US/OUS Clinical Data Requirements

SOCRA 23rd Annual Conference

Harnessing The Tides Of Innovation To Advance Clinical Research Practice

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2:30 pm – 3:15 pm

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Presented By:
Dr. Joy Frestedt
President and CEO
Frestedt Incorporated

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Joy Frestedt, PhD, CCTI, RAC, FRAPS

Frestedt incorporated

Alimentix

- Dr. Frestedt is President and CEO of Frestedt Incorporated (www.frestedt.com; 952-426-1747; jf@frestedt.com), a network of over 70 experts and eight highly skilled staff meeting specific needs in regulatory, clinical and quality affairs.
- Dr. Frestedt has over 30 years of scientific, clinical and regulatory experience in the health care, pharmaceutical, medical device and food-related industries assisting firms with strategic decisions involving clinical trials, regulatory strategies and the development of quality management systems to compete globally. She has held key positions at the University of Minnesota Academic Health Center, Johnson and Johnson's Ortho Biotech, Medtronic, Mayo Clinical Trial Services, AstraZeneca Pharmaceuticals and Orphan Medical.
- Dr. Frestedt holds a B.A. in biology from Knox College and a Ph.D. in pathobiology from the University of Minnesota Medical School. She is a member of the American Society of Clinical Oncologists, American Association of Pharmaceutical Scientists, Association of Clinical Research Professionals, Society of Clinical Research Associates and is a Fellow of the Regulatory Affairs Professionals Society.
- Dr. Frestedt founded Alimentix, the Minnesota Diet Research Center, was named one of the "100 Most Inspiring People in the Life Sciences Industry" by PharmaVOICE and one of the top 25 "Industry Leaders" a "Women in Business Award" by the Minneapolis/St. Paul Business Journal in 2011.

Audience

- Investigators
- CRCs
- CRAs
- Project Managers
- Consultants
- Educators
- Administrators

Acknowledgements

Thanks to Jillian Johnson and Jess Kessler for helping with this presentation!

Course Description

Clinical data is needed for many medical devices prior to placing the device on the market both inside the US and outside the US (OUS). This session will review the types of clinical data typically collected for medical device regulatory submissions.

Learner Objectives

- After the presentation attendees should be able to:
  - Understand clinical data collections for medical devices
  - Differentiate US and OUS clinical data requirements
  - Identify essential clinical data for regulatory files
  - Find and use available clinical data resources

Agenda

- Introduction
- Standards and Regulations
- Clinical Data Requirements
- Clinical Data Submissions/Files
- Clinical Data Collections

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Introduction

Global Clinical Research
Risk Based Approach
Valid Data

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Clinical Trials Introduction

- Who collects clinical trial data?
- What data is collected?
  - History, standards and regulations
- When are clinical trials needed?
- Where are they?
  - Data from other countries
- Why do them?
  - Device classifications

http://www.freevector.com/vector-globe/

Global Clinical Research
Medical Device Standards

http://www.vis-vitalis.com/galenics/en/index.php?id=31

Who collects clinical data in a typical clinical trial?

- The Sponsor is the person or group initiating (funding) the study
  - Responsible for overseeing study conduct (patient safety, data integrity).
- The Principal Investigator (PI) is the **team leader** for conducting the study
  - Responsible for each study subject (well being, appropriate care, safety), each experimental treatment, each required evaluation and all reports/documentation
- The Monitor represents the Sponsor
  - Responsible to oversee study progress and to flag issues

Doctors
Nurses
Scientists
Social workers
Dietitians
Data analysts
Statisticians
Monitors
Drug companies
Device companies
Food companies
Universities
Colleges
Voluntary Groups
FDA
DOD
VA
NIH
FDA
Many, many others

What Clinical Data is Collected?

- Pre-Market Clinical Trial
  - safety and performance
  - observational or interventional
- Post Market Surveillance
  - Market Expansion
  - Regulatory Requirement
- Use Data Examples
  - Sales and Other Use Reports
  - Complaints / Adverse Device Effects
  - Device Malfunctions / Deficiencies
  - MAUDE / MedWatch / MedSun
  - Insurance / Reimbursement
  - Human Factors Engineering

History[1]

500 BC – legumes and lemons
first "open" uncontrolled trial

1747 – scurvy
first "controlled" trial

1943 – patulin for common cold
first "double blind" controlled trial

1946 – streptomycin in TB
first "randomized" controlled trial

1996 – good clinical practices
first "GCP" guidance from the International Conference on Harmonization (ICH-E6)

[1]*Bhatt A. Evolution of Clinical Research: A History Before and Beyond James Lind. Perspect Clin Res. 2010 Jan-Mar; 1(1): 6–10.*
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149409/

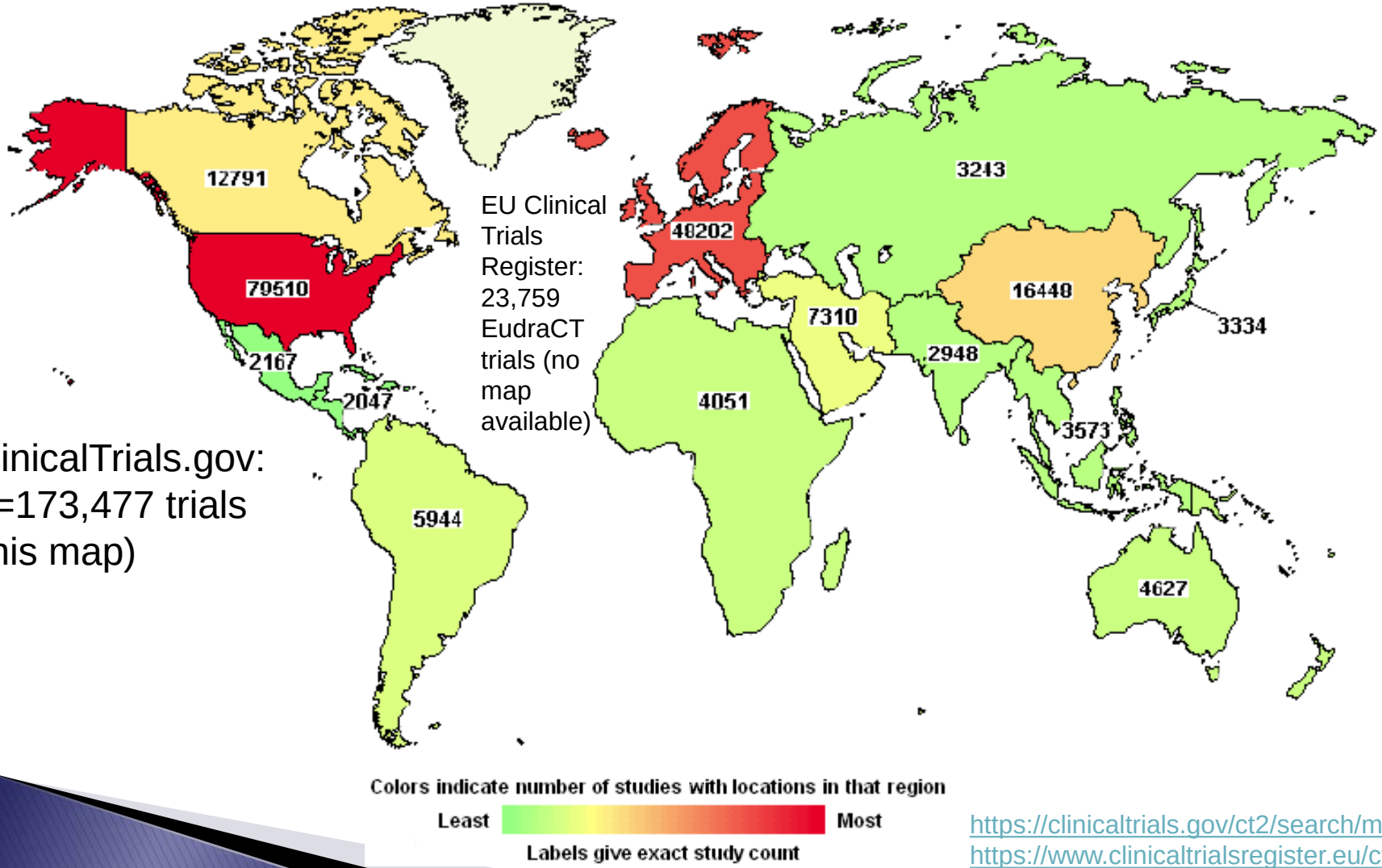
When should a clinical investigation be undertaken?

- To provide data (not available through other sources) required to demonstrate compliance with essential requirements (safety, clinical performance, acceptable risk:benefit ratio associated with use)
- For well established technologies, available clinical data may be sufficient to establish safety and performance (e.g. published literature, clinical experience, post market reports and adverse event data) as long as no new risks are identified and intended use has not changed
  - *Steps to clarify the need for a trial include: evaluating the essential requirements, completing risk management and clinical evaluation reports*
  - GHTF SG5 N2-R08 Clinical Investigations

    http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n3-clinical-investigations-100212.pdf

When will we learn anything new?

Where are the clinical trials?



EU Clinical Trials Register: 23,759 EudraCT trials (no map available)

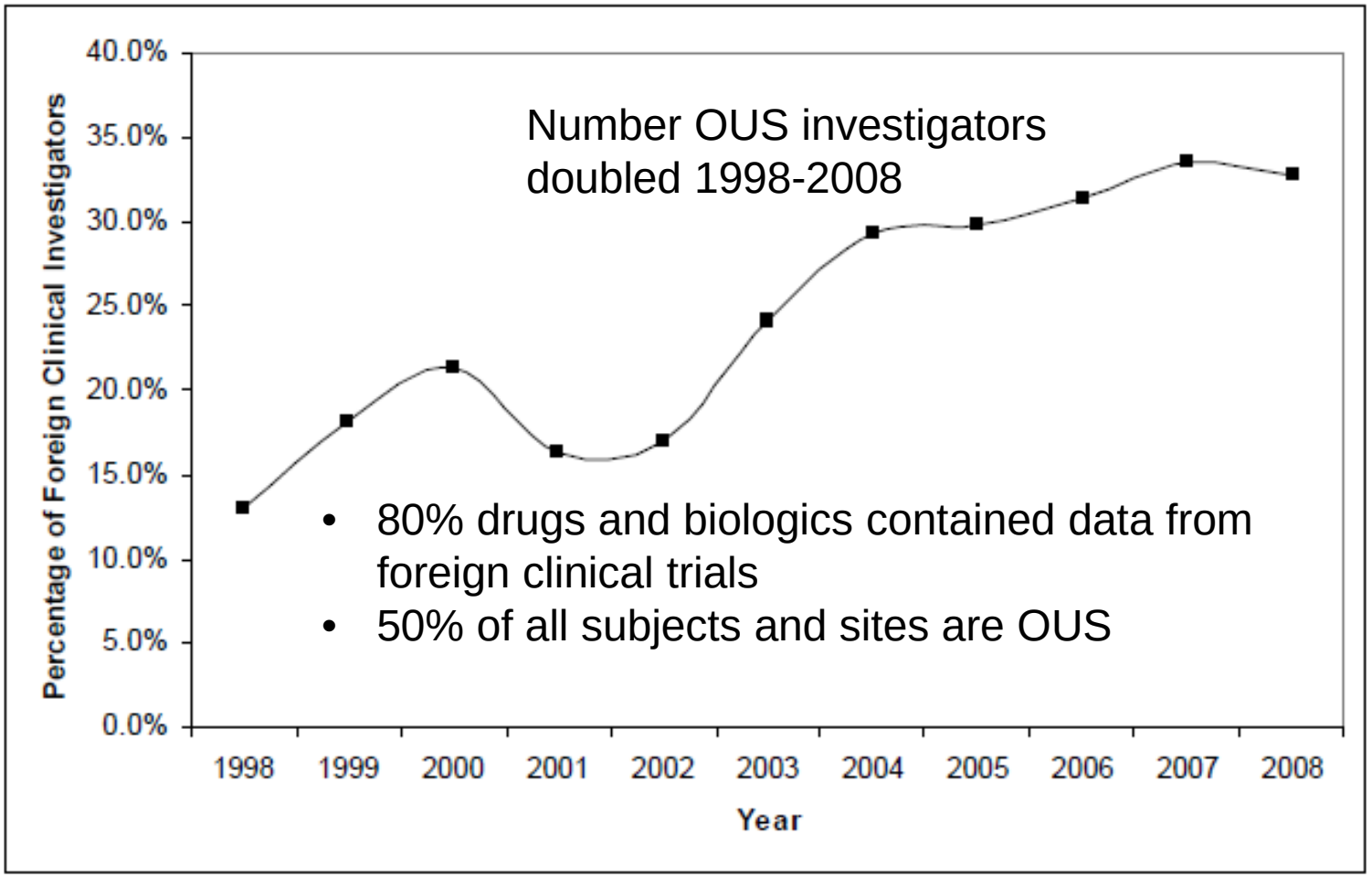
ClinicalTrials.gov: N=173,477 trials (this map)

https://clinicaltrials.gov/ct2/search/map
https://www.clinicaltrialsregister.eu/ctr-search/search - Accessed on 8-24-14

Using OUS Data in the US

- Clinical data collected OUS may be used to support FDA submissions and vice versa
- Clinical studies should comply with harmonized standards of Good Clinical Practice
- Study should be generalizable and applicable to US population
  - Patient demographics
  - Differences in medical practices
- Potential problems
  - Missing protocol elements
  - Lack of data monitoring, source documentation monitoring, accounting for protocol deviations
  - Improper follow-up

US IND Foreign Clinical Investigators

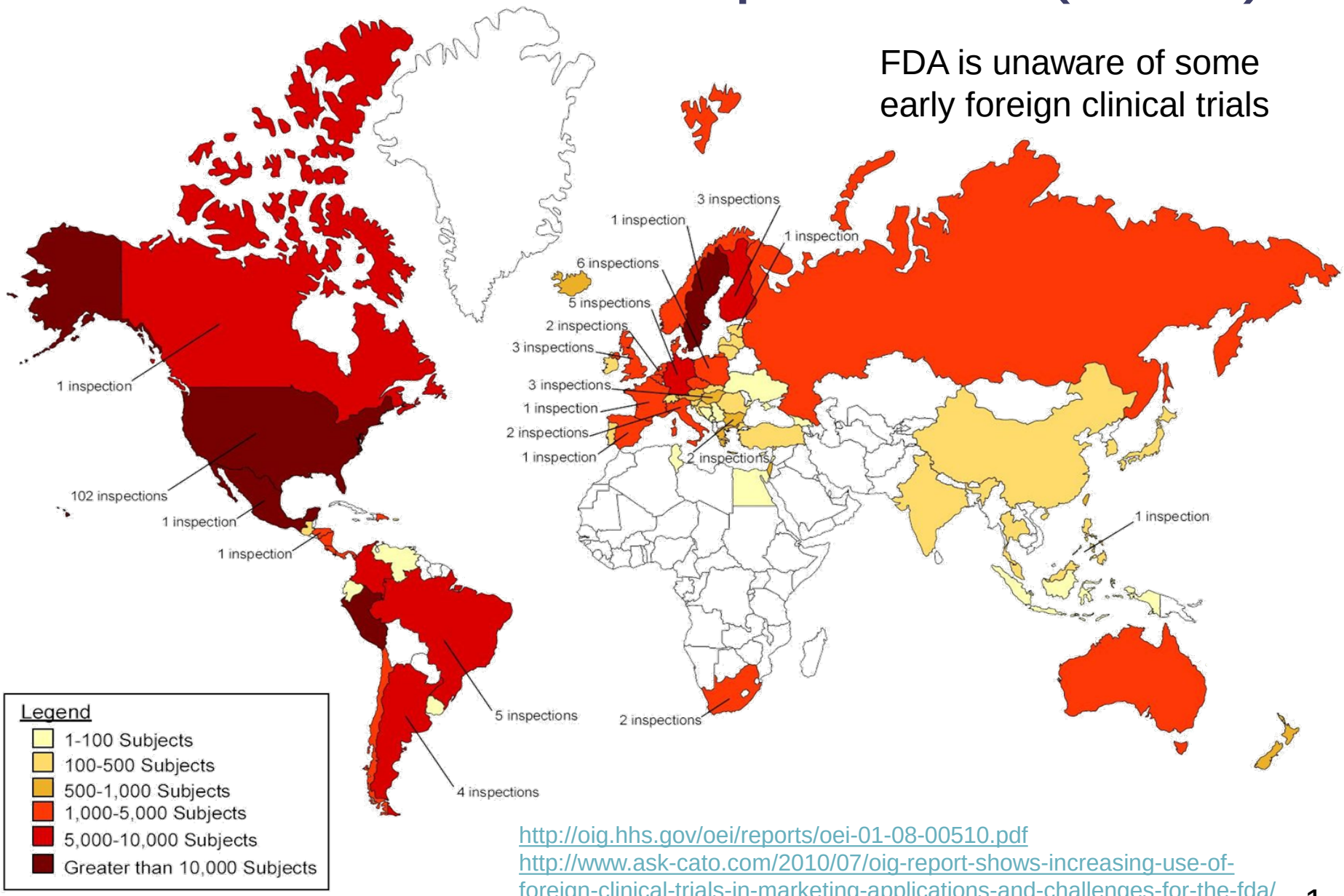


Source: OIG analysis of FDA's Bioresearch Monitoring Information System data from 1998 through 2008.

http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf

FDA Clinical Trial Inspections (2010)

FDA is unaware of some early foreign clinical trials



http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf
http://www.ask-cato.com/2010/07/oig-report-shows-increasing-use-of-foreign-clinical-trials-in-marketing-applications-and-challenges-for-the-fda/

Source: Office of Inspector General analysis of Food and Drug Administration marketing applications approved in fiscal year 2008 and associated clinical trial inspections.

Why do a clinical trial?

- To establish device safety and effectiveness/performance
- Higher risk devices require clinical data and regulatory review prior to marketing (along with registration/license, etc. which varies by country)

Increased risk, increased clinical data requirements

US	Canada	EU	China	Japan	Australia
Class I	Class I	Class I	Class I	Class I	Class I
Class II	Class II	Class II	Class II	Class II	Class II
	Class III	Class IIb		Class III	
Class III	Class IV	Class III	Class III	Class IV	Class III

General, low risk, self declaration

Special Controls

Prior authorization and clinical data review

Valid Scientific Clinical Data

In order to demonstrate the safety, effectiveness and performance of a device, clinical trial data must be robust and must support the safety, effectiveness and performance claims.

Valid Sources

- Well controlled
- Partially controlled
- Objective, no controls
- Case histories
- Human experiences

INVALID Sources

- Isolated case reports
- Random experiences
- Reports without details
- Unsubstantiated opinions

Well Controlled Investigations

- Objective is clear
- Subject Selection
  - Suitability for study
    - Inclusion & Exclusion
    - Diagnostic criteria
  - Test group assignment
  - Avoids bias
- Methods
  - Documenting results
  - Steps to minimize bias
  - Quantitative analysis
- Comparison to control
  - No treatment control
    - when placebo effect is negligible
  - Placebo control
  - Active treatment control
    - when no treatment is unethical
  - Historical control

Standards and Regulations

Declaration of Helsinki, ICH, ISO, GHTF

Essential Requirements

Many Standards & Regulations Apply

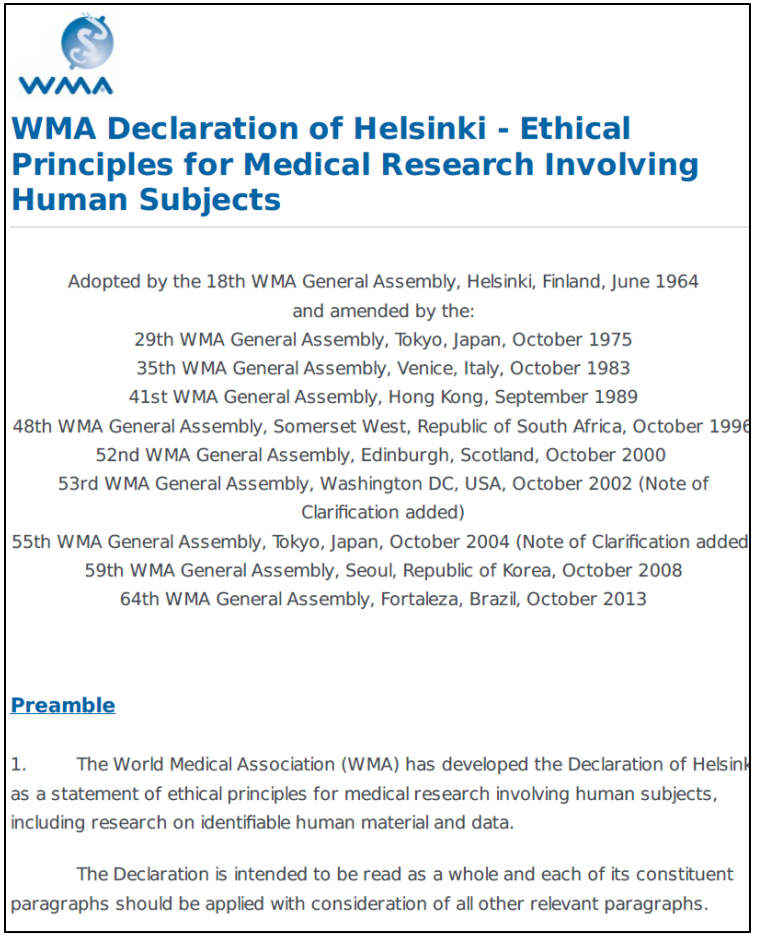
- Declaration of Helsinki
  - Ethical principles for treatment of human subjects in medical research
- International Conference on Harmonization (ICH-E6) Good Clinical Practice (GCP)
  - Harmonized pharmaceutical standards accepted in US, Europe, Japan; used for device trials
- ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects (GCP)
  - International Standard for clinical investigation of medical devices on human subjects
- BS EN ISO 14971:2012 Risk Management for Medical Devices
- Global Harmonization Task Force – Study Group 5
  - GHTF-SG5 N2R8:2007 Clinical Evaluations
  - GHTF-SG5 N3:2010 Clinical Investigations
  - GHTF SG5 N4:2010 Post Market Clinical Follow-Up Studies
- Essential Requirements (TGA Checklist)
- EU council directives
  - Directive 90/385/EEC Active Implantable Medical Devices (AIMDD)
  - Directive 93/42/EEC Medical Devices (MDD)
  - Directive 98/79/EC In Vitro Diagnostic Medical Devices (IVDMD)
  - Directive 2001/20/EC Clinical Trails Directive
  - Directive 2005/28/EC Good Clinical Practices
  - EU Regulation 536/2014
- EU Guidelines
  - MedDev 2.7/4:2010 Guidelines on Clinical Investigation
  - Med Dev 2.7.1 rev 3:2009 Clinical Evaluation (Clinical Evaluation Reports)
  - Med Dev 2.12-1 rev 8:2013 Medical Devices Vigilance System
  - Med Dev 2.12/2 rev 2:2012 Post Market Clinical Follow Up Studies (PMCF)
- US FDA: IDE, PMA, 510(k), quality systems (21CFR820)
  - FDA Guidance documents http://www.fda.gov/regulatoryinformation/guidances/ucm122046.htm

Applied any time clinical data (e.g., safety and performance data) are collected under GCP [e.g., for CER, Device Vigilance, IDE, 510(k), PMA, PMS, PMCF, publications, marketing needs, etc.]

(list is not comprehensive)

Declaration of Helsinki

- World Medical Association (WMA) statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
  - 37 parts constitute the whole
  - addressed to physicians
  - safeguard the health, well-being and rights of patients
- Medical progress requires research without taking precedence over the rights and interests of the subjects



WMA

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

HISTORY

1948 Nuremberg Code
1962 Kefauver Amendments
1964 Declaration of Helsinki
1974 National Research Act
1978 Belmont Report

ICH-E6(R1)

- ICH mission
  - harmonize requirements for **pharmaceutical** product registration
  - reduce testing duplication during research and development
- 1990 meeting
  - Drug regulatory authorities and pharmaceutical industry representatives
  - Discuss scientific and technical aspects of drug registration
  - Initial Countries: Europe, Japan and the United States
  - Global Cooperation Group formed in 1999
  - Topics: Safety (S), Quality (Q), **Efficacy (E)**, Multidisciplinary (M)
    - selected to reflect the basis for approving and authorizing new medicinal products.
- Efficacy (E) = Clinical Trial design, conduct, safety, reporting
  - E3=Structure and Content of Clinical Study Reports
  - E6=Good Clinical Practice (GCP)
  - E8=General Considerations for Clinical Trials

*ICH = International Conference on Harmonisation of Technical Requirements for Registration of **Pharmaceuticals** for Human Use (www.ich.org)*

GCP = Good Clinical Practice; E6 = Efficacy Guideline 6

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ISO 14155 and ISO 14971

- **ISO14155:2011** GCP for Device Trials
  - GCP for design justification, trial conduct, recording/reporting data (protect subjects: rights, safety, well being)
  - Definitions/reporting requirements:
    - device deficiencies
    - AE, ADE, UADE, USADE
    - vulnerable subjects
    - Investigator's Brochure for devices
    - Sponsor/investigator responsibilities
  - ISO14971 compliance is required
    - Comprehensive Risk Analysis Report with Failure Modes and Effects (FMEA)
  - Includes essential documents list, document management practices
  - Signed/dated study report is required
  - Clinical evaluation report is required to justify the study design

- BS EN **ISO 14971:2012** Risk Management
  - Manufacturer must conduct risk analysis to identify hazards
    - to estimate and evaluate associated device risks
    - to control these risks, and
    - to monitor effectiveness of the controls
  - 2012 version: no ALARP, must reduce risk <u>as much as possible</u>
    - Can not use labeling to mitigate risk
    - Must use clinical data during risk assessment

GHTF-SG5

Working Towards Harmonization in Medical Device Regulation

- Conceived in 1992 to achieve uniformity between national medical device regulatory systems
  - Enhance patient safety
  - Increase access to safe, effective and clinically beneficial medical technologies around the world
- Partner regulatory authorities/regulated industry
  - Five Founding Members: European Union, United States, Canada, Australia* and Japan (*current chair)
    - SG5/N1R8:2007 Clinical Evidence – Key Definitions and Concepts
    - SG5/N2R8:2007 Clinical Evaluation
    - SG5/N3:2010 Clinical Investigations
    - SG5/N4:2010 Post Market Clinical Follow-Up Studies

GHTF = Global Harmonization Task Force (www.ghtf.org)

SG5 = Study Group 5

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EU Regulations

- One Competent Authority for each member state
  - 27 countries
- EU Clinical Trials Directives (2001/20/EC) serves as regulatory standard for all member states; however, national laws and regulations of each country vary
  - Regulation 536/2014 New Law 16June2014, eff. 28May2016
- CE Marking (Notified Body reviews files)
  - Indicates product complies with European legislations
  - Essential for free movement of product in European market
  - Demonstrates device is safe and performs as intended
  - Level of risks acceptable when weighed against benefits
    - ER 6 “any undesirable side effects must constitute an acceptable risk when weighted against the performances intended”

http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG

EU Directives

European Commission

- EU Medical Device Regulations harmonized in the 1990s
  - Directive 90/385/EEC Active Implantable Medical Devices (AIMDD)
  - Directive 93/42/EEC Medical Devices (MDD)
  - Directive 98/79/EC In Vitro Diagnostic Medical Devices (IVDMD)
  - Last technical revision: Directive 2007/47/EC
- Directives and Regulations Added
  - Clinical Trials Directive 2001/20/EC
  - EU Regulation 536/2014
  - Council Directive 2005/28/EC GCP

MDD = Medical Devices Directive

http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/

(list is not comprehensive)

Guidance added as MEDDEVs for clinical evaluation of medical device

- MedDev 2.7.1 rev 3:2009 Clinical Evaluation (Clinical Evaluation Reports)
- MedDev 2.7/4:2010 Guidelines on Clinical Investigation
- MedDev 2.12/2 rev 2:2012 Post Market Clinical Follow Up Studies (PMCF)
- MedDev 2.12-1 rev 8:2013 Medical Devices Vigilance System

(list is not comprehensive)

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Medical Devices Directives MEDDEV

- European guidelines for clinical investigations
- Essential requirements (ERs) checklist which all devices must adhere to
- “Clinical Data” includes everything from bench testing to trials using human subjects
- Low to medium-risk devices may be supported by a compilation of literature - Clinical Evidence Report (CER)

OUS Essential Requirements

- Generalized CE Mark requirements
- Annex I, 93/42/EEC, as amended by Directive 2007/47/EC (13 areas)
  - 1 Not harm patient / user
  - 2 Safety features included
  - 3 Performs as intended
  - 4 Lifetime of device, normal use
  - 5 Transport and storage
  - 6 CER required, benefit:risk
  - 7 Design and Construction
  - 8 Infection, Microbial Contamination
  - 9 Construction and Environmental Properties
  - 10 Measuring Function
  - 11 Protection against Radiation
  - 12 Energy Source
  - 13 Information supplied

- Clinical Evidence for Essential Requirements relating to the safety and performance of medical devices
  - Principles 1, 3, 4, and 6 in particular require the medical device achieve intended performance during normal conditions of use and known, foreseeable risks, and any undesirable side-effects, are minimised and acceptable when weighed against the benefits of the intended performance.
  - Case by case decisions about acceptable clinical evidence to comply with the Essential Requirements

http://www.tga.gov.au/pdf/forms/devices-forms-ecmra-ep-checklist.pdf
http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf

US FDA CFR

21 CFR 11: Electronic records; electronic signatures
21 CFR 50: Protection of human subjects
21 CFR 54: Financial disclosure by clinical investigators
21 CFR 56: Institutional Review Boards
21 CFR 803: Medical Device Reporting
21 CFR 807 Subparts A-D: Establishment registration, device listing
21 CFR 807 Subpart E: Premarket Notification Procedures [510(k)]
21 CFR 812: Investigational Device Exemptions (IDE)
21 CFR 814: Premarket Approval of medical devices (PMA)
21 CFR 820: Quality System Regulations (QSR)
21 CFR 822: PostMarket Surveillance (PMS) for Section 522 trials

US FDA CFR = United States Food and Drug Administration Code of Federal Regulations
(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm)

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Clinical Data Requirements

Essential Clinical Data

Other Types of Clinical Data

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Essential Clinical Data

- Safety Data
  - Benefits of device use outweigh the risks
- Effectiveness
  - Device confers intended effect on user
- Performance
  - Device performs as manufacturer intends
- Quality
  - Data Integrity

Safety Data

- Evidence must demonstrate benefits of using the device (correctly) outweigh the risks
- Design trial to capture the following:
  - BENEFIT
    - Type of benefit
    - Magnitude of benefit
    - Probability of experiencing benefit
    - Duration of benefit
  - RISKS
    - Severity, types, number, and rates of harmful events associated with the device
    - Probability of harmful event
    - Duration of harmful event
    - For diagnostic devices: risk of false negative/positive

Effectiveness

- The device will provide clinically significant results demonstrating effectiveness when used:
  - As the manufacturer intends it to be used
  - With appropriate conditions for use
  - On the intended target population
- These results are supported by valid scientific evidence

Performance

- Test device under intended conditions of use and foreseeable hazard conditions
  - Above and below specified level of performance
  - Single-fault condtions
  - Environmental hazard conditions
- Acceptable risk maintained in all conditions?
- Limits of device performance and probability of reaching these limits during intended use

Quality

- Quality data requires:
  - Trained and qualified study personnel
  - Consistent data format and structure
  - Standard data collection methods
    - identify protocol deviations/violations
    - reduce missing data
  - Standard vocabularies and data requirements
  - Monitoring (ensure subject safety and data integrity)
  - Data Management Plan (minimize bias)
    - Randomization
    - Blinding
    - Statistical Analysis Plan (no early looks or premature stopping)
    - Identify adherence to standards
  - Comprehensive Training Program
  - Good Clinical Data Management Practices (GCDMP)

Other Types of Clinical Data

- Survival and Surrogate endpoints
  - Freedom from device revision
  - Freedom from disease complications
- Adverse Events (AE) and Adverse Device Effects (ADE)
- Device functional measures
- Device malfunction, breakage, etc.
- Patient Reported Outcomes (PRO)
  - Quality of Life (QoL)
  - Visual Analogue Scales (VAS)
- Laboratory Results
  - Blood Counts, Metabolic Panels, Urinalysis
  - Imaging (X-Ray, MRI, CT)

Customer Feedback (Use Data)

- Capture customer/use feedback, complaints, etc.
  - Call Center
  - Inquiries
  - Surveys
  - Market studies
  - Focus groups
  - Device servicing
  - Individual cases
  - Proctored evaluations
  - User experiences
- Report should be created at least annually

Morbidity and Mortality Data

- Incidence of illness or death associated with use of a medical device

- Rates of incidence of illness (morbidity)
- Rates of recovery
- Rates of death in the morbid population (mortality)

Sources:

- CDC
- HMDB – European Hospital Morbidity Database
- Other national hospital databases

Clinical Data Submissions/Files

US FDA submissions
Pivotal Trial Guidance
EU CE Mark requirements
Clinical Evidence Reports (CER)

US FDA Submissions

- IDE (Investigational Device Exemption)
  - Allows investigational device to be shipped and used in clinical study to collect safety and effectiveness data
    - Early feasibility study to evaluate device design
    - Basic safety and functionality
    - New indication
    - New design
- 510(k) (Pre-Market Notification)
  - Types: Traditional, Special, Abbreviated
  - Class I and II devices – typically does not need clinical trial data
  - Non-Significant Risk (NSR) devices
  - Requires Substantial Equivalence (SE) to a predicate device
- PMA (Pre-Market Approval)
  - Class III devices – 95% require clinical trial data (IDE)
  - Significant Risk (SR) devices
  - Requires demonstration of the device's safety and effectiveness
- Post Market Surveillance (Section 522)
  - Device failure may have serious adverse health consequences
  - Device implanted more than 1 year
  - Device used to support or sustain life outside a user facility

510(k) (Traditional)

- Comparison of device with predicate device
  - Demonstrates device has equivalent design and function to an existing predicate device
- Percentage of 510(k)s requiring clinical data increasing
  - Most clinical data includes performance data
- Demonstrate substantial equivalence in:
  - Safety
  - Intended use
  - Design/Materials
  - Effectiveness

510(k) Clinical Data

Clinical data is needed for a 510(k) when:

- Device has new technology or new use indication different from other cleared devices of same type
- Bench or animal testing raises questions
- Change in assessment of clinical risks

Clinical data should include

- Data regarding device performance
- Tests conducted on all sizes and models of device
- Tests conducted in manner similar to device use
- Other clinically relevant data from:
  - Engineering/Design verification
  - Bench tests
  - Human or Animal laboratory studies
- Data should indicate no significant differences in safety, design or performance from predicate device

Clinical Data for PMA Submission

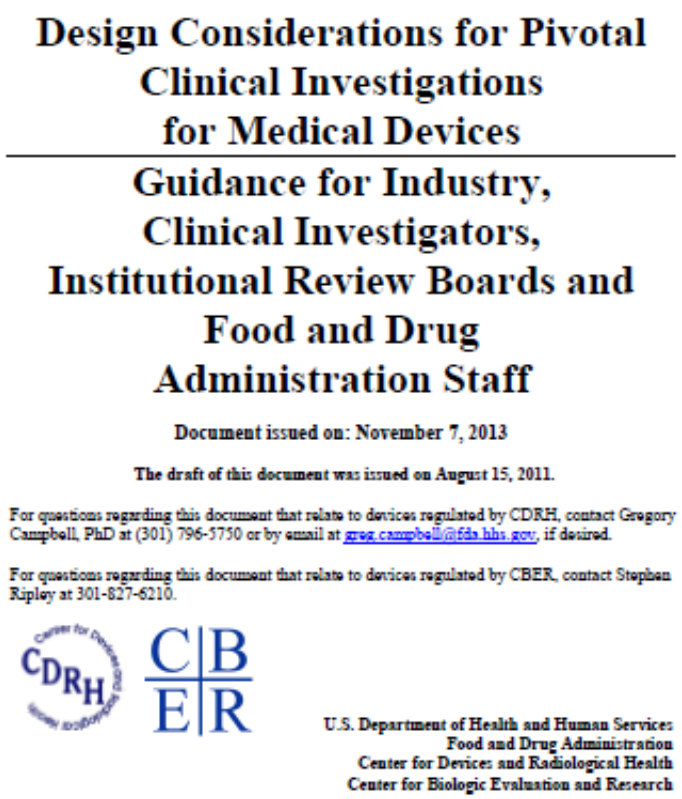
- Review all published and unpublished reports concerning the device and similar devices
- Scientifically sound, well controlled investigations to demonstrate device meets requirements for:
  - Safety
    - Toxicity
    - Device failure modes
    - Benefits outweigh minimized risks
  - Effectiveness
    - Device has intended effect on condition or disease
  - Performance
    - Levels of performance maintained in all conditions

522 Post Market Surveillance Study

- FDA may require a manufacturer to perform a PMS study if:
  - Device failure would have serious adverse health effects
  - Device is intended for pediatric use
  - Device is intended for long-term implantation
  - Device is intended to support/sustain life outside of a user facility
- Types of Surveillance
  - Randomized Clinical Trial
  - Cohort Study (Prospective, Retrospective or Hybrid)
  - Cross-Sectional Study
  - Surveillance of MDR-Reportable Events/Complaints
  - Meta Analysis
  - Case Control Study
  - Registry
  - Animal Study
  - Bench/Laboratory Study

Pivotal Trial (PT) Guidance (Nov 2013)

- Three stages of clinical testing for device
  - exploratory, pivotal, post market
- Describes appropriate clinical trial designs to fulfill premarket clinical data requirements for PMA
  - Establish safety and effectiveness
  - Meet legal requirements
  - US: 21CFR50, 56, 812
  - OUS, part of IDE: 21CFR812
  - OUS, no IDE: FDA will accept IF data are valid and in compliance with Declaration of Helsinki OR local laws/regulations (whichever has greater human subject protections, 21CFR814.15)
  - FDA may inspect US or OUS sites



Design Considerations for Pivotal Clinical Investigations for Medical Devices

Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff

Document issued on: November 7, 2013

The draft of this document was issued on August 15, 2011.

For questions regarding this document that relate to devices regulated by CDRH, contact Gregory Campbell, PhD at (301) 796-5750 or by email at greg.campbell@fda.hhs.gov, if desired.

For questions regarding this document that relate to devices regulated by CBER, contact Stephen Ripley at 301-827-6210.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologic Evaluation and Research

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf

PT Regulatory Framework

- Statutory standard: “PMA must provide reasonable assurance of safety and effectiveness of the device” FD&C Act, Sections 513(a)(1)(C) & 513(a)(2)
  - Appropriate population (intended use)
  - Appropriate conditions of use (labeling)
  - Benefits outweigh risks (risk mitigation)
- FDA interprets the statutory standard for PMA approval through regulations
  - 21CFR860.7(d)(1) reasonable assurance device is safe when probable benefits outweigh probable risks (and absence of unreasonable risk associated with the use of the device)
  - 21CFR860.7(e)(1) reasonable assurance device is effective when significant portion of target population using device provide clinically significant results
- Safety and effectiveness must be supported by data relevant to the target population and evaluated in light of the device labeling AND benefits must outweigh risks

PT Valid Scientific Evidence

- *"21 CFR 860.7(c)(2) Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable."*
- 21 CFR 860.7(d)(2) describes "types of evidence" for safety may include animal studies and in vitro studies.
- 21 CFR 860.7(e)(2) allows FDA to rely upon "other valid scientific evidence" for effectiveness

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf

PT General Study Considerations

- Consider the following:
  - Device function and mechanism of action
  - User skill level and training
  - Learning curve
  - Human Factors (esp. with software and user interface)
  - Bias
  - Variable Device Performance (required sample size?)
  - Study Objectives (claims)
  - Subject selection (inclusion/exclusion; target population)
  - Site selection (stratification)
  - Study design (parallel group, paired, cross over)

PT Outcome Study Considerations

- Endpoint
  - Clinical safety/effectiveness for desired intended use
  - Clinically meaningful / relevant – clinical benefit to subject
  - Objective, valid and minimal bias (independent evaluator)
- Randomization
- Blinding (Masking)
- Controls
  - No treatment
  - Placebo
  - Active treatment
  - Historical
  - Cross Over (subject serves as own control)

PT Performance Study Considerations

- What is measured or detected
- What is reported
- What the device examines
- How/when device is used
- Who uses the device for what condition
- Clinical reference standard (target condition)
- Study population and specimen collection
- Diagnostic comparison studies
- Bias (selection, verification, disease change, lead-time, survivor, extrapolation, reading order, and lack of independent evaluation bias)

PT Quality Considerations

- Handling Clinical Data
- Study Conduct
- Study Analysis
- Anticipating Changes

Clinical Data for CE Mark

- In order for a device to receive CE Mark, conformity with Essential Requirements (ERs) must be based on critical evaluation of all clinical investigations
  - Risk, safety, and effectiveness data
  - Characteristics of performance
  - Evaluation of side effects
  - Acceptability of benefits/risk ratio

Post Market Clinical Follow-Up

- EU MEDDEV Guideline - Circumstances where a PMCF study may be warranted:
  - Medical device is novel in design, material, operation or technology
  - Changes in claims, device design, labeling
  - High risk classification
  - Severe disease or treatment challenges
  - Unanswered questions about safety, performance, AEs
  - Interactions with other medical products or treatments
- Types of PMCF
  - Follow-up of pre-market clinical subjects
  - New clinical investigations in post market setting
  - Review data from device registry
  - Review data collected from patients exposed to the device

Clinical Evaluation Reports (CERs)

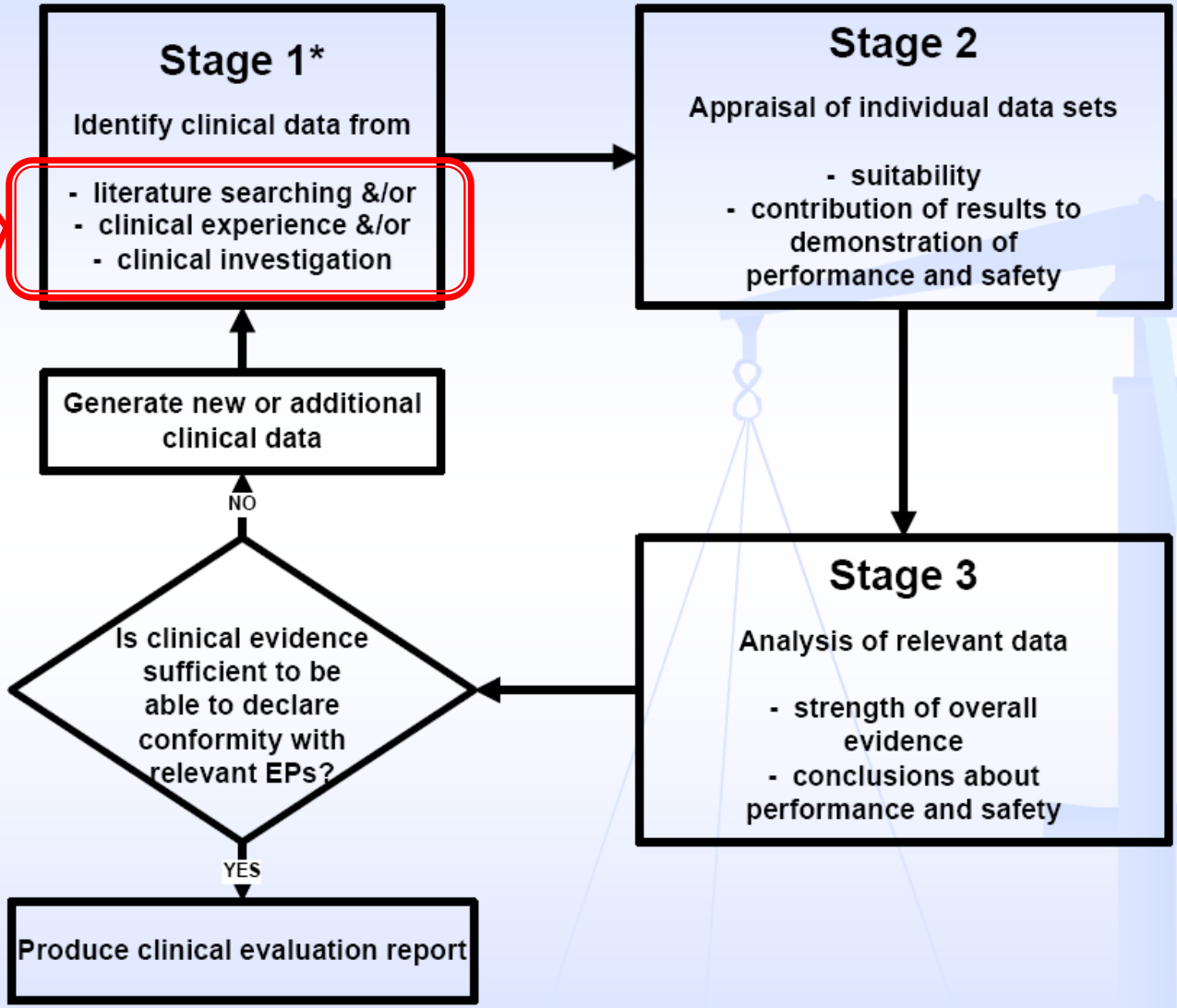
- Clinical Evaluation per GHTF SG5/N2R8:2007
  - “An assessment and analysis of clinical data pertaining to a medical device in order to verify the clinical safety and performance of the device”
- Scope
  - Comprehensive analysis of PRE and POST Market clinical data relevant to the intended use of the device
  - Includes clinical performance data and safety data for device or related/comparable devices
- Every medical device sold in Europe must have a CER on file (design dossier or technical file)
- Clinical data for CERs can be collected from
  - Clinical Trials
  - Literature searches
  - Human use sources
    - MAUDE database data
    - Recalls data
    - User surveys
    - Complaints

Clinical Evaluation Flowchart

Literature Review Data (may include non-clinical trials)

Clinical Experience/Use Data (Post Market Surveillance, Complaints, Adverse Device Events, Recalls, etc)

Clinical Trial Data



EPs = Essential Principles of safety and performance of medical devices
* Conformance to performance standards may be sufficient to demonstrate compliance to relevant EPs

SOURCE: Clinical Evaluation, Study Group 5 Final Document SG5/N2R8, May 8, 2007

Clinical Data Collections

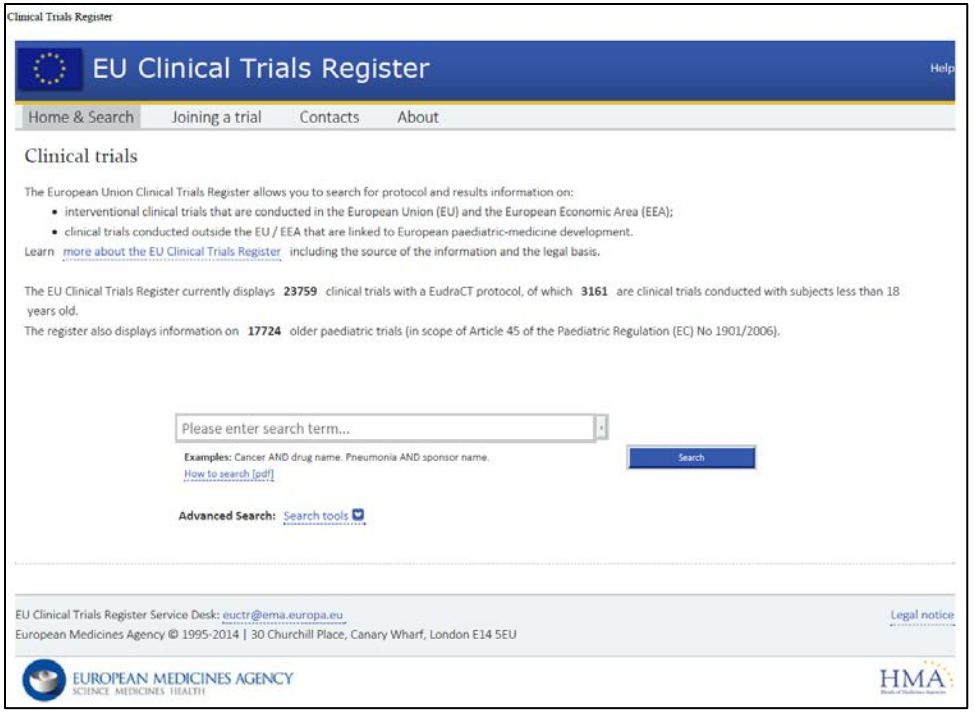
Clinical Trial Databases
Company Databases
Insurance Databases (reimbursement)
Government Databases

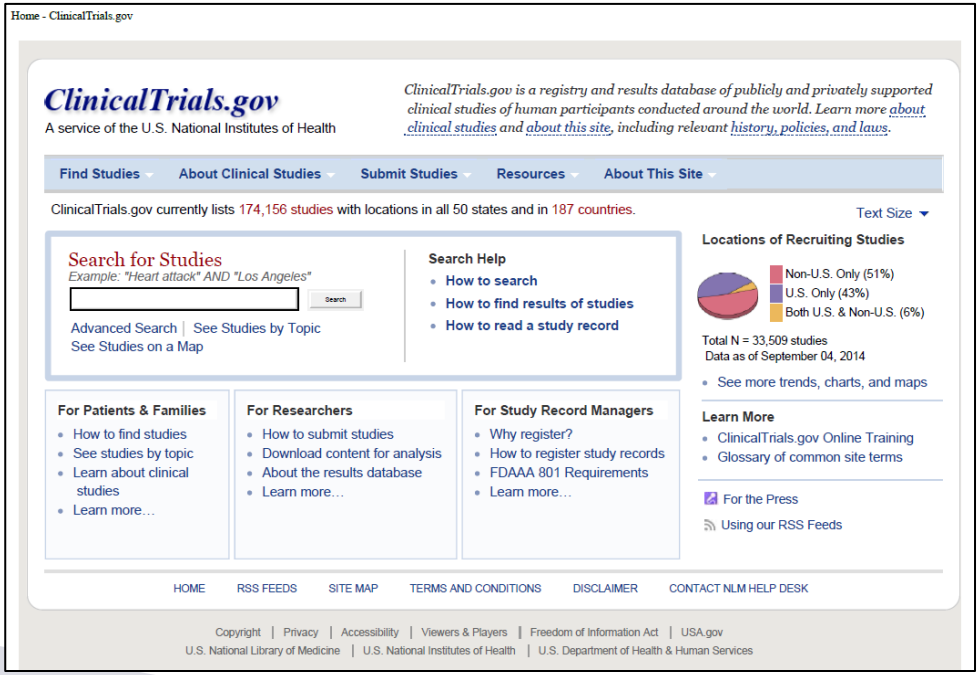
Who else collects clinical trial data?

- Several databases are not publicly available
  - Health insurance companies
    - Insurance claims and payments
    - Clinical trial coverage
  - Sites, Sponsors and Clinical research organizations (CROs)
    - Clinical trial data
    - Clinical evidence reports (CERs)
  - Eudamed
    - "Eudamed is a secure web-based portal acting as a central repository for information exchange between national competent authorities and the Commission and **is not publicly accessible**. Eudamed use is obligatory since May 2011."
      - http://ec.europa.eu/health/medical-devices/market-surveillance-vigilance/eudamed/index_en.htm
- IMPORTANT to use public databases and analyze clinical data!
  - Understand risks and benefits reported globally for class of device
  - Potential to avoid costly, new clinical trials (especially where new clinical data will only offer the same information about safety or performance)
    - Look for: Clinical trials, Literature, Use Information

Clinical Trial Databases

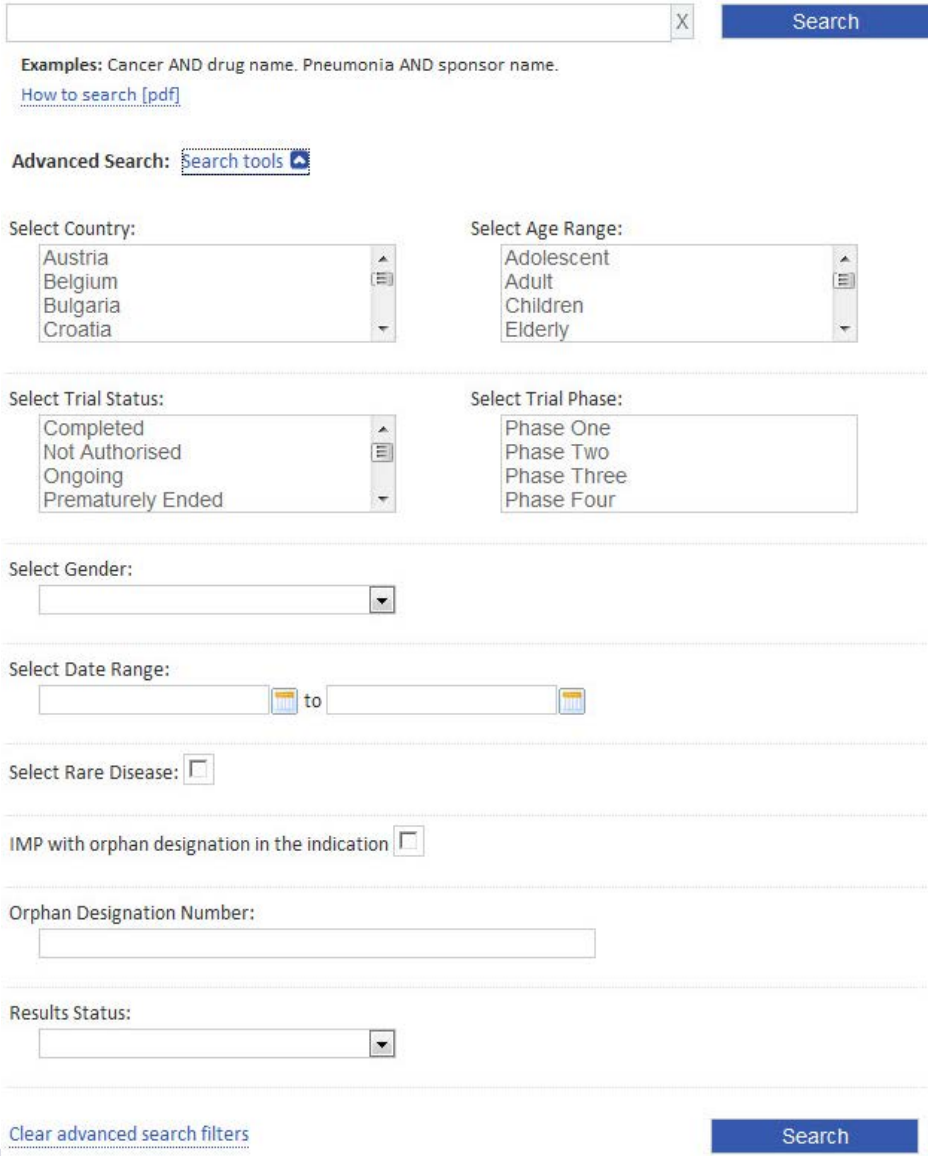
- EudraCT
  - https://www.clinicaltrialsregister.eu/ctr-search/search
- ClinicalTrials.gov
  - http://clinicaltrials.gov/
- WHO ICTRP
  - www.who.int/trialsearch
  - 14 countries including the Australian New Zealand Clinical Trial Registry
  - http://www.anzctr.org.au/default.aspx





EU Clinical Trials Register

- EudraCT database
  - Interventional clinical trials in the EU and European Economic Area (EEA) after 1May2004
  - Clinical trials outside the EU/EEA but linked to EU pediatric-medicine development
  - Company/responsible organization provides data
    - Protocol, study design, sponsor, investigational agent
    - Results (baseline characteristics, endpoints, adverse events)
  - National Competent Authority adds authorization and opinion from relevant ethics committee

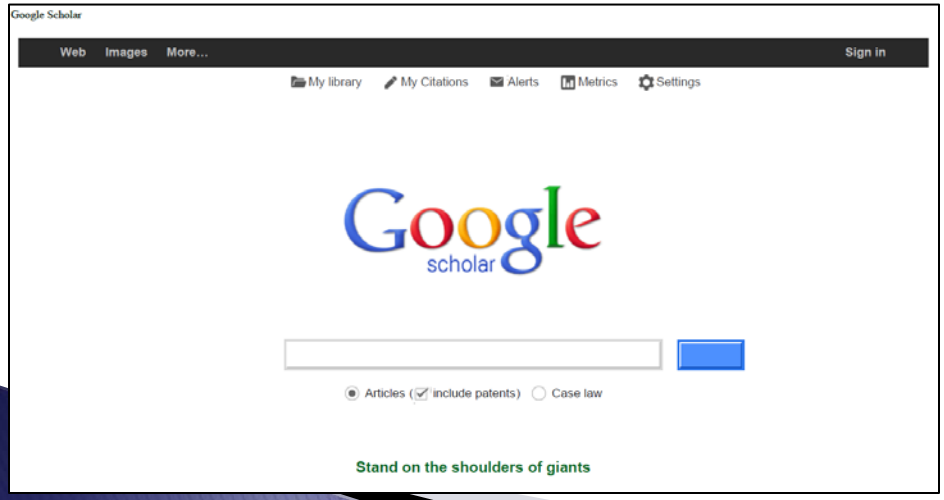


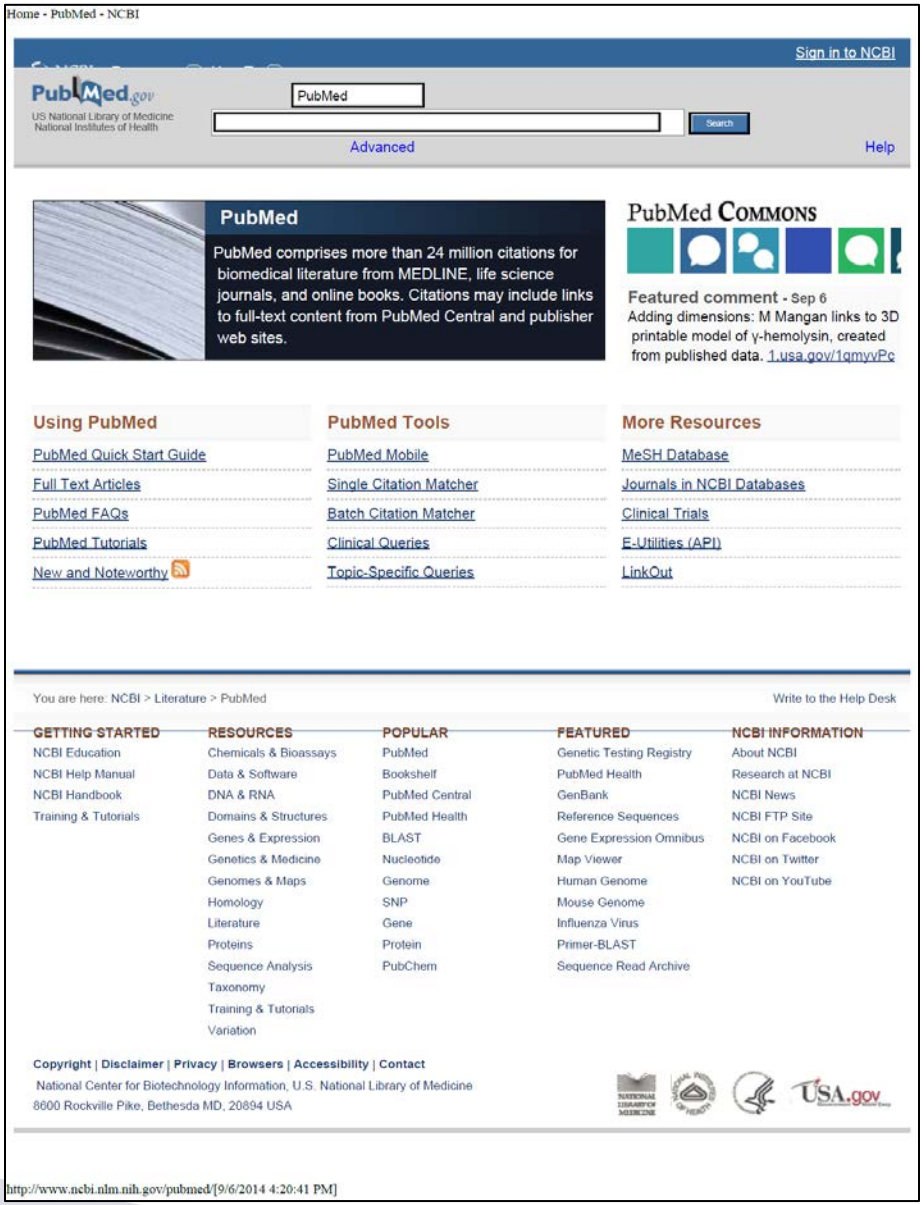
Clinicaltrials.gov

- Clinical trials in the US
  - Study design / protocol
  - Disease, condition or device
  - Recruiting status
  - Progress of study
  - Study results
  - Demographics of participants
  - Location contact information

Literature Databases

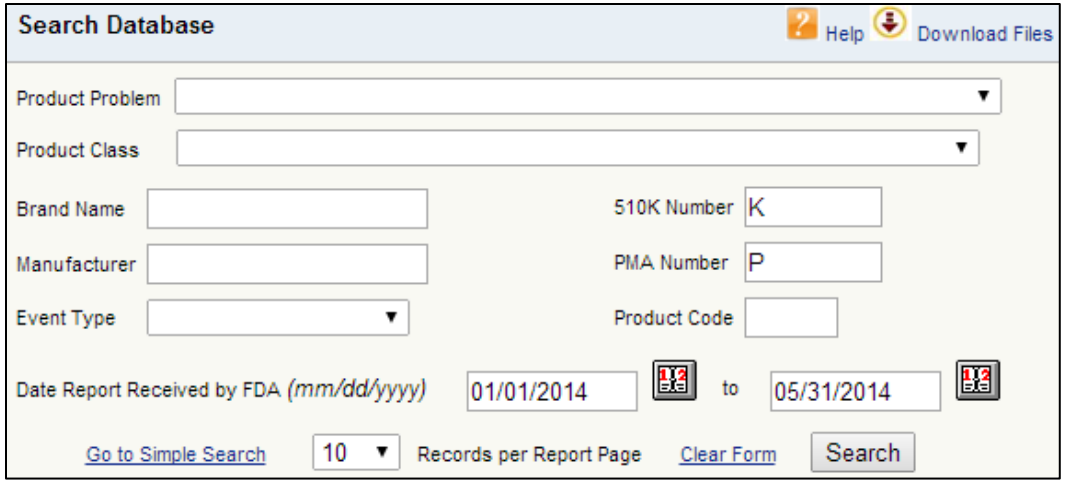
- Pubmed (24 Million citations)
  - http://www.ncbi.nlm.nih.gov/pubmed/
- Google Scholar
  - http://scholar.google.com/





Use Information Databases

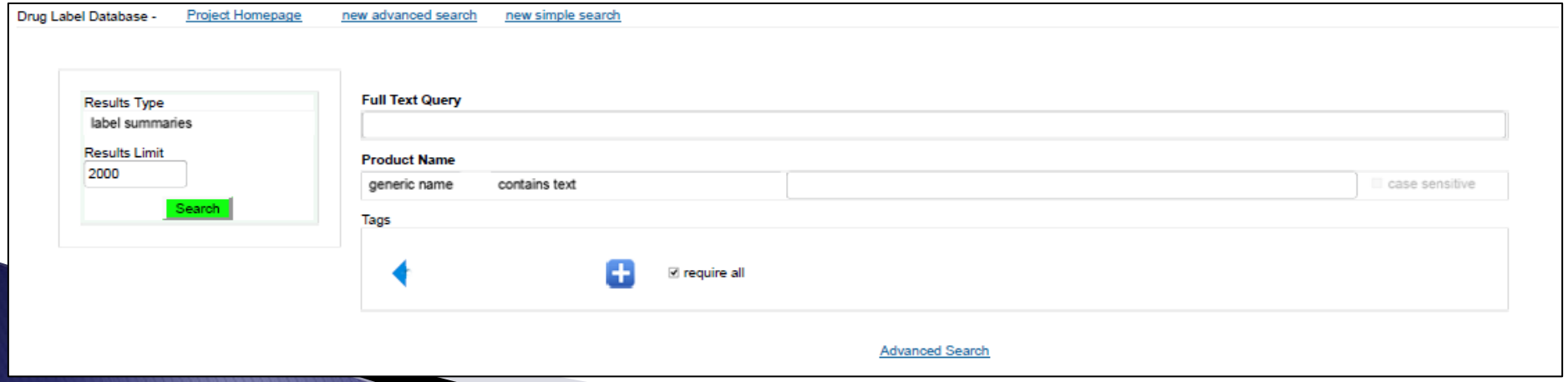
- FDAs Manufacturer and User Facility Device Experience (MAUDE) database houses Medical Device Reports (MDRs)
  - Monitor device performance and safety
  - Benefit-risk assessments
- MDRs
  - Mandatory reports
  - Voluntary reports
  - Adverse Events
  - User facility reports
  - Importer reports
  - Distributor reports
  - Manufacturer reports



http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm

Other FDA Databases

- Premarket Approvals (PMA)
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm
- 510(k) Premarket Notifications (PMN)
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm
- Total Product Life Cycle (TPLC)
  - http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhtransparency/ucm199906.htm
- Recalls
  - http://www.fda.gov/safety/recalls/
- Warning Letters
  - http://www.fda.gov/iceci/enforcementactions/WarningLetters/default.htm
- Drug Label Search
  - https://rm2.scinet.fda.gov/druglabel/#simsearch-0 (use Firefox for drug labeling info)



Conclusion

Learner Objectives

- After the presentation attendees should be able to:
  - Understand requirements for clinical data (or not)
  - Differentiate between US and OUS requirements
  - Identify essential clinical data for regulatory files

Agenda

- Introduction
  - Global Clinical Research
  - Risk Based Approach
  - Valid Data
- Standards and Regulations
  - Declaration of Helsinki, ICH, ISO, GHTF
  - Essential Requirements
- Clinical Data Requirements
  - Essential Clinical Data
  - Other Types of Clinical Data
- Clinical Data Submissions/Files
  - US FDA submissions
  - Pivotal Trial Guidance
  - EU CE Mark requirements
  - Clinical Evidence Reports (CER)
- Clinical Data Collections
  - Clinical Trial Databases
  - Company Databases
  - Insurance Databases (reimbursement)
  - Government Databases

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Questions?

- Frestedt incorporated
  - When you need clinical, regulatory and quality affairs support
  - We can be “your first call for help”
- Alimentix
  - If you need special clinical trials with foods and NSR devices
  - **Dr. Joy Frestedt, PhD, RAC, CCTI, FRAPS**
    President and CEO
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    www.alimentix.com