Best Practice for Handling and Management of Biotech and TCM Inventions

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Biotechnology

- Growing prominence
- Versatile applications
  - Genetic diagnosis
  - Gene therapy
  - Vaccine
  - Stem cell, tissue regeneration
  - Pharmaceutics, TCM
  - Nutraceuticals, functional food
  - Industrial applications
  - Green energy

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Biotechnology - High Risk Business

- Keen competition
- High R&D cost
- High failure rate
- Strict regulation: pharmaceutics and therapeutics

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Protection and Management

- Prevent misuse and misappropriation of knowledge and innovation

- How?
  - Judicial means – Patent, Trademark, Copyright, Plant Variety Protection Act etc.
  - Administrative/sui generis means– e.g. 中藥品種保護條例
  - Self-reinforcing – Trade secret, branding

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JUDICIAL AND ADMINISTRATIVE PROTECTION

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Patent Protection

- Exclusive right on using and implementing inventions
- Product-DNA, protein, pharmaceutics, TCM, cell line, plant/animal species
- Manufacture -Medical device, laboratory apparatus
- Method -Diagnosis, therapy; Manufacturing, purifying process
- Natural properties – excluded from patent protection system
- Above is 101 subject matter requirements
- 102 Novelty; 103 nonobviousness (inventiveness) and Written Description

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Patentable Natural Matters and Life Forms

Subject matter	U.S.	China	Europe	Japan
Abstract idea Mental Activities	No	No	No	No
Laws of nature Scientific discoveries	No	No	No	No
Natural phenomena	No	No	No	No
Natural products	No	No	No	No
Isolated natural products e.g. gene, protein, chemical	No	Yes	Yes	Yes
Human embryonic stem cells	Yes	No	No – if involve destruction of human embryo	Yes
Animal varieties	Yes – Transgenic non-human animals	No	No	Yes – Non-human
Plant varieties	Plant patent – Asexually reproduced Utility patent – Sexually reproduced	No	No	Yes – Invention Patent
Microorganisms	Yes	Yes	Yes	Yes
Diagnostic methods	No – General diagnostic method	No	No Yes – Outside human body	No Yes – in vitro
Treatment methods	Yes	No Yes – Medical use of compositions	No Yes – Medical use of compositions	No Yes – Medical use of compositions

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U.S. – Matters in natural form are NOT patentable

- March 4, 2014 – All natural matters must be "significantly different" from the natural form to be patentable
- Products
  - Gene, protein, cell, chemical …
  - Mandatory: structural difference; Optional: functional difference
  - "recombinant", "purified" – unpatentable unless having different sequence or structure
- Methods
  - Diagnostic method applying natural laws/correlations
  - Treatment applying natural products
  - Must be specific and non-conventional
  - Not appear to preempt the use of natural laws and products

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Rate of Rejection – U.S.

- 1,000 family applications related to natural matters filed on/before April 1, 2010
- 40% received § 101 rejections
  - 40% - natural laws/principles
  - 23% - natural products

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Rejected diagnostic claims

A method for identifying the human subject as having a genetic predisposition to increased responsiveness to drug ABC, comprising the steps of

isolating a nucleic acid sample,

amplifying a portion of the sequence, and

detecting particular alleles of the sequence at identified genomic positions,

wherein the presence of certain alleles identify the human subject as having a predisposition to increased responsiveness to drug ABC.

- This type of claim is ALWAYS rejected in the 1,000 applications: simply recites the natural correlation
- In some cases, the examiners suggested to add specific primers to amplify the sequence

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Rejected diagnostic claims

A method of detecting a particular medical condition, comprising the steps of

purifying the genomic DNA using a DNA sequence, and

genotyping the genomic DNA.

- In one case, the examiner required a specific limitation of the natural correlation by introducing two specific steps:

  Obtaining a sample, and separating the sample
- Largely increase the burden on proving infringement!
- Possible ways to overcome rejections:
  - The disease-indicative mutation has not been disclosed
  - Novel method to detect the disease-indicative mutation

    i.e., non-conventional practice to apply the natural principles

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Rejected product claims

A kit for amplifying a target nucleic acid, comprising a DNA polymerase, purified DNA from a eukaryotic source, a first primer and a second primer.

- Rejected as the above components are separable even if there is non-natural components (the primers)
- The Examiner clearly requested the applicant to combine the purified DNA and the primers, and include non-naturally occurring products in the claim

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Rejected product claims

Real examples

i) A polypeptide having a sequence of XXXXX.

ii) A polypeptide having a sequence of YYYYY, wherein the polypeptide is attached with a fluorescent label.

iii) A polypeptide having a sequence of ZZZZZWWWWW.

- Sequences XXXXX, YYYYY and ZZZZZ are all naturally occurring.
- Claim ii) can survive since it is attached to a non-natural fluorescent label.
- Claim iii) can survive since the polypeptide is a fusion protein of natural peptide ZZZZZ and non-natural peptide WWWWW.

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Possible patentable inventions in U.S.

- Natural products
  - Derivatives of natural products
  - Optimized formulations and dosages of the natural products
  - Methods of extracting or synthesizing natural products
  - Note: Remain patentable in most countries

- Diagnostic and therapeutic methods
  - Non-conventional steps e.g. new biomarkers, labels
  - Specific therapeutic regime
  - Not patentable in e.g. China, Europe, Japan

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TCM inventions

- Species varieties
  - Plant, fungus etc.
- Botanical pharmaceutics
  - Extracts
  - Concentrated dosage forms
  - Formulations – Da fang, Fu fang
- Manufacturing methods
  - Extraction, processing of botanical materials
  - Manufacturing of pharmaceutics
- Treatment methods
  - Medical use of botanical products
  - Acupuncture, qigong (氣功)

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TCM as Biological Drugs

- Most are marketed as supplements/food in the western world
- United States
  - Just a few TCM approved as drug by the FDA
  - Danshen Dripping Pill (丹參滴丸) - First FDA approved TCM, year 2010
  - For angina and coronary heart disease
  - Identified all active components
  - Well-established pharmacological mechanism
- Asian countries e.g. China, Taiwan, Japan
  - More relaxed regulation

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TCM inventions – Inadequate Protection

- Incompatible with most patent and regulatory systems
- 2000 to 3000 years history – novel?
  - New use of known materials
  - Improved formulation/dosage forms
  - Preparation with lowered toxicity, increased efficacy
- Working mechanism not well-established
  - Based on cultural, spiritual beliefs and concepts - not recognized by the West
  - Lacking scientific proof
  - Difficult to get significant clinical data for regulatory purpose
- Less well-identified and defined
  - Extract: no definite formulation, dosage and regime
  - Composition – chemical structure, physical properties?
  - Product-by-process – ambiguous
  - Treatment – adjusted on individual basis based on assessment

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Patenting TCM Prescriptions and Extracts

- Insufficient description and characterization – ingredients, dosages
- Chemical structure, physical properties (e.g. fingerprints)
- Product-by-process claims

  Rule of necessity

  - Only when there are no other possible means to define the product

  Patentability

  - Determined solely on the basis of the product regardless of the manufacturing process

  Enforcement

  - Difficult since explicit characteristics are lacking
  - Not infringed by a product made by a different process
- Suggestion: claim both the manufacturing method and product-by-process
  - In china, for novel product, infringer needs to prove the accused product was not obtained by the patented method

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Enforcement of TCM Patents

- Invalidation
  - Insufficient description and characterization – indefiniteness
  - Known "traditional knowledge" – Not novel, obvious
  - Unenforceable

- Infringement
  - Design around
  - Small modification on varieties, ratio, dosage of multiple-component TCM
  - Doctrine of equivalence – difficult to prove as mechanism is complex

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Protection of Plant Varieties

- Unpatentable in most countries
  - "Certificate" under the International Union for the Protection of New Varieties of Plants (UPOV) Convention
  - New, distinct, uniform, and stable variety

- Patent
  - US: Plant patent (Asexual), Utility patent (Sexual), also "Certificate"
  - JP: Invention patent
  - KR, PH: Plant patent (Asexual)

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Protection of TCM in China

- Plant species
  - No patent but "Certificate"
- Invention patent
  - TCM prescriptions and extracts (High thresholds – novelty, obviousness, definiteness etc)
  - Medical use of TCM prescriptions and extracts
  - Manufacturing method
  - Treatment/diagnosis not patentable
- "*sui generis*"/administrative protection 《中藥品種保護條例》
  - Protect TCM prescriptions and extracts, not technology and equipment
  - Lower thresholds – just formal registration
  - Grant a monopoly to manufacture the registered TCM
  - NOT exclusive right, NO civil right to sue or seek compensation for damages

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Regulation of the Protection of TCM 中藥品種保護條例

- Maintain quality of TCM, prevent exploitation by foreign enterprises
- Requirements
  - Manufactured within China
  - Listed in the State's drug standards
  - Special curative effects on particular diseases, or attain certain product quality and production standard
- Obtain "TCM Protection Certificate" 中藥保護品種證書
  - Monopoly to manufacture the registered TCM
- Class 1 – 10, 20 or 30 years protection
- Class 2 – 7 years protection
- Trade secret protection for Class 1
  - Manufacturer needs to keep the prescription make-up 處方組成 and manufacturing craft 工藝制法 confidential

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SELF-REINFORCING PROTECTION AND MANAGEMENT

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Trade Secret

- Protect against improper acquisition and use of information
- NOT exclusive right: others can discover a TS by any fair means
- Trade Secret Law protection
  - US ~ Contract Law
  - China ~ Anti-Unfair Competition Law
  - France ~ Civil Law
- Prior use defense e.g. US, China
  - Exempted from patent infringement if a person commercially uses a patented invention in a manufacturing or other commercial process before a prescribed time

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Trade Secret

- Criteria
  - Possess economic value, i.e. provide competitive advantage(s)
  - Kept confidential with reasonable effort to maintain secrecy
  - Useful for a business purpose
- Protectable subject matter
  - TCM prescriptions, formula, dosage etc.
  - Manufacturing processes
  - "Know-how" : Knowledge or experience related to the business/technology
  - "Show-how": For demonstrating a technique

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Patent vs. Trade Secret

	Patent	Trade Secret
Subject matter	Patentable subject matter	Virtually everything
Requirements	Novel, non-obvious, useful etc.	Need not be novel or non-obvious, but potentially useful
Disclosure	Mandatory (risk reverse engineering!)	Kept confidential (successful case 雲南白藥)
Protection	Exclusive right for usu. 20 years	Unlimited (except independent discovery)
Cost	Procuring and attorney fees, maintenance fee	Measures to keep secrecy e.g. confidential agreement, policy
Marketability	More easy to license, patent term adjustment for regulatory review	Less easy to license (& risk disclosure), Less likely to be marketed as drug (need full disclosure of formula & manufacturing process)

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Limitation of Protection and Development

- TCM prescriptions & extracts
  - Incompatible with western medicine & regulatory system
  - Stringent patentability & regulatory requirements
  - A few countries provide patent term adjustment for regulatory review e.g. US, EP, JP, KR
- Extract vs. Mixture of active ingredients
  - May compromise efficacy (e.g. ginsenosides is more defined but less potent than gingseng)
  - Hidden synergistic effects of components in the extract
- Disclosure may facilitate competitors
  - Lose advantages
  - Reverse-engineering – exact formula

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Management – Branding

- Business asset
  - Shareholders' & customers' confidence on the business
- Most pharma put little focus on brand building
  - Limited resources and effort to maintain brand
  - Common belief – value creation based on R&D, i.e. product efficacy
  - Strict regulation on advertising and labelling
- Narrow period
  - Soon decay when new/improved product is marketed

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Importance of Branding

- Minimize competition
  - Esp. generic competition when patent expires
- Customers' loyalty
  - Confidence on a wide spectrum of products and services
- Facilitate global marketing
  - Promote marketing in other countries
  - Gradual build up of an international, well-recognized brand
- Brand positioning – Distinctive
  - Target – patients and health-care providers e.g. physicians, nutritionists
  - Functional characteristics – higher potency, fewer adverse effects
  - Emotional characteristics – pleasure, sense of wellness, sociability from brand experience

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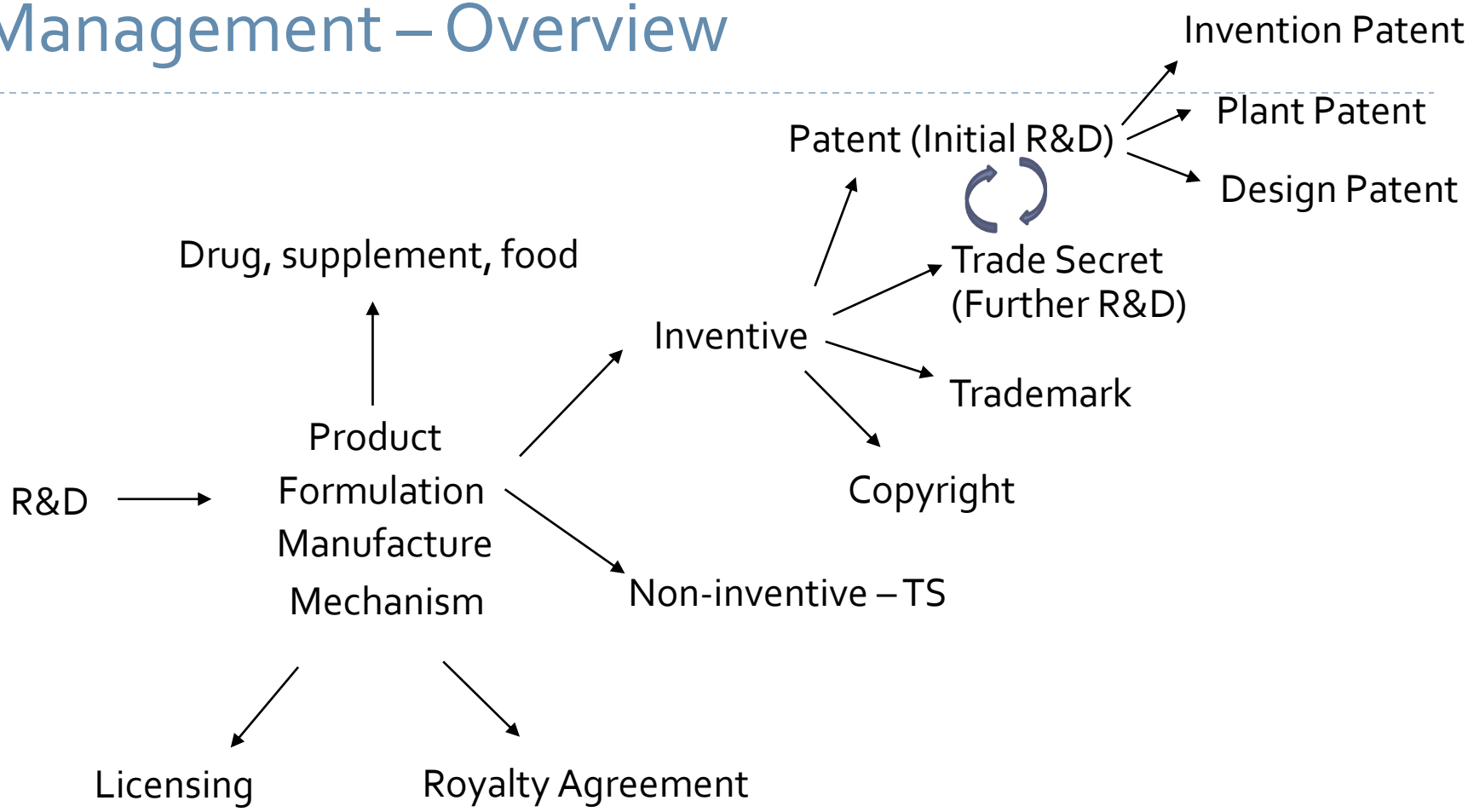
Management – Overview



- R&D – elucidate mechanism, build scientific proof
- IP strategy
  - File U.S. non-provisional asap for new invention
  - Keep application pending

- Always consider trade secret
- Seek administrative protection
- Branding

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Thank You! Questions?

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