台灣臨床試驗發展與未來展望

Chin-Fu Hsiao
Division of Clinical Trial Statistics
Division of Biostatistics & Bioinformatics
Institute of Population Health Sciences
National Health Research Institutes

Outline

- Introduction
- History
- Phase of clinical trials
- 台灣臨床試驗發展
- 未來展望

What is a Clinical Trial?

- **FDA (21 CFR 312.3, April 1994)**

  A clinical trial is the clinical investigator of a drug which is administered or dispensed to, or used involving one or more human subjects

- **Friedman, Furberg, DeMets (1996)**

  A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human subjects

Definition of a Clinical Trial

A prospective study comparing the effect and value of intervention(s) against a control in human subjects

NOTE:

- Prospective not retrospective

- Intervention/Equipment
  - preventive -drug
  - therapeutic -device
  - diagnostic -procedure
  - biologic

- Control Group
  - no intervention -current standard therapy
  - placebo (Diehl, 1938) -previous standard

- Humans not animals
  - ethics
  - informed consent

History

Clinical Trials
Natural Experiment

- **General Lancaster (1600)**
- **East Indian Shipping Co.**
  - 4 ships - Lancaster's ship luckily had lemon juice on board
  - Lancaster's ship remained free of scurvy (壞血病)
  - Natural Experiment, not planned

Clinical Trials
Planned Experiment

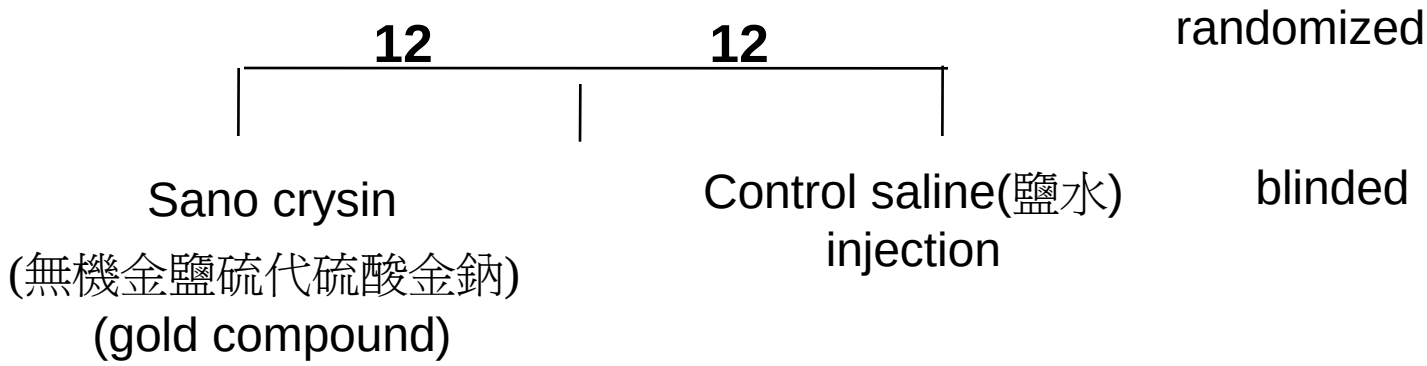
- **Smallpox Experiment (1721)**
  - **Perhaps first planned experiment**
  - **Lady Mary Wortley Montaque**
  - **Six inmates of Newgate Prison**
  - **Sentence commuted if they volunteered for inoculation**
  - **All remained free ⇒ Inoculation effective**
  - **No concurrent control group**

Clinical Trials
Concurrent Control

- **Scurvy Experiment - Lind (1747)**
  - Used control group (concurrent)
  - On board Salisbury
  - 12 patients with scurvy
  - Evaluated 6 treatments (2 subjects/treatment)
  - One treatment (oranges and lemons) had two men recovered

Clinical Trials

- Concept of Randomization in designed experiments, introduced by Fisher into agriculture in 1926
- First randomized clinical trial 1931 by Amberson in tuberculosis patients



Clinical Trials
Use of Randomization

- **Multicenter Trials (1944) - Common Cold**
  - **Medical Research Council**
  - **Treatment of common cold**
  - **Different sites all using common protocol**
  - **Patulin vs. Placebo**
- **MRC Tuberculosis Trial (1948) – "Grandfather Trial"**
  (Ref: *British Medical Journal,* 1948)
  - **Randomized (by random numbers)**
  - **Streptomycin vs. Placebo**
  - **Based on work of Bradford Hill, founder of modern day clinical trial**
- **Supported Concept of Randomization**

Clinical Trials

- The clinical trials emerged as the preferred method in the evaluation of medical interventions only in the past few decades
- Many of the principles have their origins in work by Hill

Phase of Clinical Trials

Phase of Clinical Trials

Phase 0-Preclinical

- Animal studies
- Looking for dose-response

Phase I

- Seeking maximum tolerated dose
- Volunteer patients

Phase II

- Estimate of drug activity
- Estimate of serious toxicities
- Decide if go on further testing

Phase of Clinical Trials

Phase III

- Provide effectiveness of drug or therapy
- Various designs
- Testing for treatment effect

Phase IV

- Long term post Phase III follow-up
- Concern for safety

台灣臨床試驗發展

- 台灣醫療法於民國75年11月24日公布實施，之後由藥政單位開始負責新藥臨床試驗審查
- 最早開始的臨床試驗爲癌症藥品的臨床試驗
- 研發癌症藥品的臨床試驗可適時的提供癌症病患可能極具療效的新抗癌藥物的使用

台灣癌症臨床研究合作組織

- Taiwan cooperative oncology group, TCOG
- 成立於民國78年
- 其設立乃參照美國Eastern Cooperative Oncology Group (ECOG) 之作業程序
- 是國內首次以多個醫院進行同一癌症治療方法之跨院際臨床試驗合作模式

TCOG

- 積極設立諮詢委員會、組織委員會、執行委員會、4個品管委員會、4個療法委員會
- 依國內主要癌症設立16個相關疾病委員會
- 於2008年11月進行重整
- 委員會改以依計畫研提需要而成立研究計畫工作群之模式來運作

TCOG

- 設置有作業執行中心與臨床試驗統計中心
- 作業執行中心負責院際癌症臨床研究之病患登錄、病患資料品質監督與各醫院臨床試驗工作的協調
- 依TCOG各合作醫院參與TCOG研究計畫情況派駐研究護理師，協助TCOG研究計畫於各院之個案篩選、收錄、治療追蹤等工作

TCOG

- 臨床試驗統計中心則負責協助臨床試驗研究方案之設計、審核、建議、修正、釐訂與分析等工作
- 致力於資料管理之電腦化
- 開發完成「臨床研究資訊管理系統, CTIMeS」

Cooperative Hospitals with TCOG in Taiwan

1. Taipei Veterans General Hospital*
2. National Taiwan University Hospital*
3. Tri-Service General Hospital
4. Mackay Memorial Hospital*
5. Chang-Gung Memorial Hospital (Linkou)*
6. Cathay General Hospital
7. Taipei Municipal Jen-Ai Hospital
8. Koo Foundation Sun Yat-Sen Cancer Center
9. Shin Kong Wu Ho-Su Memorial Hospital
10. Taipei Medical University Hospital

11. Taichung Veterans General Hospital*
12. China Medical University Hospital*
13. Chung Shan Medical University Hospital
14. Cheng Ching Hospital
15. Kuang Tien General Hospital
16. Changhua Christian Hospital
17. Show Chwan Memorial Hospital

24. Buddhist Tzu-Chi General Hospital*

18. Chang Gung Memorial Hospital (Chiayi)
19. National Cheng Kung University Hospital*
20. Chi-Mei Medical Center

21. Kaohsiung Medical University Chung-Ho Memorial Hospital *
22. Kaohsiung Veterans General Hospital*
23. Chang Gung Memorial Hospital (Kaohsiung)

*：TCOG dispatching nurse

台灣臨床試驗發展

- 民國82年公布七七公告
- 新藥需要在台灣執行至少40人的臨床試驗方得以查驗登記
- 民國82年開始，台灣的臨床試驗正式邁入新的里程
- 民國87年7月13日成立了財團法人醫藥品查驗中心（center for drug evaluation, CDE)

財團法人醫藥品查驗中心

- 專職於臨床試驗計畫書的科學性評估，與新藥、新醫療器材之查驗登記的風險利益評估等審查業務
- 負責評估族群差異性的銜接性試驗，除對產、官、學、研各界提供一般性法規科學諮詢
- 關鍵途徑計畫對指標性新醫藥提供深度系列法規科學諮詢

台灣臨床試驗發展

- 衛生署依據國際醫藥法規協合會的準則（International Conference Harmonization, ICH E6 guidance），於民國85年11月20日公告藥品優良臨床試驗規範 (good clinical practice, GCP)
- 88年起開始執行的臨床試驗中心之查核 (GCP inspection)

台灣臨床試驗發展

- 民國88至89年間，衛生署公布各個醫療專業領域如核醫放射性藥品、癌症、感染症、心血管疾病、內分泌及新陳代謝治療藥品等之臨床試驗基準
- 90至91年公告有關特殊族群：諸如年老病人、兒童族群、肝功能不全病人、腎功能不全者等的臨床試驗基準
- 藥品優良臨床試驗規範於91年9月20日更新，並於94年1月6日修正後，稱之爲藥品優良臨床試驗準則

藥品優良臨床試驗規範之訓練

- 98年5月20日修正後的醫療法第8條規定，本法所稱人體試驗，係指醫療機構依醫學理論於人體施行新醫療技術、新藥品、新醫療器材及學名藥生體可用率、生體相等性之試驗研究

藥品優良臨床試驗規範之訓練

依據98年12月14日衛生署新公布之人體試驗管理辦法第四條第二項及第三項規定，試驗主持人應具備的資格包括

- 最近六年曾受人體試驗相關訓練30小時以上
- 於體細胞或基因治療人體試驗之主持人，另加5小時以上之有關訓練
- 最近六年研習醫學倫理相關課程9小時以上

藥品優良臨床試驗規範之訓練

- 醫師必須完成至少30小時的GCP訓練並取得證明後，才具備試驗主持人資格
- 政府主管單位、學界、合約研究機構 (contract research organization, CRO)與醫療聯盟團體例如台灣醫界聯盟基金會(FMPAT）共同群策群力的規劃訓練課程
- 涵蓋藥物法規科學規範與指引、藥品優良臨床試驗基準之執行、醫學倫理之考量、臨床試驗計畫書的撰寫與申請、中草藥的研發、生物製劑的研發、銜接性試驗評估、藥動/藥效學、生物統計等

銜接性試驗

- **An approved local clinical trial study report is required for the new drug application in Taiwan--July 7 Announcement in 1993**

Disadvantage:

- A sample size of 40 as required would be difficult to demonstrate significant importance clinically or statistically
- The study design of the local trial usually only repeated a study that has been done in the foreign countries but in a smaller sample size; The study has not been designed based on the medical situation in Taiwan

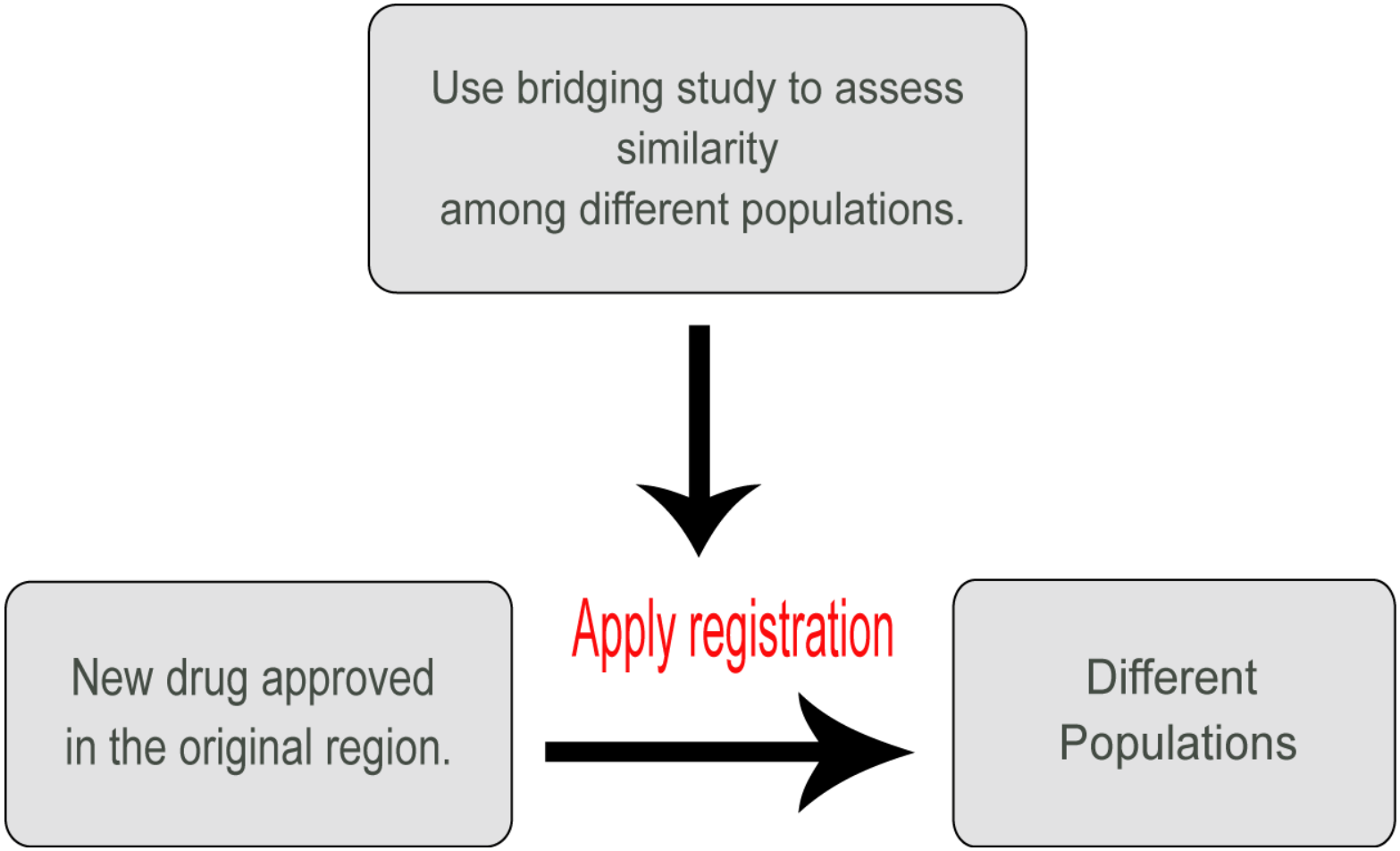
銜接性試驗

- 銜接性試驗 (bridging study) 爲評估藥物的吸收、代謝、療效、副作用、與安全性，是否具有族群差異性 (ethnic sensitivity) 的試驗
- 依循國際醫藥法規協合準則ICH E5 的精神，台灣領先亞洲各個國家，首先於民國89年12月12日訂定並執行銜接性試驗評估（bridging study evaluation, BSE）

銜接性試驗

- 衛生署於91年5月29日公布的「銜接性試驗基準－接受國外臨床資料之族群因素 (ethnic factors) 考量」
- 民國98年衛生署將銜接性試驗評估正式列入於我國藥品查驗登記應執行之項目
- 新成分新藥、基因工程藥品、疫苗類藥品、生物相似性藥品、屬新成分藥品之血漿製劑及過敏原製劑須於我國申請查驗登記前或是同時進行銜接性試驗評估，若具有顯著的族群差異性存在時，必要時得於國內執行銜接性的臨床試驗

銜接性試驗


Use bridging study to assess similarity among different populations.
New drug approved in the original region.
Apply registration
Different Populations

銜接性試驗

- Smoothly convert compulsory Local Clinical Trial (LCT) to meaningful bridging study
- Gradually, stepwise announce waived local clinical trial
- Create an environment: (1) meet international regulation, ICH
  (2) require optimized dosage for Taiwanese patient
- Communicate with local and international pharmaceutical industry
- Announce new regulation according to the international norm and the consensus from communications
- Create an international platform “ APEC – Taipei”
- Implement Double Twelve Announcement – Bridging Study

銜接性試驗

- 1998 Announce: two years later, switch from LCT to bridging study
- 1998 Five announcements of LCT wavier
- Many communications and negotiations with IRPMA and PMA.
- 2000, Dec.12, (Double Twelve Announcement) – public announce bridging study regulation
- Two years transition periods: both LCT and bridging studies acceptable from 2000 ~ 2002
- Many international conferences held in Taipei and other Asian countries, regarding BS, through the APEC platform
- Ask CDE to complete the practical issues relate to implement BS
- 2004, Jan. 1, Bridging evaluation

人體試驗委員會

- 醫學雜誌要求論文需有人體試驗委員會同意函
- 研究資助單位要求申請之計畫書需有人體試驗委員會同意函
- 美國從1981年起，政府贊助的各項研究，一定要有人體試驗委員會同意函
- 國家衛生研究院自1999年起
- 衛生署自2000年起
- 國科會自2001年起

人體試驗委員會

- 民國86年成立聯合人體試驗委員會(Joint Institutional Review Board, JIRB)，參與聯合人體試驗委員會的醫院共有93家，其中17家爲醫學中心
- 98年成立台灣臨床研究倫理審查學會(Taiwan Association of IRB, TAIRB)的設置

臨床研究中心

- 民國88年開始，衛生署在20個醫學中心與地區教學醫院成立了臨床研究中心 (general clinical research center, GCRC)
- 目標爲整合各個醫院與實驗室的醫療資源，發展訓練課程，設置研究單位，以期提昇台灣臨床試驗研究的能力
- 民國95年，以臨床研究中心做爲基礎，進一步設立了國家級卓越臨床試驗與研究中心 (national centers of excellence in clinical trials and research, CECTR)

臨床研究中心

- CECTR初始時分設置於台灣大學附設醫院、成功大學附設醫院、三軍總醫院、台北醫學大學萬芳醫院
- 民國99年再增加中國醫藥大學附設醫院與長庚紀念醫院

現階段臨床試驗

- 台灣單一試驗中心
- 台灣多個試驗中心
- 多國多試驗中心的臨床試驗
- 國內查驗登記所作之臨床試驗(local trials for local registration)
- 學術界之臨床試驗研究 (academic research)
- 政府支持的新藥研發計畫 (governmentsponsored new drug development projects)
- 試驗主持人發起之臨床試驗研究 (investigator initiated study, ISS)

我國執行各期臨床試驗

	2004		2005		2006		2007		2008		2009		2010	
	P	S	P	S	P	S	P	S	P	S	P	S	P	S
第一期	8	12	14	26	12	20	10	18	11	14	18	19	19	21
第二期	22	57	33	78	32	98	46	158	46	120	60	167	49	137
第三期	85	237	69	242	86	300	106	391	132	527	95	407	119	527
第四期	4	10	4	5	3	4	6	14	16	21	14	19	21	30
總和	119	316	120	351	133	422	168	581	205	682	187	612	208	715

台灣優勢

- 亞洲國家中，參與臨床試驗(sponsored clinical trial)計畫與試驗中心的數目，以日本排名第一，接著爲印度、中國、韓國，台灣排名第五
- 參與多國多中心的臨床試驗城市評比，則台灣台北的排名爲第二
- 臨床試驗計劃在台灣執行所需的費用，約爲在歐美執行所需費用的50-70%

台灣優勢

- 交通便利快捷，臨床試驗中心的地理位置，並未造成試驗執行上的不便
- 民國89年開始每年舉辦的亞太經合會之藥物法規科學網絡會（APEC network of pharmaceutical regulatory science conference），持續推動我國臨床試驗的法規科學保持與國際接軌
- 具有深諳臨床試驗的試驗主持人與專家群，以及完善的臨床試驗環境

台灣生醫科技產業起飛之鑽石計畫 (The diamond actionplan for biotech takeoff)

- 於商業生產過程中強化產業具有價值的生產線與臨床前之研發
- 設置生物科技發展基金，促進整合性的培養機制
- 成立台灣藥物與食品檢驗局
- 期許透過整合機制，吸引並培育更多人才投入，以確保台灣在亞洲的領先優勢

未來展望

臨床試驗瓶頸

- Currently, only 10% of investigational new drug (IND) applications to the FDA result in clinically approved agents, and in oncology it is only 5%
- The development of a new agent is a lengthy and expensive process and many of these agents fail relatively late in that process
- Annual spending on biomedical research nearly doubled in the USA between 1994 and 2003, reaching US$94.3 billions

臨床試驗瓶頸

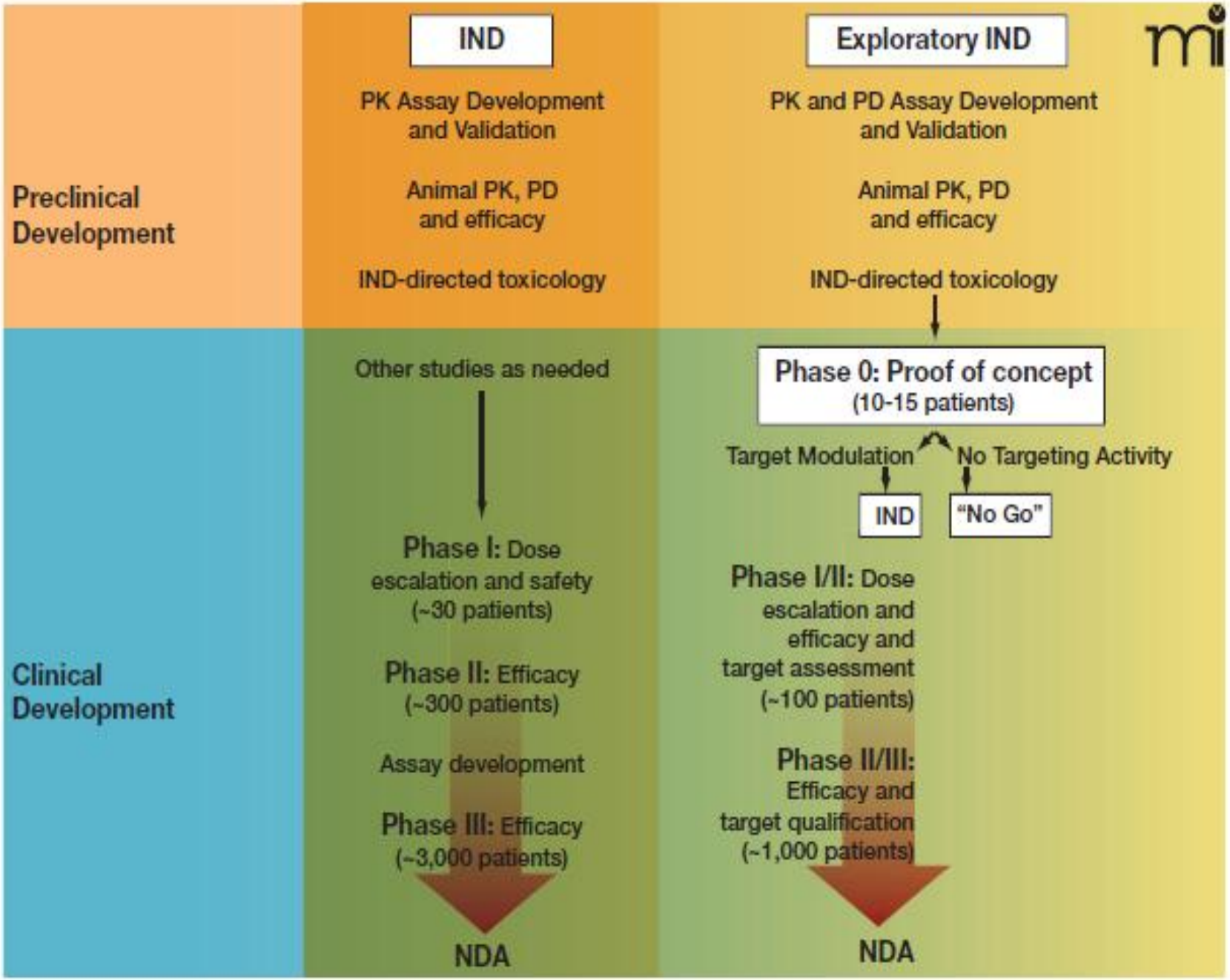
- Many drug products were recalled due to safety issues after regulatory approval
- Current paradigm was developed for the twenty century
- No longer functioning for the 21st century
- New Concepts
- New Strategies
- New Methodologies

未來趨勢

- Phase 0 trial
- Global drug development
- Adaptive design

Phase 0 Trials

- An increasing proportion of IND agents is molecularly targeted
- Testing the agent for effectiveness against the target by means of a pharmacodynamic (PD) assay very early in the drug development process may be necessary
- The FDA issued a new Exploratory IND Guidance in 2006, to allow for such studies as small first-in-man trials


IND
Exploratory IND
PK Assay Development and Validation
PK and PD Assay Development and Validation
Animal PK, PD and efficacy
Animal PK, PD and efficacy
IND-directed toxicology
IND-directed toxicology
Preclinical Development
Other studies as needed
Phase 0: Proof of concept (10-15 patients)
Target Modulation
No Targeting Activity
IND
"No Go"
Phase I: Dose escalation and safety (~30 patients)
Phase I/II: Dose escalation and efficacy and target assessment (~100 patients)
Phase II: Efficacy (~300 patients)
Assay development
Phase II/III: Efficacy and target qualification (~1,000 patients)
Phase III: Efficacy (~3,000 patients)
Clinical Development
NDA
NDA

Global Drug Development

- Bridging Studies
  - For clinical trials without including Taiwan patients, how to conduct a bridging study in Taiwan for assessment of similarity of treatment effect between Taiwan and other counties?
- Multi-regional Trials
  - For clinical trials including Taiwan patients, how to assess the similarity of treatment effect between Taiwan and all regions?

ICH E5 (1998)

ICH (International Conference on Harmonisation) E5

Ethnic Factors in the Acceptability of Foreign Clinical Data

The purpose of this guidance is to facilitate the registration of medicines among ICH regions by recommending a framework for evaluating the impact of ethnic factors upon a medicine's effect, i.e., its efficacy and safety at a particular dosage and dose regimen.

Multi-Regional Clinical Trials

- A bridging study is usually conducted in the new region after the test product has been approved in the original region

- Extensive duplication of clinical evaluation in the new region not only requires valuable development resources but also delay availability of the test product to the needed patients in the new regions

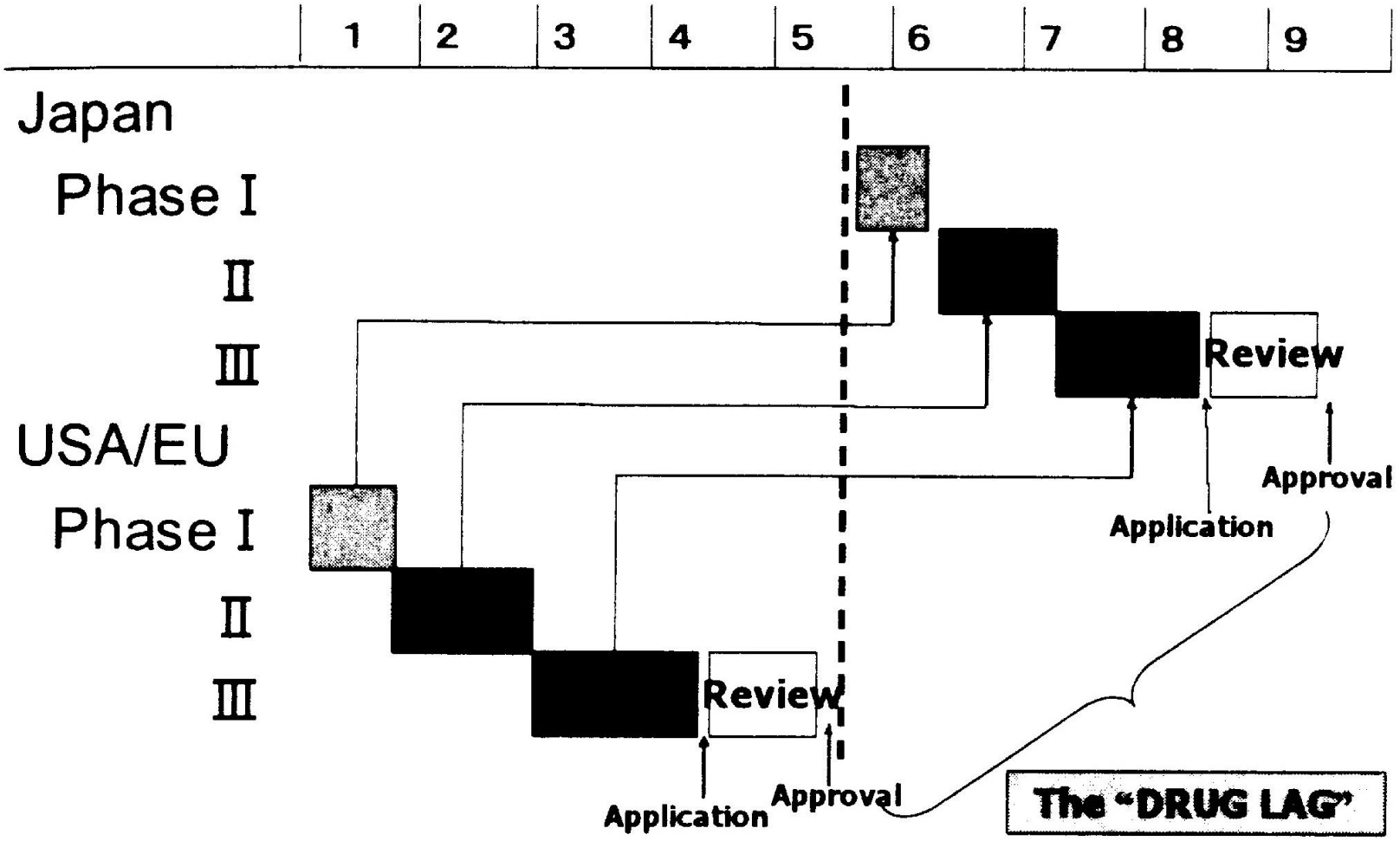
- To shorten the drug lag or the time lag for approval, simultaneous drug development, submission, and approval in the world may be desirable

Drug Lag

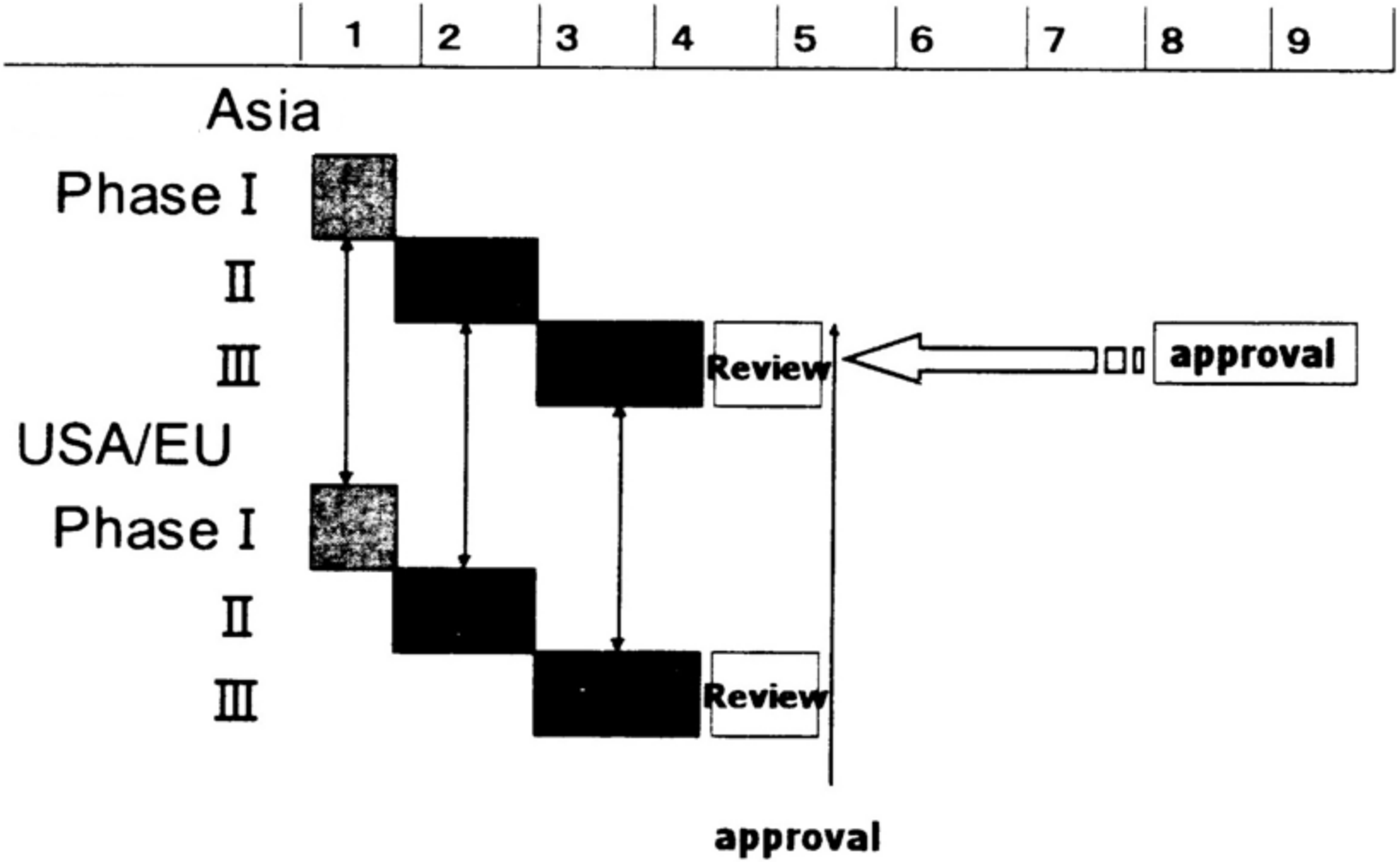
Number of products waiting for marketing among world's top 88 selling-products in 2004

- Japan: 28
- Russia: 27
- Singapore: 22
- Taiwan: 12
- France: 9
- Korea: 5
- Germany: 2
- UK: 1
- USA:0

Full development in each region



Involvement in Global Clinical Study



Japanese Ministry of Health, Labour and Welfare (MHLW)

The guideline "*Basic Principles on Global Clinical Trials*" (2007)

"global clinical studies refer to studies planned with the objective of world-scale development and approval of new drugs in which study sites of a multiple number of countries and regions participate in a single study based on a common protocol and conducted at the same time in parallel."

Key Words in Q11 Answer

- Multiregional Trials serving as a bridging study
- Hierarchy of persuasiveness
  - The most persuasive results
    - Statistical significant in overall result AND
    - Statistical significant in region of interest
  - Still persuasive results
    - Statistical significant in overall result AND
    - Region of interest could not reach statistical significance BUT
    - Consistent trends across regions

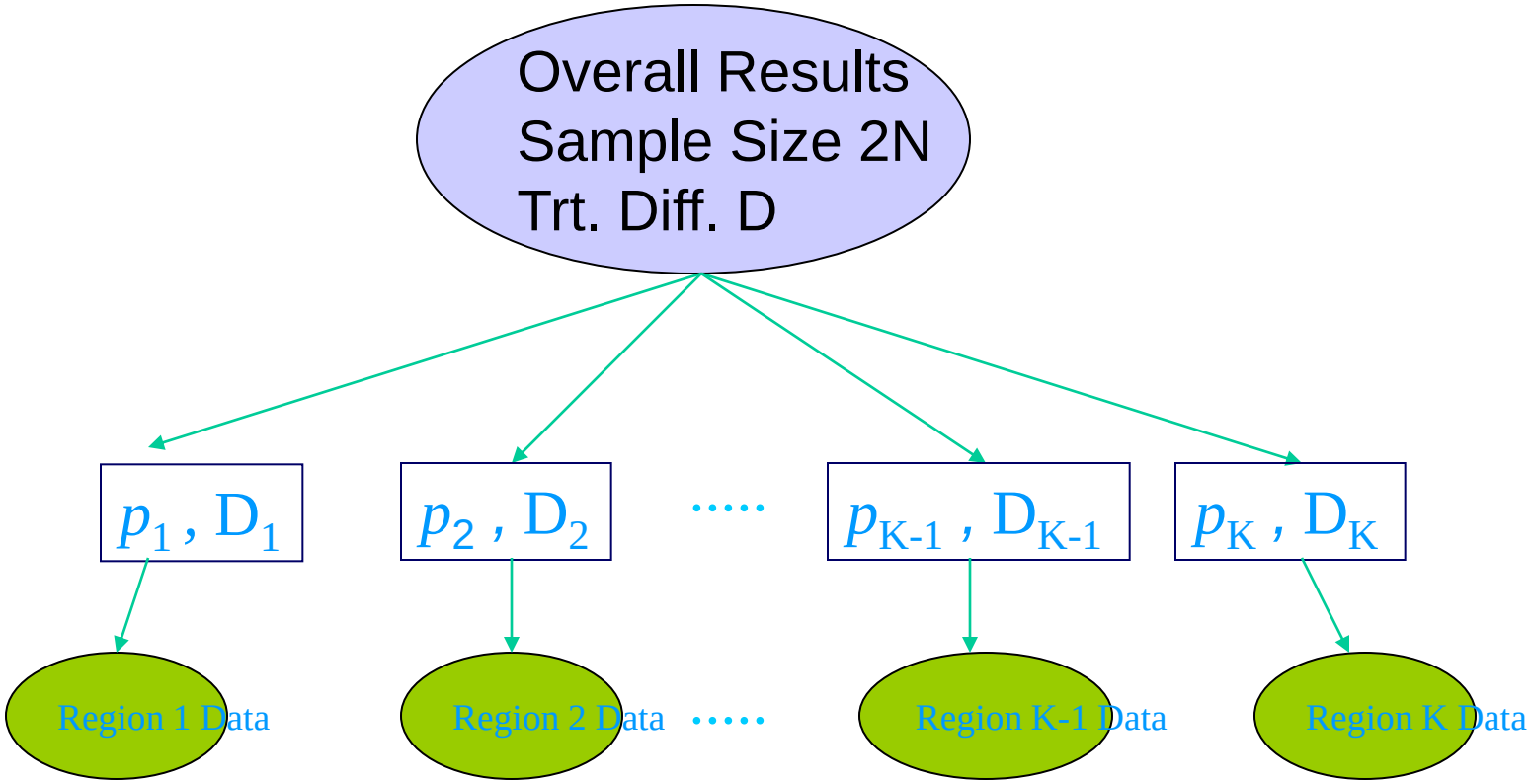
Multi-Regional Clinical Trials

- For clinical trials including Taiwan patients, how to assess the similarity of treatment effect between Taiwan and all regions?
- How large should the sample size be required for Taiwan?

Assumption and Notation

- p_i is the proportion of patients in the i^{th} region
- D_i is the observed mean difference in the i^{th} *region*
- D is the observed mean difference from all regions

Multi-Regional Results



Japanese Criterion

Given that the overall result is significant at α level, we will judge whether the treatment is effective in the Region 1 by the following criterion.

$D_1 \geqq \rho D$, for some $\rho > 0$

Aim

To determine p_1 to ensure that the assurance probabilities of the consistency criterion given $\Delta=\delta$ are maintained at a desired level, say 80%.

α =0.025, β=0.1, and ρ=0.5

p_1	AP
0.10	0.72
0.15	0.76
0.20	0.80
0.25	0.83
0.30	0.86
0.35	0.89
0.40	0.91
0.45	0.93
0.50	0.94
0.55	0.96
0.60	0.97
0.65	0.98
0.70	0.99
0.75	0.99
0.80	1.00
0.85	1.00
0.90	1.00

我國參與多國多中心之臨床試驗

	2004		2005		2006		2007		2008		2009		2010	
	P	S	P	S	P	S	P	S	P	S	P	S	P	S
台灣單一試驗中心	32	32	24	24	11	11	21	21	34	34	38	40	47	55
台灣多個試驗中心	25	88	10	43	22	74	20	81	16	49	9	35	17	60
多國多試驗中心	62	196	86	284	100	337	127	479	155	599	140	537	144	600
總和	119	316	120	351	133	422	168	581	205	682	187	612	208	715
多國多中心比率%	52.1%		71.1%		75%		75.6%		75.6%		74.9%		69%	

Key Issues in Global Clinical Trials

- Global communication
- Translation
- Differentiation and less understanding
- Local requirements and adjustment
- Long preparation period

Critical Path Initiative

- In its 2004 Critical Path Report, the FDA presented its diagnosis of the scientific challenges underlying the medical product pipeline problems.
- On March 16, 2006, the FDA released a Critical Path Opportunities List that outlines 76 initial projects (six broad topic areas) to bridge the gap between the quick pace of new biomedical discoveries and the slower pace at which those discoveries are currently developed into therapies.

65

Critical Path Opportunities List

- Better evaluation tools
  - Biomarker qualification and standards
- Streamlining clinical trials
  - Advancing innovative trial designs
- Harnessing bioinformatics
- Moving manufacturing into the 21st century
- Developing products to address urgent public health needs
- Specific at-risk populations - pediatrics

66

What Is Adaptive Design?

- There is no universal definition
  - Adaptive randomization, group sequential, and sample size re-estimation, etc.
  - Chow, Chang, and Pong (2005)
  - PhRMA (2006)
  - FDA (2010)
- Adaptive design is also known as
  - Flexible design (EMA, 2002, 2006)
  - Attractive design (Uchida, 2006)

67

FDA Guidance

An adaptive design clinical study is defined as a study that includes a **prospectively planned** opportunity for **modification** of one or more specified aspects of the study design and hypotheses based on **analysis of data** (usually interim data) from subjects in the study

Adaptive Two Stage Designs

Stage 1 / Stage 2

Phase II B / Phase III

Phase II A / Phase II B

Early Aspect / Late Aspect

- Purpose: Combining data into one trial
- Nature of Study: Exploratory vs. Confirmatory

Adaptive Seamless Phase II/III Design

An adaptive seamless phase II/III design is a seamless phase II/III trial design that would use data from patients enrolled before and after the adaptation in the final analysis

Adaptive Seamless Trial Design

- Characteristics
  - Combine two separate trials into a single trial
  - The single trial consists of two phases
    - Learning phase
    - Confirmatory phase
  - Opportunity for adaptation based on accrued data at the end of learning phase

Advantages of Adaptive Seamless Design

- Opportunities for saving
  - Stopping early for futility
  - Stopping early for efficacy
- Efficiency
  - There is no lead time between the learning and confirmatory phases
- Combined analysis
  - Data collected at the learning phase are combined with those data obtained at the confirmatory phase for final analysis

Thanks for Your Attention!