Ministry of Health & Family Welfare
Government of India

Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION
MINISTRY OF HEALTH, GOVERNMENT OF INDIA

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22nd Asian Harmonization Working Party Annual Meeting

MAKE IN INDIA

MAKE IN INDIA

4-8 December, 2017 I New Delhi

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It's more than the Clinical Study Report!

International Evolution of Clinical Evidence Requirements

Arthur Brandwood

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Questions?

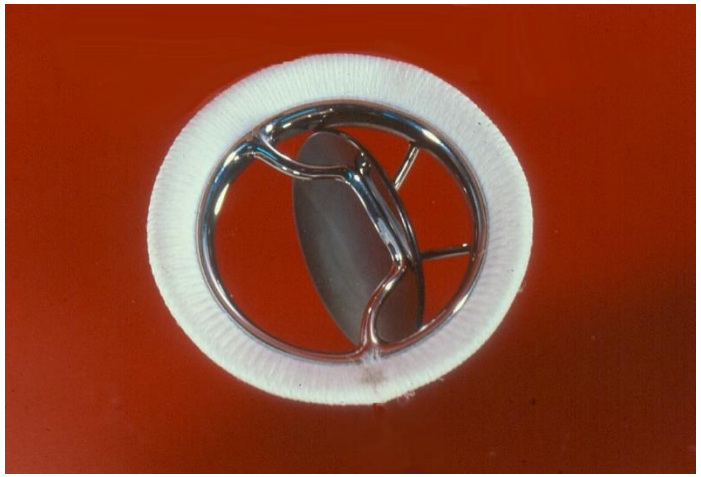
Copy of Slides?

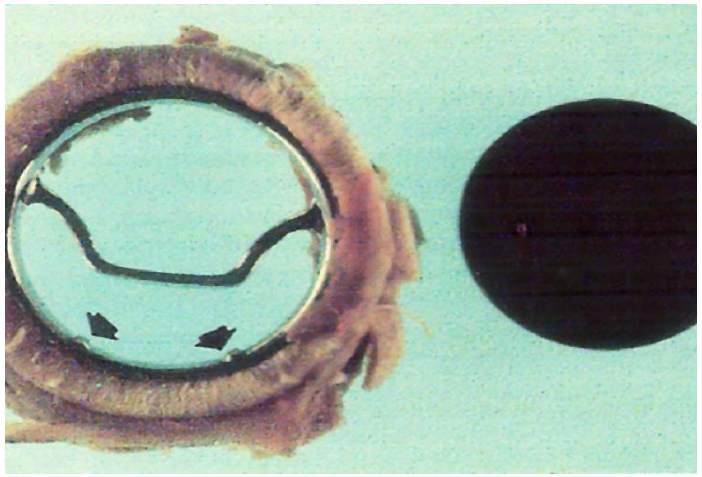
Arthur@brandwoodbiomedical.com

Agenda

- Some History
- What is Clinical Evidence?
- National and Regional examples
- Global Approach

Postmarket Begets Premarket





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MDD Annex X

CLINICAL EVALUATION

ORIGINAL 1993 TEXT

1. General Provisions

1.1. *As a general rule*… confirmation of conformity… must be based on clinical data, in particular in the case of implantable devices and devices in Class III. …the adequacy of the clinical data must be based on

1.1.1. *either* a compilation of the relevant scientific literature

1.1.2. *or* the results of all the clinical investigations made.

Report on the Functioning of the Medical Devices Directive

Medical Devices Expert Group, June 2002.

"Shortcomings… in the implementation of the Directives' provisions on clinical data"

- Evidence not always available
- Notified bodies not assessing rigorously enough
- Directive requirements ambiguous

ANNEX X

CLINICAL EVALUATION

1. General provisions

1.1. As a general rule, confirmation of conformity with the requirements concerning ~~[illegible]~~red to in Sections I 1 and 3 of Annex I under the normal conditions of use of the device and the ~~[illegible]~~nd of the acceptability of the benefit/risk ratio referred to in Section I 6 of Annex I must be ~~[illegible]~~ ~~e case of implantable devices and devices in Class III.~~ Taking account of any relevant harmonize~~[illegible]~~~~ey of the clinical data must be~~ clinical evaluation must follow a defined and methodologically sou~~[illegible]~~

1.1.1. either a ~~compilation~~ critical evaluation of the relevant scientific literature currently ~~[illegible]~~~~evice and the techniques employed as well as, if appropriate, a written report containing a critical ~~[illegible]~~~~he safety, performance, the design characteristics and the intended purpose of the device, where th~~[illegible]~~he device with that to which the data relates and the data adequately demonstrate compliance with the rele~~[illegible]~~nal requirements;

1.1.2. or ~~the results of all the clinical investigations made, including those carried out in confe~~[illegible]~~with Section 2.~~a critical evaluation of the results of all clinical investigations made;

1.1.3. or a critical evaluation of the combined clinical data provided in 1.1.1 and 1.1.2 abo~~[illegible]~~

1.1b In~~[illegible]~~vices in class III clinical investigations shall be performed unless it is duly justified to rely on existi~~[illegible]~~

1.1c ~~[illegible]~~hall be documented. This documentation shall be included and/or fully referenced in the techn~~[illegible]~~

1.1d ~~[illegible]~~ion have to be actively updated. Where Post Market Clinical Follow Up as part of the post mark~~[illegible]~~, this must be duly justified and documented.

1.1e ~~[illegible]~~nal requirements based on clinical data is not deemed appropriate, adequate justification for a~~[illegible]~~ on risk management output and under consideration of the specifics of the device-body interact~~[illegible]~~d and the claims of the manufacturer. Adequacy of demonstration of conformity with the essential requirements by performance evaluation, bench testing and preclinical evaluation alone has to be duly substantiated.

Clinical trials *expected* for all implants and class III's unless justified

Continuous update – including postmarket trials

NOTES&THEORIES
DISPATCHES FROM THE SCIENCE DESK

theguardian

Lack of clinical data for medical devices is putting patients' lives at risk

The true extent of medical device recalls in the UK is currently unknown, and hundreds, if not thousands, of patients each year are suffering serious injury as a result or are dying

Posted by Dr Carl Heneghen
Monday 16 May 2011

http://www.guardian.co.uk/science/2011/may/16/medical-devices-lack-clinical-data

"Appalled"

"…appalled at how many devices are brought to market with a lack of appropriate clinical data,"

Suzanne Ludgate
Medical Director
UK MHRA

Going Further?

For innovative high-risk devices, [MDD] should move away from “safety and “performance” to also require pre-market data that demonstrate “clinical efficacy or effectiveness”

Centralising the evaluation of high-risk devices at the European level should be considered

The pre-market clinical evaluation of innovative high-risk medical devices

Belgian Healthcare Knowledge Centre, 2011

European MDR – What's Changing

Governance

Fewer, stronger Notified Bodies

- *Stronger criteria*
- *Stricter process with central oversight*
- *Unannounced inspections*

Stricter rules on Authorized representatives

- *Greater competence*
- *Product liability*

Requirements

Classification update

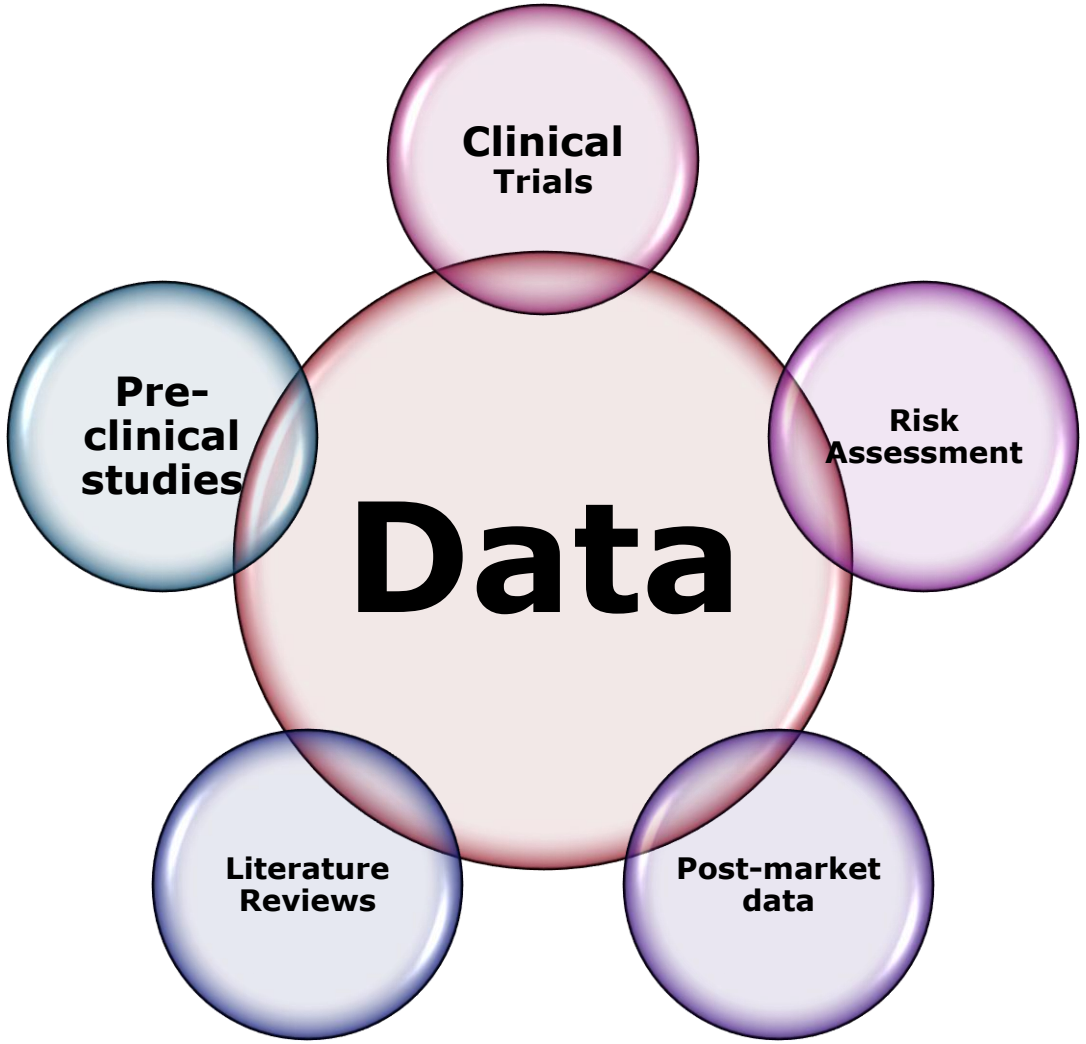
- Adjustment of Class III
- Software

Clinical Evidence

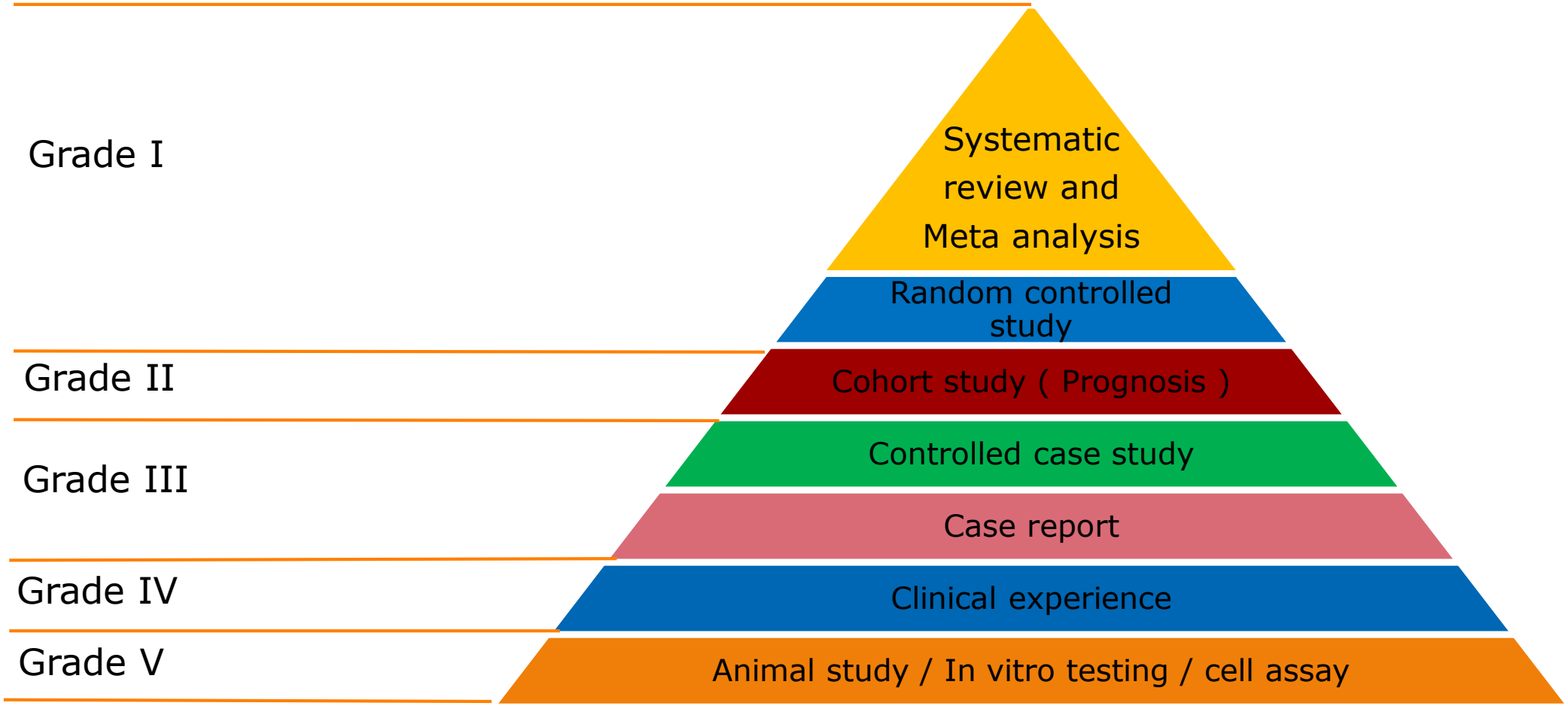
- *Trials mandated for Class III*
- *Manufacturers may consult expert panel on strategy*

What is Clinical Evidence?

What is Clinical Evidence?



Strength level of evidence data



EUROPEAN COMMISSION
DG Internal Market, Industry, Entrepreneurship and SMEs
Consumer, Environmental and Health Technologies

Health technology and Cosmetics

MEDDEV 2.7/1 revision 4

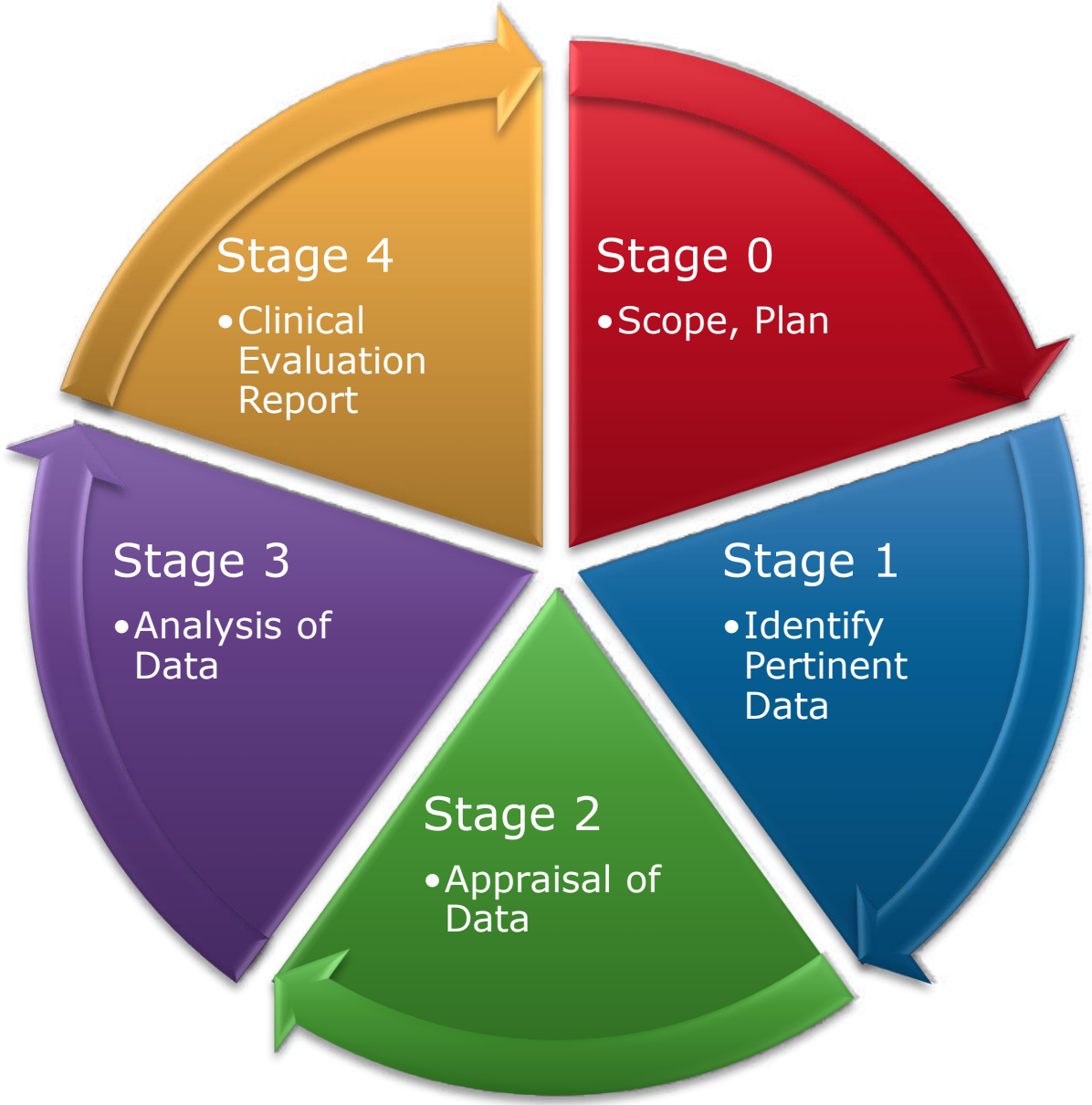
June 2016

GUIDELINES ON MEDICAL DEVICES

CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES UNDER DIRECTIVES 93/42/EEC and 90/385/EEC

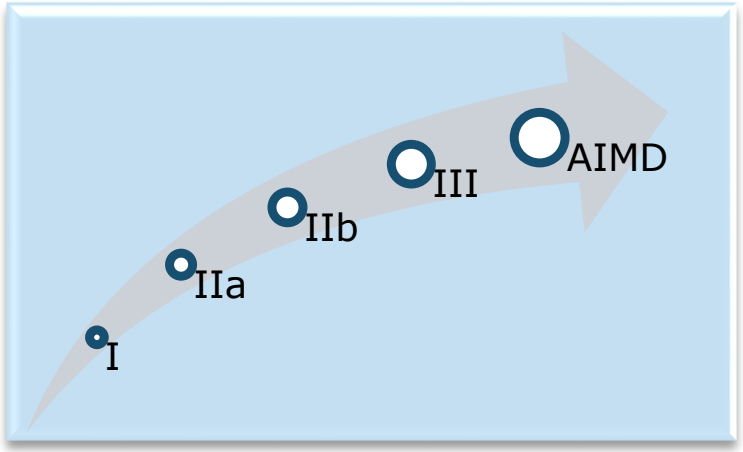
Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical Devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts where circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector. These guidelines incorporate changes introduced by Directive 2007/47/EC amending Council Directive 90/385/EEC and Council Directive 93/42/EEC.



Key Requirements

Clinical evaluation is required for **every device** irrespective of class



Clinical Trial for Class III and AIMD

… unless justified to rely on existing data alone (unlikely…)

Thorough Literature review

- Must detail search criteria as well as inclusion/ exclusion criteria

Comparison to substantially equivalent device(s)

- Non CE marked devices – justify applicability to European use

Substantial Equivalency is based on similar intended purpose and key technical / biological characteristics

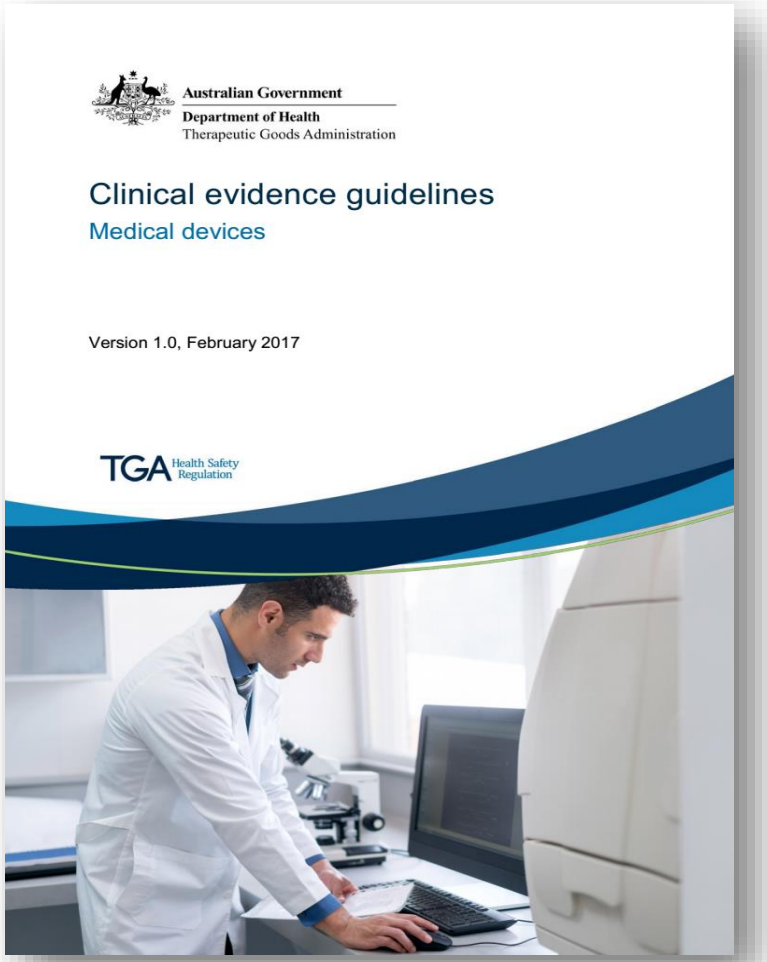
Who Does the Clinical Evaluation? Individual or Team?

- **Qualifications**
  - *Degree + 5 years experience*
  - *OR*
  - *10 years experience alone*

- **Knowledge**
  - *the Device and its application E.g.* ***Specialist Clinical Expertise***
  - *Research methods, (including statistics)*
  - *Regulatory Requirements*
  - *Medical Writing (including practices of systematic review)*

MEDDEV 2.7.1/4 Section 6.4

Clinical Evidence Guidance (Feb 2017)



Requirements for specific high risk devices

- *Total and partial joint prostheses*
- *Cardiovascular devices to promote patency or functional flow*
- *Electrical impulse generators*
- *Heart valve replacement using a prosthetic valve*
- *Supportive devices - meshes, patches and tissue adhesives*
- *Demonstrating the safety of Implantable Medical Devices (IMDs) in the Magnetic Resonance (MR) environment*

Regulations for clinical evidence

Effective date	Subject	Doc No
Apr 1, 2004	Rule of medical device clinical study	Reg No 5
Jun 1, 2014	Administration and inspection rule of medical device	Order No 650
Oct 1st,2014	Medical device registration procedure – Class II & III	Reg No 4
Oct 1, 2014	Exemption list of Class II & III device from local clinical study	[2014] No 12 & 13
Oct 1, 2014	List of high risk Class III MD need pre-approval for local clinical study	[2014] No 14
Oct 16, 2014	Administration rule for Medical institute to conduct clinical study	[2014] No 80
Jul 3, 2015	Medical device clinical study notification procedure	2014] No 87
May 19, 2015	CFDA guidance on medical device clinical evaluation report (CER)	[2014] No 14
June 1, 2016	Good Clinical Practice (GCP)	Order 25

CFDA Expectations – Clinical Evidence

Example : Coronary drug-eluting stent

Study design: Prospective, randomly controlled, multi-center

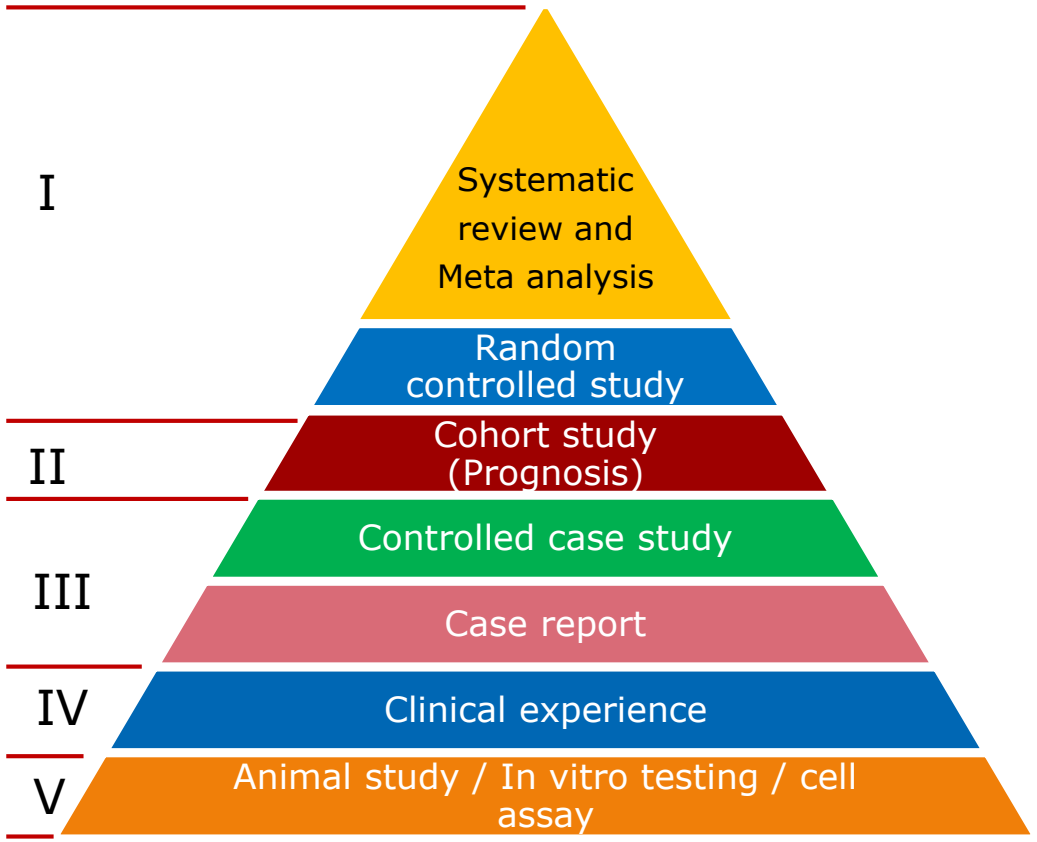
Sample size:

- Random controlled group
- Single group
- Total > 1000 cases

Follow up: 9, 12 months, 5 years (post-market)

Evaluation criteria:

- Surgery success rate
- Post-operative safety: death, myocardial infarction, thrombogenesis in stent
- Post-operative effectiveness: Target Lesion Revascularization (TLR), Target Vessel
- Revascularization (TVR), Late Loss, Restenosis
- Composite criteria: Target Lesion Failure (TLF)

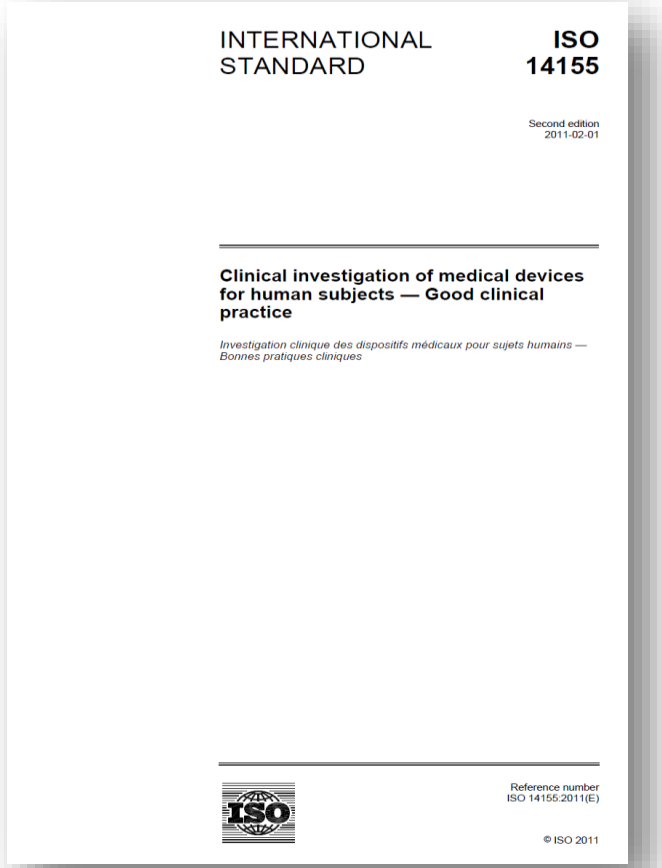


GCP – Good Clinical Practice

GCP – Order 25

(effective Jun 1 2016, replaced Order 5)

- Pre-Study preparation
- Responsibilities of Sponsor
- Study protocol design
- Protection of patient rights and benefits
- Study reports and records
- Responsibilities of Investigator institute
- Responsibilities of Ethic committee
- Management of device in trial
- Documentation management



INTERNATIONAL STANDARD

ISO 14155

Second edition
2011-02-01

Clinical investigation of medical devices for human subjects — Good clinical practice

Investigation clinique des dispositifs médicaux pour sujets humains — Bonnes pratiques cliniques

Reference number
ISO 14155:2011(E)

© ISO 2011

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The waves of exemptions

Original ("1st Wave") exemption list

- *488 Class II, 79 Class III*

September 2016

- *267 Class II, 92 Class III (Included 15 IVDs)*

May 2017

- *130 IVDs*
- *22 Class II, 6 Class III*

A total of Total 954 Devices, 145 IVDs

NON EXEMPT Devices: Predicate Comparisons
Meet all 3 Conditions

- ✓ Predicate is same class
- ✓ Predicate is approved in China for same intended use
- ✓ No significant technical differences which impact safety or performance

Submit a Clinical Evaluation Report

Simple comparison of EXEMPTED device to a listed and marketed device in China

Item	Listed device	Subject device	Variance	Supportive material
Basic principles (working principles/action mechanism)				
Structural composition				
Manufacturing materials of products or those in contact with human body				
Sterilization/ disinfection methods				
Intended use				
Application methods				
Others (if any)				

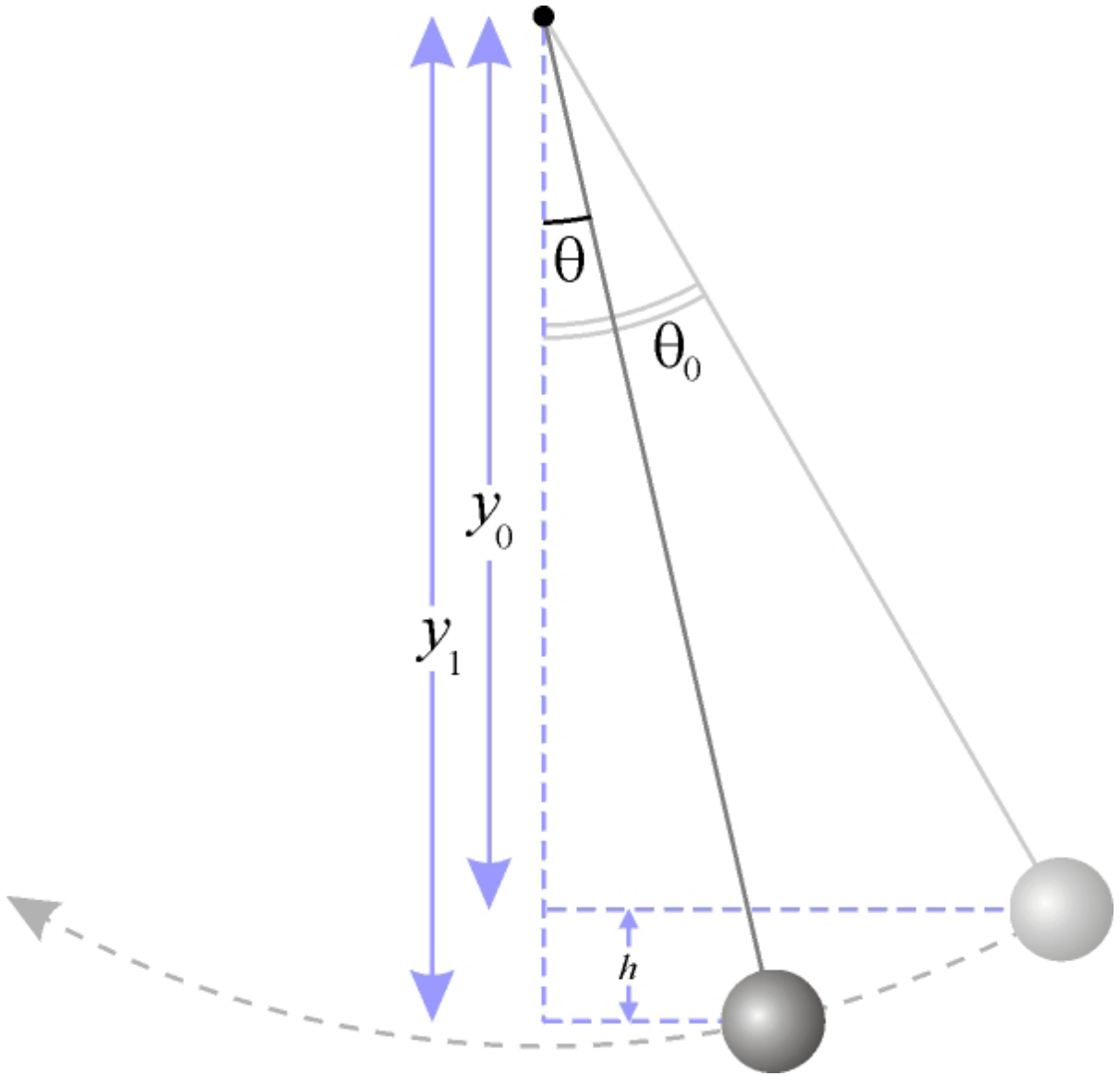
BUT... Evidence requirements for predicate comparisons are stringent...

Detailed Comparison to predicate device

<table>
<tr><td>1. Basic principles</td><td>5. Performance requirements</td><td>10. Contraindications</td></tr>
<tr><td>2. Structural composition</td><td>6. Safety evaluation (such as biocompatibility, biosafety, etc.)</td><td>11. Precautions and warnings</td></tr>
<tr><td>3. Manufacturing process</td><td>7. Applicable national/industrial standards</td><td>12. Delivery status</td></tr>
<tr><td rowspan="4">4. Manufacturing material (such as material mark, animal-derived material, allograft material, ingredient, pharmaceutical ingredient, bioactive substance, applicable standard and other information)</td><td rowspan="3">8. Scope of application:
(1) Target population
(2) Applicable site
(3) Contact with human body
(4) Indications
(5) Applicable disease phase and degree
(6) Application environment</td><td>13. Sterilization/ disinfection methods</td></tr>
<tr><td>14. Package</td></tr>
<tr><td>15. Label</td></tr>
<tr><td>9. Application method</td><td>16. Instructions for Use</td></tr>
</table>

The only feasible predicate is an earlier variant of the new device for which the manufacturer holds primary testing and international clinical data for both devices

Has the Pendulum Swung?



China Thinks Again on Foreign Clinical Data

JULY 3, 2017 BY **ARTHUR BRANDWOOD**

Will China open the door to foreign clinical data?

Recent announcements from CFDA suggest that China is thinking again on the stringent requirements for manufacturers to conduct in-China clinical trials. The agency is accelerating the production of exemption lists and recent draft policy circulars open the door to acceptance of foreign clinical data and to post market trials of devices which address unmet clinical need.

The 2014 Decree 650 reforms in China dramatically tightened CFDA's regulatory controls. Most controversially, China moved to require all devices not specifically exempted to be supported by direct clinical trials in China unless the manufacturer could show equivalence to already approved devices. The standards for equivalence were set so high that in practical terms it's only possible to demonstrate equivalence to an already approved earlier variant of the device from the same manufacturer.

In May 2017, a series of announcements CFDA suggested the pendulum has started to swing backwards.

CFDA first announced a "Third wave" of exemptions for Class II and III medical devices. This was followed by publication of the first separate list of 130 IVDs exempted from clinical studies in China.

Then CFDA published draft policy documents Circulars 52 and 53 which if implemented could dramatically streamline clinical evaluation for some devices.

Practice Updates and More Audits

Circular 53:
Modernise Clinical Trial Practice and Controls

Ethics reviews will move to a Lead Site model (secondary sites accept the lead site decision without further review)	• *Similar to emerging practice in e.g. USA, Australia*
Abolish certification of clinical study sites	• *Replace with Objective criteria and Site Notification process*
CFDA to increase on site audits clinical trials	• *Failure of audit = registration refusal for applications supported by the study*

2017: CFDA Proposed Regulatory Changes

Draft Revision to Order 650 Medical Devices Regulations
October 30, 2017

- Improve Administrative Processes
- Abolish Mandatory in-China Testing
- Stronger Postmarket and Penalties
- Accept International Clinical Data

Draft Technical Guidelines of Accepting Overseas Clinical Trial Data for Medical Devices Nov. 14, 2017

- Basic Principles for acceptance
- Essential Items to be submitted
- Approaches to Evaluation

CFDA: Basic Principles for Acceptance of International Clinical Data

1.Ethical principles

- Follow Helsinki declaration
- Follow National Regulations and Standards of trial country(ies)

1.Legal principles

- Meet local clinical trials quality management regulations
- In line with China GCP
- Specify any differences and justify

1.Scientific principles

- Data authentic, scientific, reliable and traceable
- Data are complete not screened
- Appropriate aim and design, clear results, protected subjects, controlled risks

CFDA: Minimum Clinical Data Set

Protocol

1.Ethics committee opinion

1.Detailed Clinical trial report (should include the analysis and conclusion of the complete clinical trial data)

Key aspects CMDE will consider in evaluation

1.Review Practices

- Evidence of differences between overseas and CFDA requirements

1.Population difference

- Race, gender, age
- Diet, religious beliefs, smoking and drinking, obesity, disease incidence, rare or regional comorbidities, socio-economic, medical compliance

1.Clinical trial condition difference

- Medical practice
- Clinical infrastructure
- Researchers' ability (learning curve)
- Diagnosis and treatment concepts or guidelines
- Impact on translation to Chinese setting?

CFDA: Practical Approach to International Data

1.Chinese population difference is emphasized

-Include ethnic Chinese in the overseas clinical trials

-Analysis on population difference in submission Clinical Evaluation

1.Clinical design difference is articulated

What are local expectations? Performance only – or multiple endpoints

-Consider specific CFDA requirements e.g. China GCP

1.Difference re clinical trial conditions is considered

-Consider Chinese clinical practices and standards of care

-Determine differences and address in trial design or justify in Clinical Evaluation Data file

1.CFDA requirements on traceability of sample sources

-Source

-Unique traceable ID

-Age, gender

-Sample types

-Clinical background information

A Global Approach?

Know the local requirements

Clinical Trial Requirements

Robust Literature Review

Post-market data *(In-house, FDA MAUDE, TGA DAEN, etc.)*

Predicate Device Requirements

Clinical Expertise Requirements

Global Approach

Know your guidances

Draft clinical evidence guidelines - Medical devices

MEDDEV. 2.7.1 Rev. 4

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