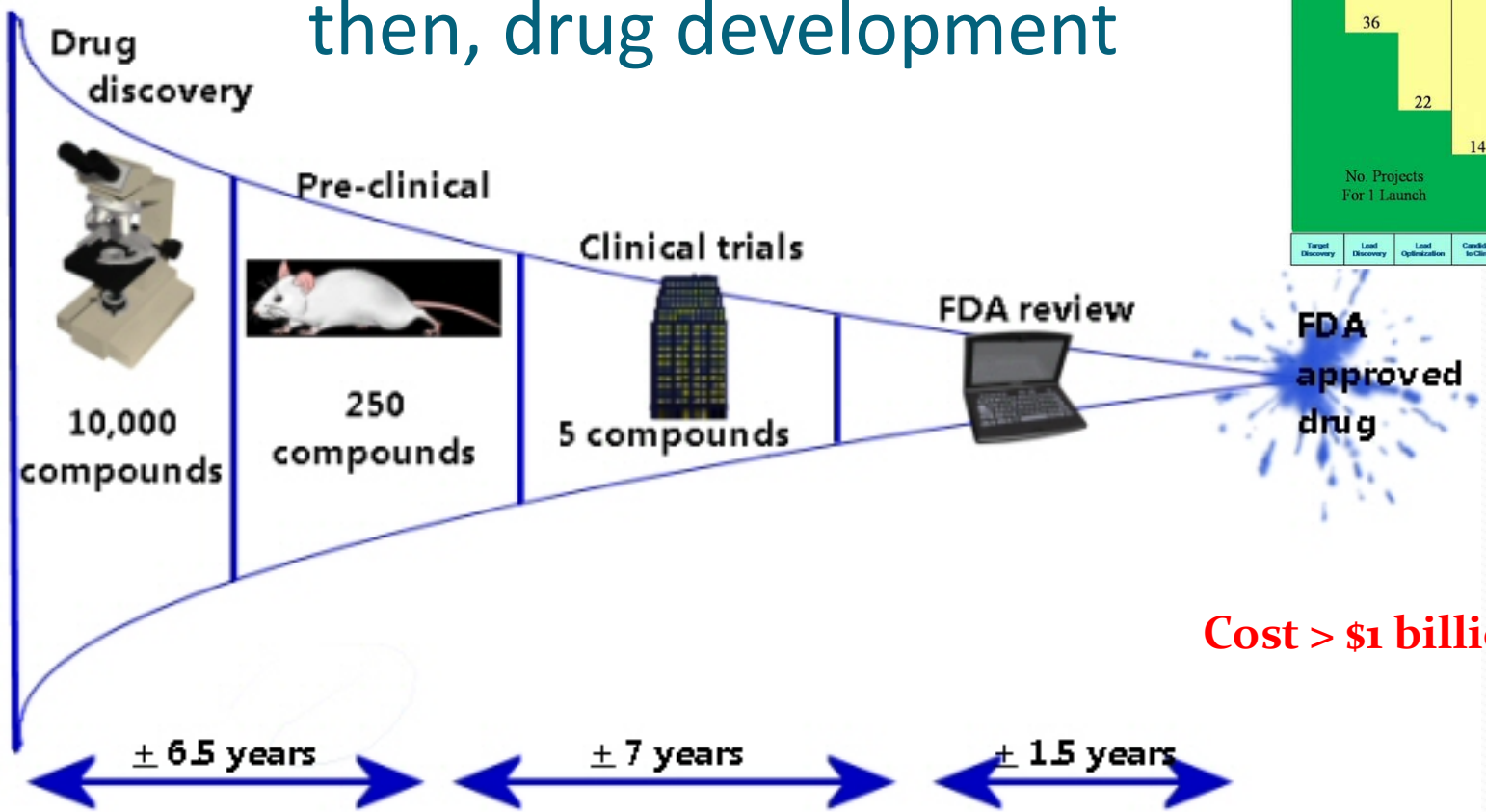
[a] Availability of generics may change due to litigation and patent exclusivities. Products listed may be either approved or tentatively approved and waiting for patent expiration or the resolution of litigation to obtain final approval.
ER: extended release; HCT: hydrochlorothiazide; XR: extended release.
Source: Reference 6.

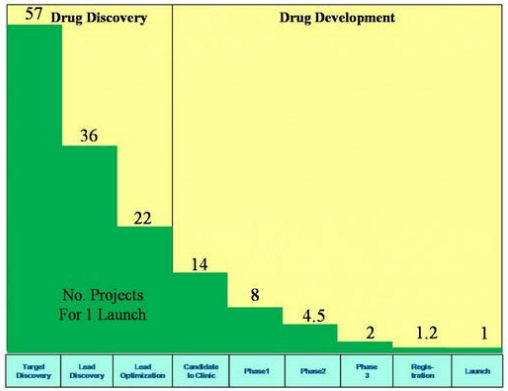


Reuters graphic/Scott Barber



Drug discovery/design; then, drug development





Cost > $1 billion euros

It is costly, and time-consuming; but, maybe medicines used – for thousands of years - by indigenous peoples, are a way to fill pharma's pipelines? Can/should these be commercialized?

http://www.clinical-trials-info.com/wp-content/uploads/2009/03/drug-discovery-1.jpg\

Dr. Anji Reddy quoting George W. Merck:

"We try to never forget that medicine is for the people. It is not for profits. The profits will follow, and if we have remembered that, they never failed to appear."

DR. REDDY'S

- There are > 7,000 rare diseases
- Most have no cure
- Pharma often won't pursue

What is the solution?

Traditional Medicines?

Traditional Medicine as a Source of New Drugs

- Natural medicines used for hundreds of years by indigenous peoples; safe & effective; need clinical studies
- Why not benefit the entire world?

- Problems:
  - Patent law not designed to protect *natural* medicines; no patent means no financial incentive to do clinical trials
    - Can't patent "products of nature" (35 USC §101; Myriad case)
  - Pharmaceutical development is inherently biased for drugs as defined in western (U.S.) medical practice (single active ingredients)
    - Difficult to do clinical trials on "mixtures"
  - Indigenous communities exploited by others looking to make profits
    - Need international law to protect their rights

Traditional Medicine as a Source of New Drugs

Case Study – ayahuasca, from Amazonia (Peruvian rain forest)

- Used by Shamans to treat neurological problems; CNS
- A drink made from multiple components, including ayahuasca root
- Hallucinogenic properties

Picture of a live ayahuasca root (left panel), and a piece of the root sold in a Peruvian market (right panel).

Photo is courtesy of Dr. Dean Arneson

Traditional Medicine as a Source of New Drugs

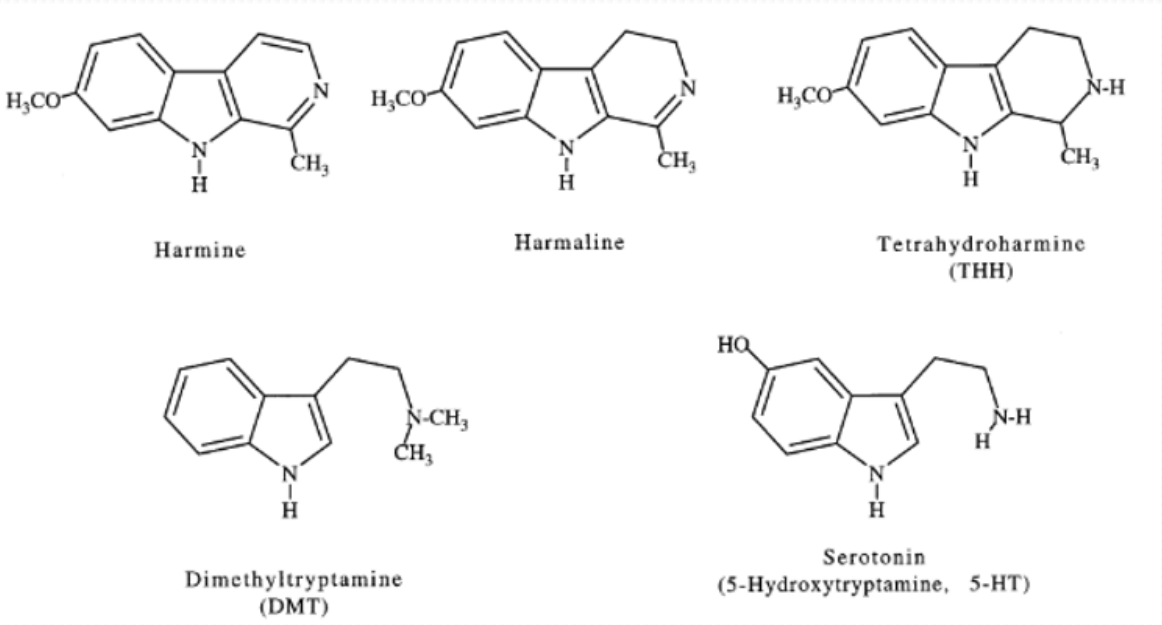
Traditional medical knowledge (TMK) is defined by the **World Health Organization (WHO)** as: "the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses."

Photos courtesy of Dr. Dean Arneson

Traditional Medicine as a Source of New Drugs

Case Study – ayahuasca, from Amazonia (Peruvian rain forest)

- Active chemical ingredient is DMT; has psychotropic effect (mixed also with plant extract that blocks monoamine oxidase)
- Discovered by Harvard biologist Richard Evans Schultes, the father of ethnobotany

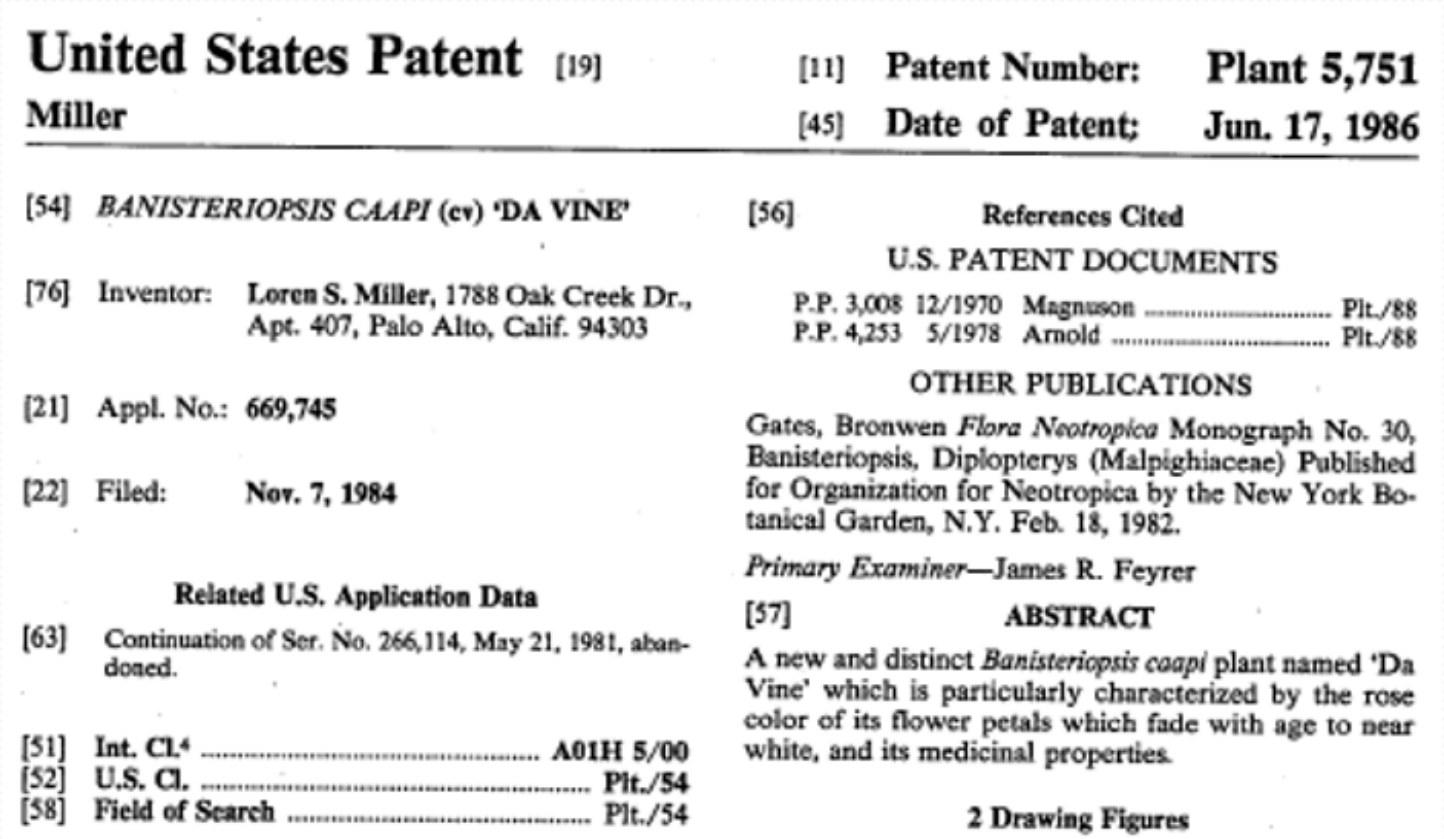


Dr. Richard Evans Schultes in the Amazon

Traditional Medicine as a Source of New Drugs

Case Study – ayahuasca, from Amazonia (Peruvian rain forest)

- Can't develop drug w/o patent; Loren Miller filed a Plant patent
- "Bioprospecting;" David Downs & Glen Wiser file request for reexamination
- Patent invalidated; but, big impact on Peru's desire to protect TMK



United States Patent [19]

Miller

[11] **Patent Number: Plant 5,751**

[45] **Date of Patent: Jun. 17, 1986**

[54] *BANISTERIOPSIS CAAPI* (cv) 'DA VINE'

[76] Inventor: **Loren S. Miller**, 1788 Oak Creek Dr., Apt. 407, Palo Alto, Calif. 94303

[21] Appl. No.: **669,745**

[22] Filed: **Nov. 7, 1984**

Related U.S. Application Data

[63] Continuation of Ser. No. 266,114, May 21, 1981, abandoned.

[51] Int. Cl.⁴ A01H 5/00
[52] U.S. Cl. Plt./54
[58] Field of Search Plt./54

[56] **References Cited**

U.S. PATENT DOCUMENTS

P.P. 3,008 12/1970 Magnuson Plt./88
P.P. 4,253 5/1978 Arnold Plt./88

OTHER PUBLICATIONS

Gates, Bronwen *Flora Neotropica* Monograph No. 30, Banisteriopsis, Diplopterys (Malpighiaceae) Published for Organization for Neotropica by the New York Botanical Garden, N.Y. Feb. 18, 1982.

Primary Examiner—James R. Feyrer

[57] **ABSTRACT**

A new and distinct *Banisteriopsis caapi* plant named 'Da Vine' which is particularly characterized by the rose color of its flower petals which fade with age to near white, and its medicinal properties.

2 Drawing Figures

Traditional Medicine as a Source of New Drugs

Case Study – ayahuasca, from Amazonia (Peruvian rain forest)

- The challenge from a patent perspective is that this use – part of an oral tradition – may not have been documented in any printed publication; and, U.S. patent law does not prevent patenting of subject matter that was simply "in use" in a foreign country
- Downs & Wiser argue that accession sheets of plants from herbarium collections can be categorized as prior art within the meaning of 35 U.S.C. §§ 102 and 103"; so, can't patent

Sample of herbarium sheet from Cayetano University, Peru *Photo is courtesy of Dr. Dean Arneson*

35 U.S.C. §102 (key elements underlined):

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent

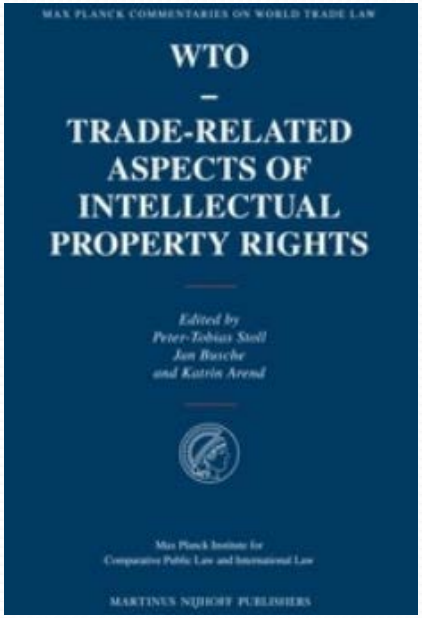
New Patent Law Makes it Impossible to Patent Previously "Used" (e.g. Oral tradition) Inventions

- America Invents Act of 2013; US now more in line with international patent law
- TRIPS: an international treaty that seeks to harmonize IP laws between member countries, while still honoring and respecting national laws and sovereignty
- Must sign TRIPS to be a WTO member (US and Peru are signatories)

The new 35 U.S.C. § 102:

"the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention" {anywhere in the world !}

Less of a need to create herbarium "sheets" as prior art



Traditional Medicine – New Legal Protections

- TRIPS; international intellectual property law alignment
- Trade Promotion Agreement (TPA), signed by the US and Peru, in 2006.
  - Within the TPA is a benefit to the so-called Andean Community countries (Bolivia, Peru, Ecuador, Columbia), via the Andean Trade Protection Act (ATPA). This benefit to the Andean Community countries required that IPRs (Intellectual Property Rights) be protected adequately under WTO, as specified by TRIPS standards.
- Article 68 of the Peruvian Constitution provides a related protection: "The State is obliged to promote the conservation of biological diversity, and protected natural areas."

  (Also Bolivian and Chilean constitutional law)
- *Sui Generis* Protections in Peru: Law No. 27811

Traditional Medicine – New Legal Protections

Peru Law - "Protective Regime for the Collective Knowledge of Indigenous People Derived from Natural Resources" (Law No. 27811; article 5):

(a) To promote respect for and the protection, preservation, wider application and development of the collective knowledge of indigenous peoples;

(b) To promote the fair and equitable distribution of the benefits derived from the use of that collective knowledge;

(c) To promote the use of the knowledge for the benefit of the indigenous peoples and mankind in general;

(d) To ensure that the use of the knowledge takes place with the prior informed consent of the indigenous peoples;

(e) To promote the strengthening and development of the potential of the indigenous peoples and of the machinery traditionally used by them to share and distribute collectively generated benefits under the terms of this regime;

(f) To avoid situations where patents are granted for inventions made or developed on the basis of collective knowledge of the indigenous peoples of Peru without any account being taken of that knowledge as prior art in the examination of the novelty and inventiveness of the said inventions

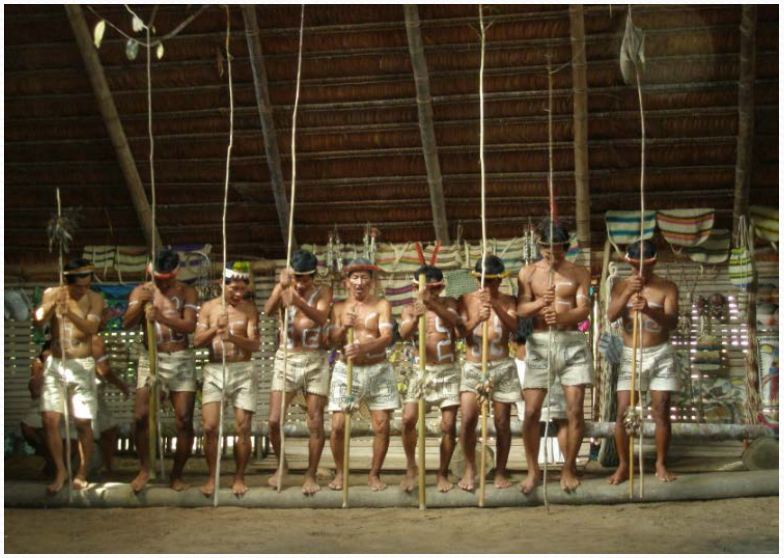
Traditional Medicine – New Legal Protections

International Treaty: TPA with the US - "Understanding Regarding Biodiversity and Traditional Knowledge"

The Parties recognize the importance of traditional knowledge … to cultural, economic, and social development. The Parties recognize the importance of the following: (1) obtaining informed consent from the appropriate authority prior to accessing genetic resources under the control of such authority; (2) equitably sharing the benefits arising from the use of traditional knowledge and genetic resources; and (3) promoting quality patent examination to ensure the conditions of patentability are satisfied

Traditional Medicine as a Source of New Drugs

- TMK is a source of new medicines; world-wide benefit
- Must use with mutual respect: informed consent; sharing of benefits
- Must provide a fair and robust route to patent protection



THANKS
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