香港中藥臨床試驗的規管:現況與前瞻

Regulations of Clinical Trials of Chinese Medicines in Hong Kong : Current Situation and the way forward

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1. 中藥科研對公共衛生的貢獻 Contribution of Chinese Medicines Research to public health

青蒿素 (Artemisinin)

東晉葛洪著的肘後備急方-記載以青蒿治療瘧疾。
(Use of Artemisiae Annuae Herba for malaria treatment was recorded in Zhou Hou Bei Ji Fang of Dong Jin (317-420AD))

自2001年世衛已建議使用以青蒿素為基礎的合併治療方法治療瘧疾

Artemisinin-based combination therapy has been recommended for malaria treatment by WHO since 2001

2011年屠呦呦為發現青蒿素為抗瘧疾
藥物而榮獲拉斯克－狄貝基臨床醫學研究獎
Lasker~DeBakey Clinical Medical
Research Award 2011 winner-
Tu Youyou for discovery of artemisinin

三氧化二砷-白血病治療的作用
Arsenic Trioxide – Role in Leukaemia treatment

上世紀70年代初，黑龍江民間偏方以砒霜治療癌症
During the 1970s, folk remedies from Chinese medicine practitioners were found to be using arsenic to treat cancers

2012年美國國家癌症研究基金會聖捷爾吉癌症創新成就獎得主黃振義和陳竺2012 NFCR Szent-Györgyi Prize Winners Zhen-Yi Wang and Zhu Chen for Progress in Cancer Research

嚴重急性呼吸系統綜合症 –中藥的應用
SARS – Chinese medicine application

新英格蘭醫學雜誌就對照性與有效性草藥製劑臨床試驗的系統性綜述
NEJM systematic reviews of Controlled Trials of Efficacy of Herbal Preparations (N E J M 2002 347:2050)

- 亞洲人參(Asian Ginseng)
  - 未能清晰顯示每一個適應症的效用Efficacy is unclear for each indication
- 大蒜(Garlic)
  - 就某些血脂或抗血小板的效用可能有細少及短期的益處Possible small, short-term benefits on some lipid and anti-platelet effects
- 生薑(Ginger)
  - 就治療噁心及嘔吐有初步有效的數據Promising data in nausea and vomiting
- 貫葉連翹 (St. John's wort)
  - 對輕微及中度的憂鬱症較安慰劑有效Superior to placebo for mild to moderate depression
- 纈草(Valerian)
  - 未有結論性數據去支持失眠症療效Data inconclusive for treatment of insomnia

在美國國家衛生研究院 註冊的臨床試驗
Clinical Trials registered with National Institutes of Health (NIH) in USA

直至2014年6月30日

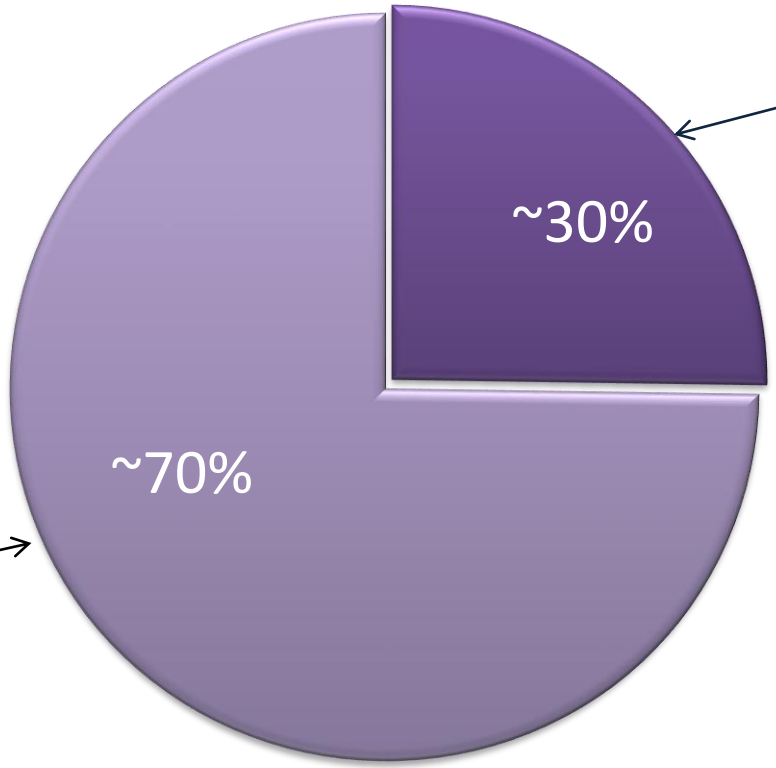
Up to 30 June 2014:

- 總共大約有170,000個已在美國 NIH 註冊的臨床試驗
- Approximately 170,000 clinical trials is registered at U.S. NIH

Reference : www.clinicaltrials.gov, accessed on 14 July 2014

已在NIH註冊的中草藥臨床試驗
NIH Registered Clinical Trials using Chinese Herbs

~80 trials of Chinese herbs registered up to 30 June 2014



registered before June 2009

Registered on or after 1 June 2009

- 直至2014年6月30日，大約有80個已註冊的臨床試驗採用中草藥作為試驗藥物
- 而大約70%中草藥臨床試驗是2009年以後註冊的

Reference : www.clinicaltrials.gov , accessed on 14 July 2014

中西藥的特性比較
Comparison on the special properties of Chinese and Western Medicines

中藥 Chinese Medicines	西藥 Conventional/Western Medicines
◆ 有長遠的使用歷史及文獻記載 Long history of use and literature record	◆ 新發現的化學或生物物質 Newly found chemical or biological entity
◆ 建基於中醫藥理論，多採用多種草藥合成的複方 Based on Chinese medicine theory and use of combination herbal therapy at large	◆ 通常無人類使用歷史 No history of use in human
◆ 藥食同源傳統觀念 Traditional concept of the same source of food and drug in herbs	◆ 通常無人類使用歷史 No history of use in human

Reference :
1. New Perspectives on Chinese Herbal Medicine (Zhong-Yao) Research and Development, Evidence-Based Complementary and Alternative Medicine Volume 2011, Article ID 403709
2. The quest for modernization of traditional Chinese medicine, BMC Complementary and Alternative Medicine, 2013, 13:132

中西藥的特性比較(續)
Comparison on the special properties of Chinese and Western Medicines (cont.)

中藥 Chinese Medicines	西藥 Conventional/Western Medicines
◆ 主要有效成份未必能完全瞭解 Active ingredient may not necessarily be understood	◆ 已確定有效成份，並須於臨床前考核它的藥理毒理及制定相關標準 Active ingredient is confirmed and its pharmaco-toxicology are assessed and quality standards are set before clinical use
◆ 藥材由於是生物，原料質量可因來源地、氣候等因素而導致產品質量有差異 Herbs are living moieties and the quality of raw materials can differ due to its source and weather.	◆ 化學物質質量可由控制生產過程而得到保證 Quality of the chemical substance can be ensured by controlling the manufacturing process.

1. New Perspectives on Chinese Herbal Medicine (Zhong-Yao) Research and Development, Evidence-Based Complementary and Alternative Medicine Volume 2011, Article ID 403709
2. The quest for modernization of traditional Chinese medicine, BMC Complementary and Alternative Medicine, 2013, 13:132

中藥臨床試驗的特性
Distinct properties for Clinical trials of Chinese Medicines

- 傳統中醫藥理論的基本特點是其整體觀念 (holistic approach) 及辨証論治 (syndrome differentiation and treatment)
  - 如何應用中醫辨証論治於西方正統醫學的病証 How to apply the differential treatment of Chinese medicine to the Western medicine's definition of symptoms and disease
- 藥材原料監控非常重要。藥材的化學成分可因天氣、產地、採擇期、製造工藝、炮制方法引致批與批之間不一致而導致每批產品質量不一致。Control of Raw herbs is very important. Chemical composition of herbs may vary from batch to batch due to climate, source, harvest time, product manufacturing and processing methods and lead to inconsistent quality in herbal products.

中藥臨床試驗的特性
Distinct properties for Clinical trials of Chinese Medicines

- 所以中藥臨床研究新思維包括:

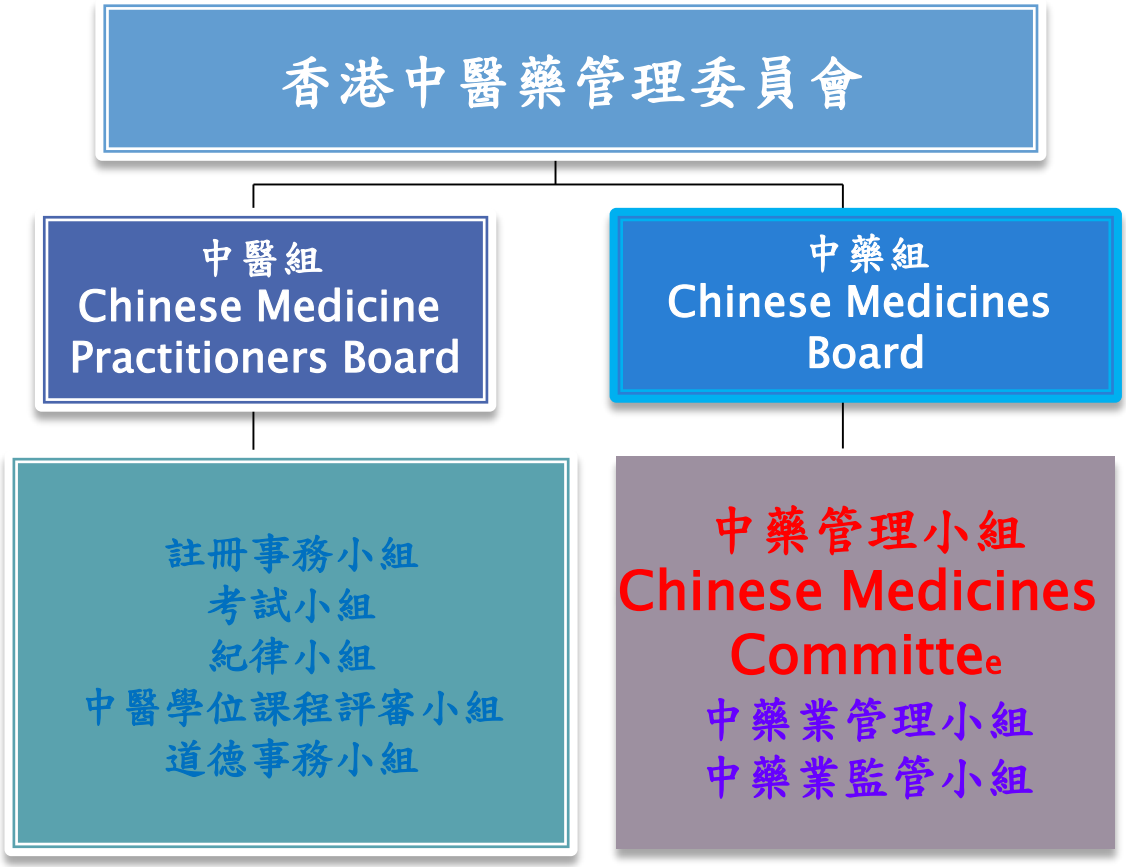
  Therefore， novelty in clinical research of TCM include:
  - 適應症　Indications
  - 試驗設計Study designs
  - 評估指標Endpoints

2. 臨床試驗法規要求及相關指引 Legislative Requirements and Guidelines relating to clinical trials

香港中醫藥管理委員會
Chinese Medicine Council of Hong Kong

根據《中醫藥條例》(第549章)成立的獨立法定組織，於1999年 9月13日成立，負責制訂及實施各項中醫中藥的規管措施。

Established under the Chinese Medicine Ordinance (Cap. 549) in 1999 and responsible for develop and implement the regulatory measures relating to Chinese medicine



中藥業的規管
Regulation of Chinese Medicine Trade

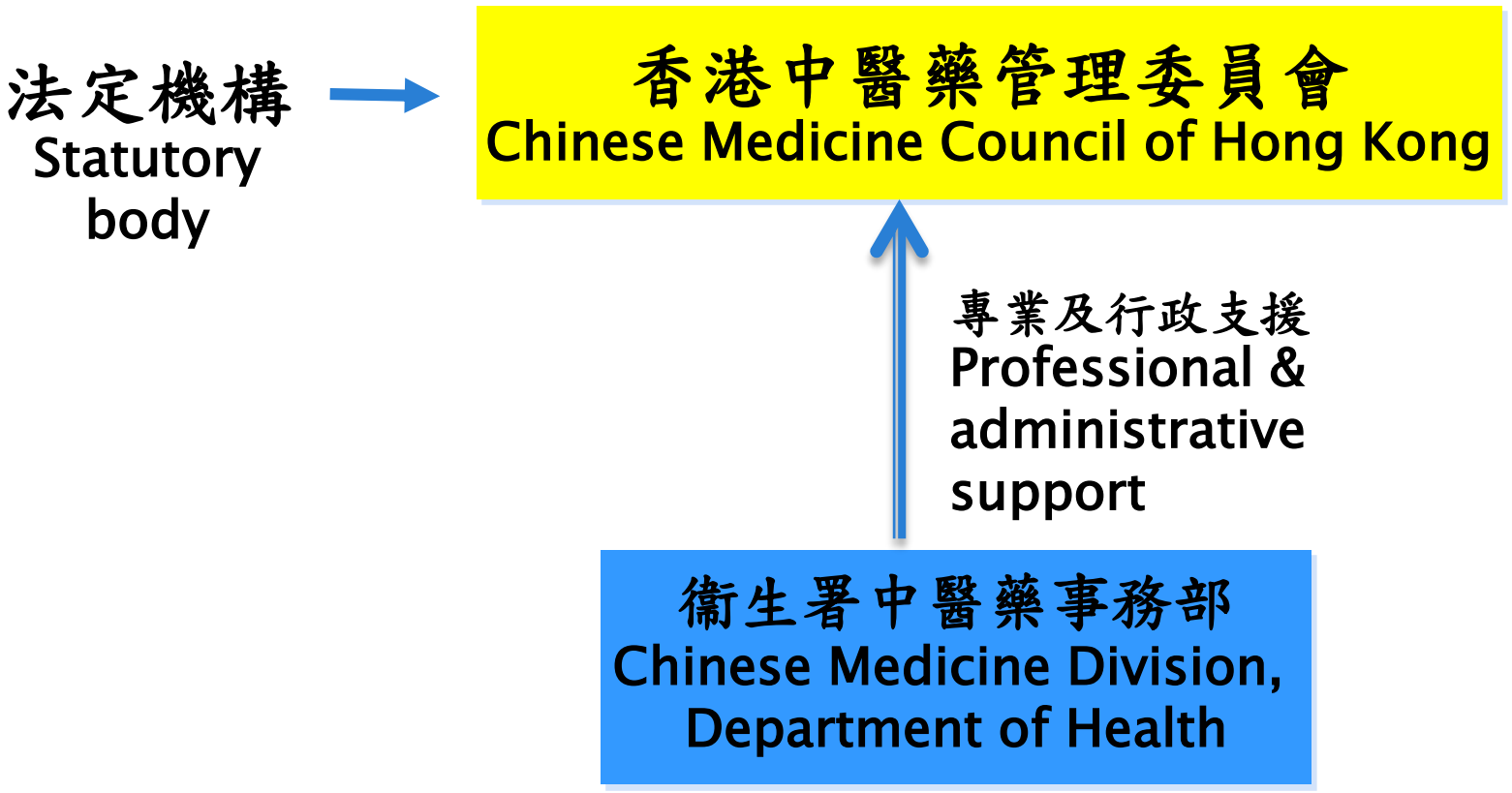
中藥材 Chinese Herbal Medicines

- 中藥發牌制度（零售/批發）Licensing of traders (Retail/wholesale)
- 進出口管制
- 香港中藥材標準
- 市場監測
  - 藥材化驗/不良事件滙報

中成藥 proprietary Chinese Medicines

- 中藥發牌制度（製造/批發）
- 進出口管制
- 中成藥註冊制度 Registration system of proprietary Chinese medicines
- 香港中成藥生產質量管理規範 GMP
- 市場監測
  - 成藥化驗/不良事件滙報

中醫藥規管架構
Regulatory Regime of Chinese Medicines



《中醫藥條例》(第549章)
Chinese Medicines Ordinance (Ch. 549)

中成藥 的釋義 Definition of proprietary Chinese medicine (pCm)—

根據《條例》第2條，“**中成藥**”是指任何符合下述說明的專賣產品
According to s2 of the Ordinance, pCm means：

a) 純粹由下述項目作為有效成分組成 composed solely of the following as active ingredients —

   (i) 任何**中藥材** any Chinese herbal medicines；或

   (ii) **慣常獲華人使用**的任何源於植物、動物或礦物**的物料** any materials of herbal, animal or mineral origin customarily used by the Chinese；或

   (iii) **第(i)及(ii)節分別提述的任何藥材及物料**any medicine materials referred to in (i) & (ii)；

b) 配製成**劑型形式** formulated in finished dose form；及

c) 已知或聲稱用於診斷、治療、預防或紓緩人的**疾病或症狀**，或用於調節**人體機能狀態** known or claimed to be used for the diagnosis, treatment, prevention or alleviation of any disease or symptom of a disease in human beings or for the regulation of functional states of the human body。

《中醫藥條例》（第549章）
Chinese Medicines Ordinance (Ch. 549)

第119條（s119）中成藥須註冊規定proprietary Chinese medicines must be registered —

- 任何人不得銷售；或進口；或管有任何並無根據第121條註冊的中成藥

  No person shall sell, import or possess any proprietary Chinese medicines (pCm) unless it is registered in accordance with s121

- 除非該中成藥的詳情與註冊中成藥的註冊詳情相同，否則不得被視為已根據第121條註冊

  The particulars of a pCm must be identical to that of a registered pCm or it will not be taken as registered

- 2010年12月3日生效

  Effective 3 December 2010

《中醫藥條例》(第549章)
Chinese Medicines Ordinance (Ch. 549)

第158(1)條 (豁免) –
s158(1) exemption –

中藥組可在不論是否有施加條件或限制的情況下，豁免任何與教育或科學研究有關的人士或機構為教育或科學研究目的所需的中成藥:

The Chinese Medicine Board may exempt a person or institution for the purpose of education or scientific research purpose from the requirement on :

a) 中成藥註冊(s119) Registration of a pCm
b) 製造中成藥領有製造商牌照(s131) manufacturing licence for pCm
c) 管有中成藥領有批發商牌照(s134) Wholesale Licence for wholesaling pCm

《中醫藥條例》(第549章)
Chinese Medicines Ordinance (Ch. 549)

- 第129條 (s129) (臨床證驗及藥物測試 Clinical Trial and Medicinal Test)—

- 為方便就任何中成藥進行臨床證驗或進行藥物測試，中藥組可因應申請而發出「臨床證驗及藥物測試證明書」
  To facilitate the conduct of clinical trial or medicinal test of any proprietary Chinese medicines, the Chinese Medicines Board may issue a certificate for clinical trial and medicinal test upon application

《中醫藥條例》(第549章)
Chinese Medicines Ordinance (Ch. 549)

第158(5)(b)條(豁免) Exemption under s158(5)(b) :

第119條的規定並不適用於下述說明的中成藥 —
Nothing in s119 shall apply in respect of a pCm

- 由持有根據第129條發出的有效臨床證驗及藥物測試證明書的人進口並為該證明書所關乎的臨床證驗或藥物測試而使用If it is imported by a holder of a valid Certificate for clinical trial and medicinal test issued under s129 and to be used for the purpose of clinical trial or medicinal test to which the certificate relates

中成藥臨床試驗相關指引
Guidelines relating to clinical trials involving proprietary Chinese medicines

- 臨床證驗及藥物測試證明書申請指引(供業界參考) Guidance Notes on the Application for Certificate for Clinical Trial and Medicinal Test (Reference for Industry)
- 臨床證驗及藥物測試證明書申請須知 Guidance Notes on the Application for Certificate for Clinical Trial and Medicinal Test
- 臨床證驗及藥物測試證明書持有人須知 Guidance Notes for Holders of the Certificate for Clinical Trial and Medicinal Test
- 《中成藥藥品臨床試驗質量管理規範》
  Good Clinical Practice for Proprietary Chinese Medicines

http://www.cmchk.org.hk/pcm/chi/#main_down02.htm#CT_Cert

《中成藥藥品臨床試驗質量管理規範》
Good Clinical Practice for Proprietary Chinese Medicines

- 中藥組於2003年制定，並於2013年修定 formulated in 2003 and revised in 2013
- 為保證臨床試驗過程規範、結果科學可靠、保護受試者的權益並保障其安全 To provide assurance that the trial process is standardized, results are scientific and reliable and protecting the right and safety of trial subjects
- 臨床試驗過程的標準規定，包括方案設計、組織、實施、監查、稽查、記錄、分析總結和報告 serve as standard requirement for the process of a clinical trial, including protocol design, organizing, conducting, monitoring, auditing, recording, analyzing and reporting
- 凡進行各期臨床試驗，包括人體生物利用度或生物等效性試驗，均須按本規範執行 applied to all phases of clinical trial, including bioavailability and bioequivalence studies

《中成藥藥品臨床試驗質量管理規範》（續）
Good Clinical Practice for Proprietary Chinese Medicines (cont.)

重點 Important points：

- 必須符合《世界醫學大會赫爾辛基宣言》的原則

  conducted in accordance with the principles of the Declaration of Helsinki

- 試驗用藥的製造、處理及儲存應按照適用的《藥品生產質量管理規範》（GMP）執行

  Manufacturing, handling and storage of trial drugs should be in accordance with applicable GMP standard

- 臨床試驗應遵循事先已經得到倫理委員會批准的方案進行 conducted in accordance with the protocol approved by the Ethics Committee

- 訂明各方的職責，例如申辦者、研究者等

  Specify the responsibilities of all parties, e.g. sponsor, investigator, etc.

- 訂明臨床試驗的標準規定

  Set out the standard of the clinical trial

審核準則
Assessment Criteria

中藥組已制定相關的審核準則 The Chinese Medicines Board has developed relevant Assessment Criteria

- 《教育及科研人士或機構根據《中醫藥條例》第158(1)條之豁免申請的審核準則》(2013年修訂版)
  Assessment criteria for application for exemption in accordance with section 158(1) by a person or institution concerned with education or scientific research
- 《處理中成藥「臨床證驗及藥物測試證明書」申請的審核準則及程序安排》(2010年)
  Assessment criteria for application for Certificate for Clinical trial and Medicinal Test

3.進行臨床試驗的標準及個案分享
Standards for conducting clinical trials and case sharing

進行臨床試驗的標準
Standards for conducting Clinical Trials

- 《中成藥藥品臨床試驗質量管理規範》
  Good Clinical Practice for Proprietary Chinese Medicines
  - 進行臨床試驗的標準 Standard requirement for conducting clinical trials

- 赫爾新基宣言Declaration of Helsinki
  - 醫學研究的倫理原則Ethical Principles for medical research

國際草藥/傳統藥物臨床研究指引
International herbal/traditional medicine clinical research guidelines

- 世界衛生組織於2000年公佈了傳統藥物研究及評審指引 (WHO General Guidelines for Methodologies of Traditional Medicines)
- 美國食物及藥物管理局 (US FDA)於2004年6月頒佈了草藥產品指引 (FDA Guidance For Industry – Botanical Drug Products June 2004)
- 加拿大藥監局於2005年10月亦製訂了天然健康產品臨床試驗指引 (Health Canada Guidance Document on Clinical Trials for Natural Health Products Oct. 2005)

4.面對的挑戰
Challenges Ahead

面對的挑戰 Challenges Ahead

1. 試驗設計與試驗用藥(Trial Design & Trial Drug)

- 中醫藥主張配製或混合草藥用，用法用量和用藥時間的選擇是針對病人特有的體質而定。此種用藥模式，源於古代，有助於增強藥效及減輕副作用。因此，受試人群共用同一試驗用藥可能未必會得到統一性的結果。

  System of Chinese herbal medicine advocates the use of multi-herbs with specific combination which suits the individual patient and also enhancing efficacy whilst mitigating adverse effects. Therefore, the administration of a trial drug to a study population of various constitutions may not yield uniform outcomes.

- 中藥與西藥或食物的相互作用

  Drug-herb or Drug-food interactions

- 未必有臨床前或前期臨床數據去確定安全

  May not have pre-clinical or previous clinical data to establish safety

面對的挑戰 Challenges Ahead

2.試驗藥物品質控制 Quality control of trial drug product

- 研究過程中所採用的藥物質量維持穩定均一

  Maintaining the same quality of the trial drug throughout the research process

  - 草藥品質會因採藥地理位置、天氣、環境影響、種植方法及採收方法而異。因此，監控草藥以至草藥提取物品質以達致指定標準很困難。

    The quality of the crude herbs varies according to different geographical location of plantation, climate, environmental hazards, cultivation methods and harvest conditions. This leads to difficulty in standardization of the quality of the herbs and herbal products manufactured in different batches.

- 製備對照安慰劑的困難

  difficulty in preparation of placebo control

  - 中药特殊的顏色、氣味、口感很難用完全無治療作用的成份加以模拟

    difficult to produce placebo with the colour, smell and texture identical to the Chinese herbs without using materials of no treatment effect

面對的挑戰 Challenges Ahead

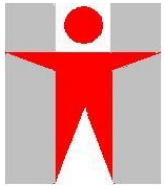
3.中藥現行監管狀況Current Regulatory Environment of Chinese Medicines

- 現時中成藥註冊仍處於過渡性階段，大約仍有八千多個中成藥獲發「確認中成藥過渡性註冊通知書」（GMP製造非強制性要求）
  Currently, registration of proprietary Chinese medicines is still in transitional phase and there are still over 8000 products holding "Notice of confirmation of transitional registration of pCm" (GMP requirements for manufacturers is not mandatory)
- 現時只有12間符合中成藥生產質量管理規範的中成藥製造商
  Only 12 GMP manufacturers in Hong Kong at present time

前瞻 The Way Forward

- 本港中成藥製造商逐漸GMP規範化 GMP Compliance for local manufacturers
- 政策對中醫藥發展的支持 Policy support to the development of Chinese Medicines
- 中醫院的成立 Establishment of a Chinese Medicine Hospital

有助中藥臨床試驗的發展 will facilitate the development of Chinese medicine clinical trials



有效的監管可改善及推進研究
Effective Regulations can improve Research

謝謝
Thank you