



Taiwan: New Regulation Changes

– *Things We Need To Know*

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Rules for CPP in NDA



- Article 38 of Drug Registration Rule
- Condition 1:
For NDA application, one CPP is permitted. But at least 2 CPPs OR EMEA approval are required for NDA approval (Article 7)
*CPP: Certificate of Pharmaceutical Product
- Condition2:
For NDA application, no CPP is required if the drug is under NDA review process in one of 10 top countries AND with one of below conditions
 1. Had conducted statistical and clinical significant clinical trial in Taiwan
 2. Applicant has GMP plant in Taiwan
 3. The new drug is locally produced by local GMP plant
 4. The applicant's country has reciprocal recognition of GMP plant with TaiwanBut at least 2 CPPs OR EMEA approval are required for NDA approval

*10 top countries: USA, UK, Japan, Switzerland, Canada, France, Australia, Germany, Belgium, Sweden

Rules for CPP in NDA



- Condition 3:
For NDA approval, one CPP is required if ALL of below conditions fulfilled
 1. Had conducted statistical and clinical significant clinical trial in Taiwan AND no bridging study is requested
 2. Applicant has GMP plant in Taiwan OR the new drug is locally produced by local GMP plant
 3. The applicant's country has reciprocal recognition of GMP plant with Taiwan
- Condition 4:
Significant improvement on drug safety or efficacy, OR highly beneficial to patients, OR special condition, approved by DOH

New Rules for CPP in NDA



- Article 38-1 of Drug Registration Rule
 - September 3, 2009
- No requirement on CPP for NCE drug registration, provided that clinical trials have been conducted in Taiwan simultaneously with those in other countries during the drug development stage and the following conditions are satisfied:
- During the development stage, Phase I and Phase III pivotal trial, or Phase II and Phase III pivotal trial, clinical trials were conducted in Taiwan at the same time as in other countries; also, the number of subjects in Taiwan should meet the following criteria:
 - In principle, there should be at least 10 evaluable Taiwanese subjects for a Phase I clinical trial, such as PK study, PD study or dosage finding study
 - There should be at least 20 evaluable Taiwanese subjects for a Phase II clinical trial
 - There should be at least 80 evaluable Taiwanese subjects for a Phase III pivotal clinical trial, and the trial result should be similar between Taiwan and other countries

New Rules for CPP in NDA



- At the end of a clinical trial, the report should be submitted to the central health competent authority for assessment and approval
- A Risk Management Plan for Post Market Surveillance should be submitted to the central health competent authority for approval
- Upon the Health Authority's request, applicants should be obliged to assist in the inspection of overseas clinical trials and provide sufficient documents and information to justify that the clinical trials conducted overseas are in compliance with the Medical Act and the GCP Guideline in Taiwan
- It is up to the central health competent authority's judgment to decide whether the results of clinical trials that satisfy all the above-mentioned conditions are qualified for an exemption of, or a substitution for bridging studies

Request for BSE Report

BSE – Bridging Study Evaluation

- February 13, 2009
- Bridging Study Evaluation Report is needed for
 - NCE
 - Drug Class decided by DOH
- September 3, 2009
 - Drug Class decided by DOH
 - New gene-engineered drug, vaccine, bio-similar drug
 - New blood preparation
 - New allergen



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN
USE

ICH HARMONISED TRIPARTITE GUIDELINE

ETHNIC FACTORS IN THE ACCEPTABILITY
OF FOREIGN CLINICAL DATA
E5(R1)

Current Step 4 version
dated 5 February 1998

*(including the Post Step 4 corrections
agreed by the Steering Committee on 11 March 1998)*

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Guideline for Bridging Study

July 9, 2009



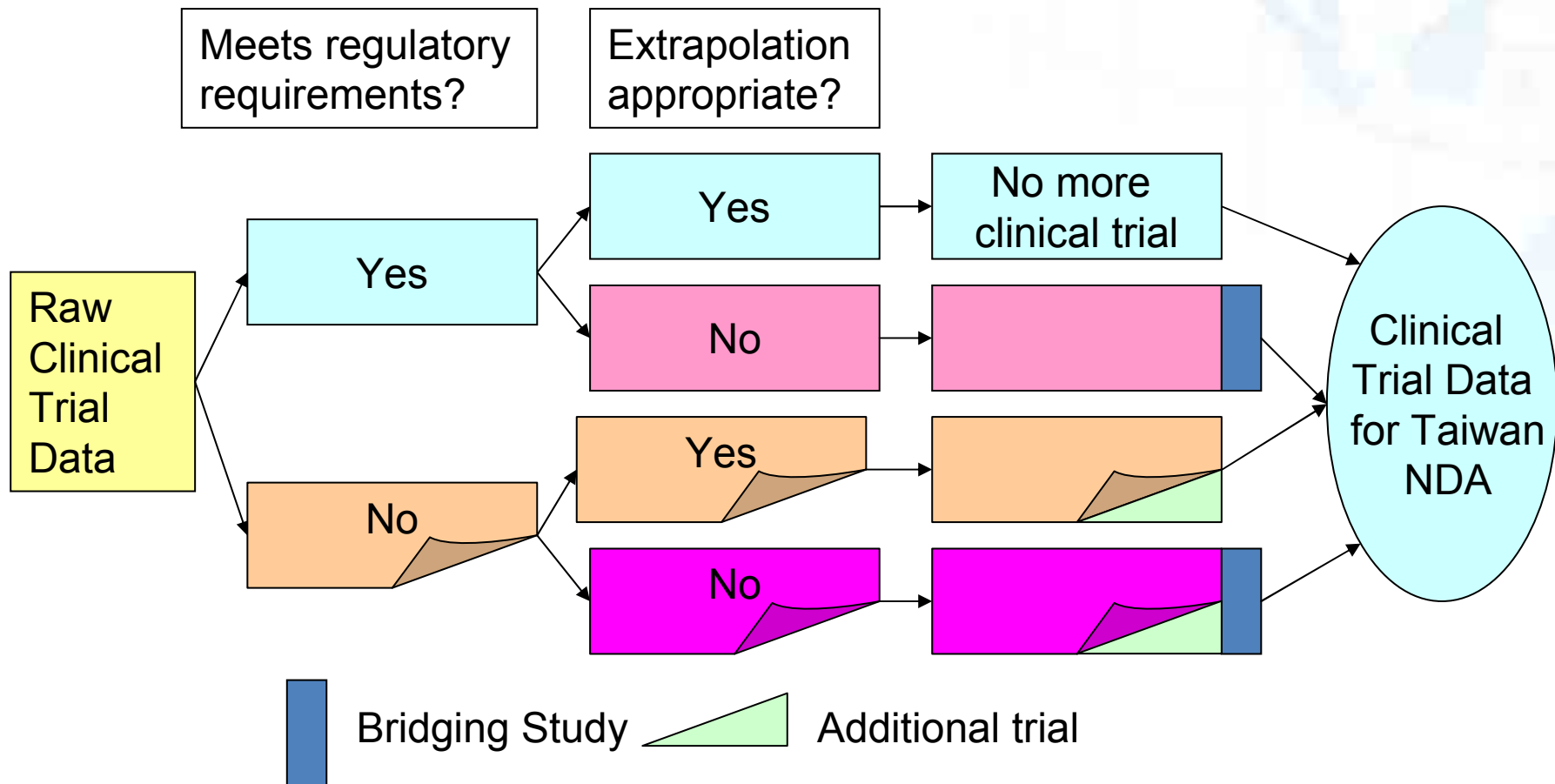
- Frame of intrinsic and extrinsic ethnic factors in the acceptability of foreign clinical data
- Evaluation of foreign clinical trial data with regulation requirement
 - Complete Clinical Data Package
 - Pharmacokinetics, Pharmacodynamics, dose response, efficacy and safety
 - Standard: compliance with GCP, adequate and well-controlled, suitable endpoint, acceptable diagnosis
 - If any deficiency, local clinical trial or bridging study would be requested
 - In subset population: renal or liver failure
 - With local approved drug and dosing regimen
 - Drug-drug interaction

Guideline for Bridging Study

July 9, 2009



- Flow of Bridging Study Evaluation



Guideline for BA/BE Study



- April 2, 2009
- Waive of BA/BE study
 - IV injection
 - Generic oral solution
 - Generic injection other than IV with same formulation as brand
 - Inhaled gas/vapor
 - Generic transdermal drug
 - Generic ophthalmologic or ear drug
 - For new unit dose or any production change, DOH approves that BA/BE can be replaced by Dissolution Comparison Test
- Preservation of study drug and reference drug
 - For DOH auditing
 - At least 5 years after final report is approved by DOH
 - Enough quantity (at least 2 folds of used units are suggested)

Guideline for Botanical Drug



- Guideline for Botanical Drug
 - March 31, 2009
 - Similar to FDA version (2004)

Guidance for Industry

Botanical Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2004
Chemistry

New Rules for Specimen



- Biobank Law (Draft, August 27, 2009)
 - Collection of genetic information in certain population or patient
 - Only Article 6 and Article 15 related to clinical trial
- Article 6
 - ICF needed
 - ICF notified to DOH
 - Apply with Protocol Submission
 - Export permit from DOH (~3 weeks)
- Article 15
 - Specimen usage limited to authorized range, duration, and method

New Rules for Trial Products



- January 17, 2009
 - The trial product can't be destroyed or exported until DOH approval of final report
 - Drugs used as combinational therapy are also “trial product”
 - Needle can be destroyed after usage

- November 9, 2009
 - The Management and Dispensing of Trial Products **at site** should be only conducted by **Pharmacist**

Rules for Clinical Trial Management

- December 14, 2009
- Qualification of Investigator (Article 4)
 - Certified Physician for more than 5 years
 - More than 30 hours of DOH-registered clinical research training within 6 years
 - More than 5 hours cell/gene therapy training for the related trial
 - More than 9 hours training of medical ethics within 6 years.
 - No record of punishment due to GCP violation



Rule for Clinical Trial Management

- Audit Frequency of IRB (Article 9)
 - At least once per year
- Trial Expense (Article 11)
 - No study expense paid by study subject/patient
 - Expense not related to study procedure paid by patient or insurance
 - Expense related to study procedure paid by sponsor



Rule for Medical Device

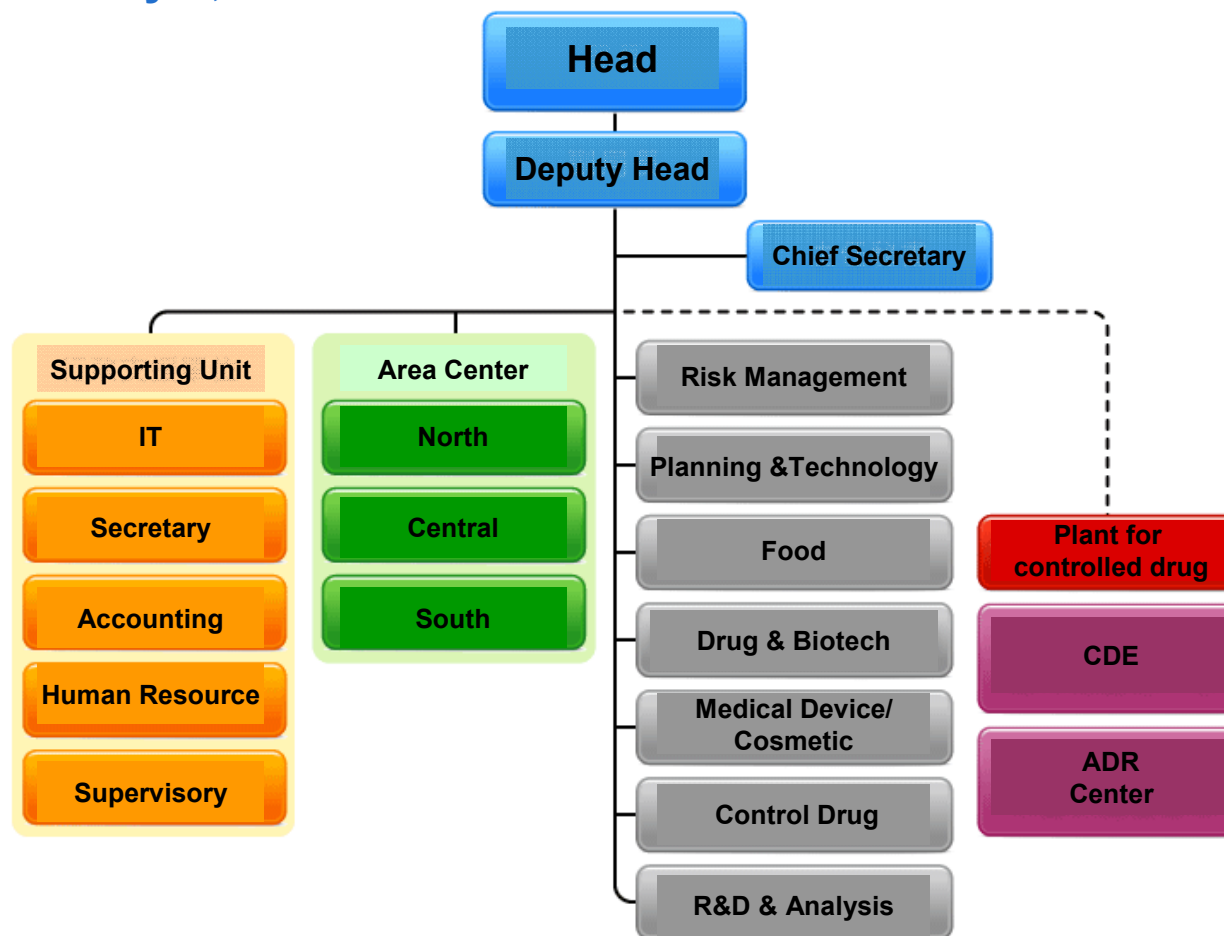


- May 30, 2007
 - GCP for Medical Device related Clinical Trial
 - Application for Medical Device related Clinical Trial Protocol
 - Format of Medical Device related Clinical Trial Report

=> Similar to Drug Regulation

Review of IND/NDA Moves from BPA/CDE to TFDA

Since January 1, 2010



Economic Cooperation Framework Agreement (ECFA) between Taiwan and China



- Mutual Recognition of Clinical Trial Data
 - FDA approved protocol
 - Selected sites in China
- Strategy to shorten time to market
 - For China registration, conduct
 1. Local Phase I/II Study in Taiwan
or part of Global/Regional Phase I/II Study in Taiwan
 2. Part of Global/Regional Phase III Study in Taiwan and China

Government Support to Clinical Trial



- Subsidiary to clinical research center of foreign pharma
 - About 30% of trial expense
 - Phase I, II, III trial in Taiwan
 - GSK/Novartis/BI had built clinical center in Taiwan
- DOH inspection
 - Purpose: Improve trial quality
 - Audit IRB: annually
 - Inspect trial site: every registration trial
- Shorten time to market
 - Less CPP requirement