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# **Global Regulatory Affairs for Medical Products**

**BEC 475 / 575**

**Module 2.2 – European Union & Other  
Regulatory Agencies**

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In this presentation, I'll describe the regulatory agencies in the European Union and Japan. I'll talk about harmonization efforts supported by the United States, EU, and Japan. Finally, I'll summarize the World Health Organization and International Organization for Standardization.

# European Union (EU)



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Source: [http://www.nationsonline.org/oneworld/europe\\_map.htm](http://www.nationsonline.org/oneworld/europe_map.htm)

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The European Union consists of 28 member states. Its ruling body, the European Commission, is responsible for drafting and proposing new laws to European Parliament and Council of Europe. With the creation of the European Union in 1993, regulatory authority is now centralized and much easier to gain product approval for sale in multiple countries with a single filing.

# **EMA**

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- European Medicines Agency
- Mission: foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the European Union (EU)
- Began operation in 1995
- Headquartered in London

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The EMA is the EU's equivalent to the FDA.

## **EMA Responsibilities**

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- Facilitate development and access to medicines
- Evaluate applications for marketing authorization
- Monitor the safety of medicines across their lifecycle
- Provide information to healthcare professionals and patients

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The responsibilities of the EMA are very similar to those of the FDA.

# EMA Resources

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- Management Board
  - 35 members
  - Appointed to act in the public interest
  - Duties:
    - Sets the Agency's budget
    - Approves the annual work program
    - Responsible for ensuring that the Agency works effectively and co-operates successfully with partner organizations across the EU and beyond

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The Management Board rules over the EMA. None of its 35 members are affiliated with a government or organization.

# EMA Resources

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- Executive Director
  - Legal representative of the Agency
  - Responsible for all operational matters, staffing issues, and drawing up the annual work program
- Agency staff
  - Support the Executive Director in carrying out his responsibilities, including administrative and procedural aspects of EU law related to the evaluation and safety-monitoring of medicines in the EU

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The Executive Director is an employee of the EMA and is its legal representative. Agency staff support the Executive Director.

# EMA Committees

- **Committee for Medicinal Products for Human Use (CHMP)** is responsible for preparing the Agency's opinions on all questions concerning medicinal products for human use, in accordance with Regulation (EC) No 726/2004.
- **Committee for Medicinal Products for Veterinary Use (CVMP)** is responsible for preparing the Agency's opinions on all questions concerning veterinary medicinal products, in accordance with Regulation (EC) No 726/2004.
- **Committee for Orphan Medicinal Products (COMP)** is responsible for reviewing applications from persons or companies seeking 'orphan medicinal product designation' for products they intend to develop for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the European Union.

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Six scientific committees, composed of members of all EU and EEA-EFTA states, some including patients' and doctors' representatives, conduct the main scientific work of the Agency. This slide shows three of these.

## EMA Committees (cont.)

- **Committee on Herbal Medicinal Products (HMPC)** was established in September 2004 in accordance with Regulation (EC) No 726/2004 and Directive 2004/24/EC, which introduced a simplified registration procedure for traditional herbal medicinal products in EU Member States.
- **Pediatric Committee (PDCO)** assesses the content of pediatric investigation plans and adopts opinions on them in accordance with Regulation (EC) 1901/2006 as amended.
- **Committee for Advanced Therapies (CAT)** was established in accordance with Regulation (EC) No 1394/2007 on advanced-therapy medicinal products (ATMPs). It is a multidisciplinary committee, gathering together some of the best available experts in Europe to assess the quality, safety and efficacy of ATMPs, and to follow scientific developments in the field.

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Here are the rest of the six committees.

# Regulatory Approval

- The EMA is responsible for the Centralized Authorization Procedure (also known as the “Centralized Procedure”)
- The Centralized Procedure results in a single marketing authorization
- This authorization is valid across the European Union, as well as in the EEA/EFTA states Iceland, Liechtenstein and Norway

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The Centralized Procedure allows manufacturers of certain types of products to obtain approval in all EU countries. This was not possible 25 years ago. If a drug was approved before the EU was formed or the product is out of the scope of the centralized procedure, then it must be approved at the national level.

We'll discuss EU regulatory approvals in Topic 11 of this course.

# Regulations

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 of the publication "The rules governing medicinal products in the European Union":

**Volume 1 – EU pharmaceutical legislation for medicinal products for human use**



The most important set of regulations is called "The rules governing medicinal products in the European Union". Volume 1 gives an overview of the requirements.

## **Regulations (cont.)**

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The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

**Volume 2** - Notice to applicants and regulatory guidelines for medicinal products for human use

**Volume 3** - Scientific guidelines for medicinal products for human use

**Volume 4** - Guidelines for good manufacturing practices for medicinal products for human and veterinary use

**Volume 8** - Maximum residue limits

**Volume 9** - Guidelines for pharmacovigilance for medicinal products for human and veterinary use

**Volume 10** - Guidelines for clinical trial

Medicinal products for pediatric use, orphan, herbal medicinal products and advanced therapies are governed by specific rules.

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Volumes 2-4 and 8-10 give more details. In Volume 4, you can find the details of GMP.

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# JAPAN

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Now we'll spend a little time on the regulatory environment in Japan.

## PMDA

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- Pharmaceuticals and Medical Devices Agency
- PMDA works with the Ministry of Health, Labour and Welfare
- Charged with protecting the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices

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Japan's regulatory agency is the Pharmaceuticals and Medical Devices Agency or PMDA.

## PMDA's Three Pillar System



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The PMDA has what they call a “Three Pillar System” made up of Review, Safety, and Relief functions. The Relief function is unique to Japan. I’ll present each of the functions in the upcoming slides.

## **PMDA - Drug and Medical Device Reviews**

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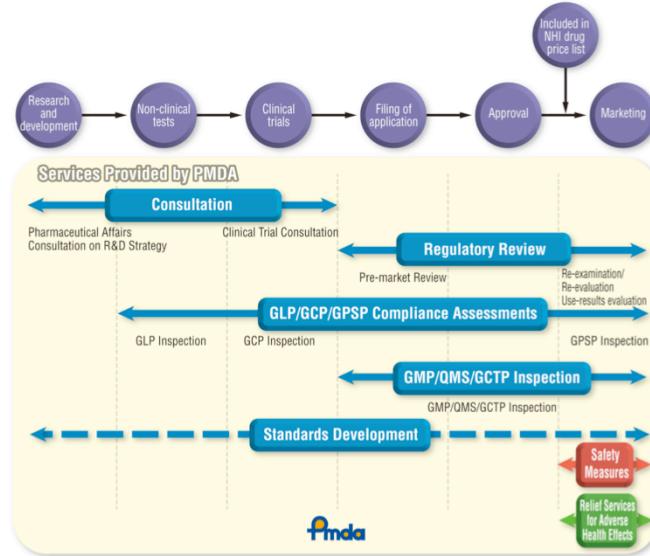
- Scientific reviews of pharmaceuticals and medical devices for marketing authorization based on the Pharmaceutical Affairs Law of Japan
- Consultation (planning and implementation of clinical trials and preparation of NDA dossiers, etc.)
- GLP / GCP / GPSP inspections and conformity audit on dossiers submitted as initial application, re-examination and re-evaluation application
- GMP / QMS inspections on manufacturing sites, processes and quality management system of pharmaceuticals and medical devices
- Confirmation of re-examination and re-evaluations based on the Pharmaceutical Affairs Law

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Japan's review functions are similar to those of the FDA and EMA.

# PMDA – Review Cycle



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Here's a graphic that shows the Review functions and when they occur during the product life cycle.

# PMDA - Approval Process

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The graphic shows how PMDA works with applicants and the Minister of Health, Labour, and Welfare to ensure approval of new drugs. PMDA doesn't actually do the approval.

## **PMDA - Post-marketing Safety**

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- Collection, analysis and dissemination of information related to the quality, efficacy and safety of pharmaceuticals and medical devices
- Consultation services for consumers about safe use of pharmaceuticals and medical devices
- Advice and instruction for marketing authorization holders to enhance safety of pharmaceuticals and medical devices
- Research relating to the development of standards for pharmaceuticals and medical devices

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The second pillar in the PMDA framework is post-marketing safety. PMDA ensures that pharmaceuticals and medical devices are safe and effective.

## PMDA - Inspections

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- Good Manufacturing Practice (GMP)
- Quality Management System (QMS)
- Good Gene, Cellular, and Tissue-based Manufacturing (GCTP)

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PMDA conducts inspections to ensure post-marketing safety. They check GMP at domestic and foreign sites that manufacture products classified as “high-risk,” such as new drugs, biological products or biotechnological products. For manufacturers of medical devices and in-vitro diagnostics, they check the Quality Management System. PMDA has separate regulations for GCTP or Good Gene, Cellular, and Tissue-based Products Manufacturing and conduct inspections for those. Only a small number of the inspections are conducted on-site, while the rest are paper or document inspections. This type of inspection is unique to PMDA. FDA and EMA inspectors conduct on-site inspections.

# PMDA - Regulatory Information

Home > Reviews and Related Services > Regulatory Information

Reviews and Related Services
<a href="#">Outline</a>
<a href="#">Consultations</a>
<a href="#">Reviews</a>
<a href="#">GLP / GCP / GSP Compliance Assessments</a>
<a href="#">GMP / QMS / GCTP Inspections</a>
<a href="#">Regulatory Information</a>

## Regulatory Information

### Regulations and Guidance

- [Ministerial Ordinances](#)
- [Notifications and Administrative Notices](#)

### Regulatory Procedures

- [Accreditation of Foreign Manufacturers](#)
- [Master File System](#)
- [GMP](#)
- [QMS](#)

### Other Related Information

- [New Regulations of Non-Corrective Colored Contact Lenses under the Pharmaceutical Affairs Law](#)
- [Issuance of Certificates for Medical Devices for Export](#)
- [Revision of Japanese Medical Device QMS requirements](#)

### Frequently Asked Questions (FAQ)

- [Application for Product Approval](#)
- [Acceptance of Medical Device Foreign Clinical Data](#)
- [Accreditation of Foreign Manufacturers](#)
- [Master File System](#)

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<http://www.pmda.go.jp/english/review-services/regulatory-info/0002.html>

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Here's a screen shot of the regulatory procedures made available by PMDA. You don't need to know any of them – just know how to find them.

## PMDA - Relief Services

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- Providing medical expenses, disability pensions, bereaved family pensions, etc. for people who have suffered from severe illness and disabilities caused by adverse drug reactions of pharmaceuticals or infections from biological products
- Providing healthcare allowances, etc. to SMON (subacute myelo-optico-neuropathy) patients and commissioned benefits services to HIV-positive and AIDS patients infected by blood products
- Providing compensations in accordance with "the Special Measures Law concerning the Payment of Benefits to Relieve the Patients of Hepatitis C Infected through Specified Fibrinogen Preparations and Specified Blood-Coagulation Factor IX Preparations Contaminated by Hepatitis C Virus"

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The pillar that provides relief services for adverse health effects demonstrates how Japan follows through on its commitment to providing safe drugs to its constituents.

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**ICH**

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Now let's discuss how all the regulatory agencies try to work together.

# ICH

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Makes recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objectives of such harmonization include the following:
  - More economical use of human, animal and material resources
  - Elimination of unnecessary delay in the global development and availability of new medicines
  - Maintain safeguards on quality, safety and efficacy, and regulatory obligations to protect public health

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Now that we've talked about the regulatory agencies for US, EU , and Japan, let's discuss some groups that represent multiple countries. One is the ICH. Luckily, it's called ICH and not ICHTRRPHU, because its full name is "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use". The ICH works to harmonize certain regulations across the United States, European Union, and Japan. The objectives of such harmonization are shown on this slide.

# ICH Representatives

- USA
  - Food and Drug Administration (FDA)
  - Pharmaceutical Research and Manufacturers of America (PhRMA)
- Europe
  - European Union (EU)
  - European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Japan
  - Ministry of Health, Labour and Welfare (MHLW)
  - Japan Pharmaceutical Manufacturers Association (JPMA)
- Additional Observers:
  - World Health Organization (WHO)
  - European Free Trade Association (EFTA)
  - Canada

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ICH members include representatives from regulatory agencies and manufacturers. This representation helps make sure the regulations are practical.

## ICH History

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- First discussions between Europe, Japan and the US on possibilities on international harmonization took place in the 1980s
- At the World Health Organization (WHO) Conference of Drug Regulatory Authorities, in Paris, in 1989, specific plans for action began to materialize
- Finally, the ICH was birthed at a meeting in April 1990, hosted by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in Brussels

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Here's a little history on how the ICH came to be.

## ICH Guideline Procedure

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The ICH devised a procedure for developing and implementing international guidelines. It involved the steps below:

- Step 1:** Consensus building
- Step 2:** Confirmation of six-party consensus
- Step 3:** Regulatory consultation and discussion
- Step 4:** Adoption of an ICH Harmonized Tripartite Guideline
- Step 5:** Implementation

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The ICH uses a rigorous process to implement new guidelines. It works quite well, but as you can imagine, it takes a long time to implement a new guideline.

## ICH Products

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- Over 50 harmonized guidelines, including the Common Technical Document (CTD), which describes the common format for the preparation of a well-structured CTD for applications that will be submitted to regulatory authorities
- International electronic communication through the provision of Electronic Standards for the Transfer of Regulatory Information (ESTRI), including the Electronic Common Technical Document (eCTD)
- The Medical Dictionary for Regulatory Activities (MedDRA) Terminology

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Since its inception, the ICH has developed these “products”. The Common Technical Document, or CTD, is the most important.

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# **WHO**

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Now we'll look at the World Health Organization.

# WHO

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- World Health Organization
- When diplomats met to form the United Nations in 1945, one of the things they discussed was setting up a global health organization
- WHO's constitution finalized on April 7, 1948

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The World Health Organization is another organization that influences drug manufacturers. It started in 1948. Each year, we still celebrate April 7 as World Health Day.

# WHO Governance

- World Health Assembly is the supreme decision-making body
- Meets in Geneva in May each year, and is attended by delegations from all 194 Member States
- Main function is to determine the policies of the organization
- The World Health Assembly appoints the Director-General, supervises the financial policies of the Organization, and reviews and approves the proposed program budget. It similarly considers reports of the Executive Board, which it instructs in regard to matters upon which further action, study, investigation or report may be required.
- The Executive Board is composed of 34 members technically qualified in the field of health. Members are elected for three-year terms.
- The main functions of the Board are to give effect to the decisions and policies of the Health Assembly, to advise it and generally to facilitate its work.

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WHO is governed by the World Health Assembly. With representation from all 194 member states, you can imagine that their meetings are quite complex. Luckily, there is an Executive Board to do most of the work.

## **WHO Core Functions**

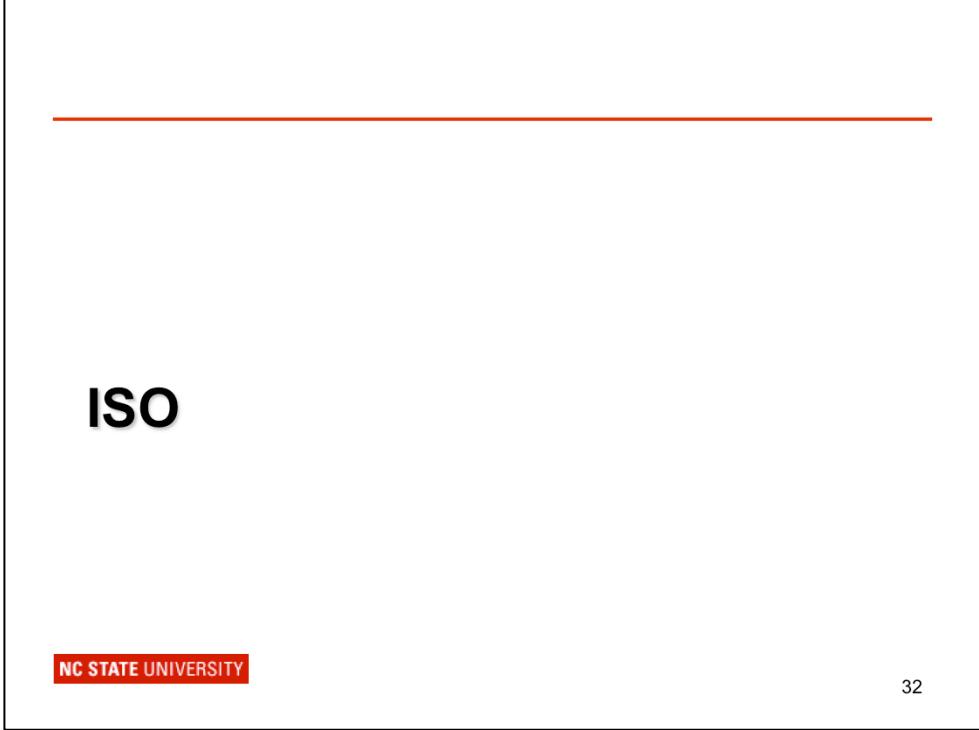
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- Provide leadership on matters critical to health and engaging in partnerships where joint action is needed
- Shape the research agenda and stimulating the generation, translation and dissemination of valuable knowledge
- Set norms and standards and promoting and monitoring their implementation
- Articulate ethical and evidence-based policy options
- Provide technical support, catalyzing change, and building sustainable institutional capacity
- Monitor the health situation and assessing health trends

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The WHO considers these functions to be their core responsibilities.



**ISO**

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And now for some ISO ....

# ISO

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- International Organization for Standardization
- Founded in 1947 and is based in Geneva, Switzerland
- “ISO” comes from the Greek “isos”, meaning “equal”
- Not an official body of any government or government agency, nor does it receive government sanction

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Another organization worth mention is ISO, or the International Organization for Standardizations. The acronym ISO comes from the Greek word “isos”, which means “equal”. This was the simplest way to bridge the language boundaries between the various European countries that subscribe to ISO practices.

## ISO Standards

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- Consortium with the ability to set standards that often become law, either through international agreements or through national standards
- Initial influence began in Europe, but the ISO system has also established itself in North America
- The ISO and the American Society for Testing and Materials (ASTM) recognize each other and have worked to produce harmonized technical documents and standards

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ISO is an independent organization that sets standards that often get adopted by the regulatory agencies. The use of ISO classifications for clean rooms is a good example. You'll hear more about that later.

# ISO 9000

- The ISO 9000 family of international quality management standards and guidelines has been used for establishing effective and efficient quality management systems in companies and organizations. Its influence has grown to global status since the collection of standards was first published in 1987.
- More specifically, the ISO 9000 series provides the basic concepts and principles towards addressing the following:
  - Organizations seeking advantage through the implementation of a quality management system
  - Organizations seeking confidence from their suppliers that their product requirements will be satisfied

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Some of you may have heard or read of ISO 9000. The ISO 9000 family of international quality management standards and guidelines has been used for establishing effective and efficient quality management systems in companies and organizations. Its influence has grown to global status since the collection of standards was first published in 1987.

# ISO 9001

- ISO 9001 is one of the most cited and visible guidance passages of the ISO 9000 family. The purpose of ISO 9001 is to achieve the first level of performance as defined by ISO 9000. As such, ISO 9001 specifies requirements for a quality management system where an organization:
  - Needs to demonstrate its ability to consistently provide product that meets customer and applicable statutory and regulatory requirements, and
  - Aims to enhance customer satisfaction through the effective application of the system, including processes for continual improvement of the system and the assurance of conformity to customer and applicable statutory and regulatory requirements.

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ISO 9001 standards present the requirements for quality management.

## ISO for Medical Devices

There are several ISO standards covering medical devices. Many of these standards are harmonized with the ISO 9001 standard. Some of the key ISO standards covering medical devices:

- ISO 10993 (standards for evaluating the biocompatibility of a medical device prior to a clinical study)
- ISO 13485 (requirements for a comprehensive management system for the design and manufacture of medical devices)
- ISO 14971 (requirements for a risk management system for medical devices during the product life cycle as required by ISO 13485)
- ISO 14969 (guidance for the application of the requirements for quality management systems contained in ISO 13485)

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ISO is most relevant to companies that manufacture medical devices.

## Summary

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There are many similarities between the largest regulatory agencies and standard organizations, probably because all of them have the same goal in mind: to ensure that safe and effective medical products are available to their constituents.

For the most part, the guidelines developed by each organization were adopted from best practices of other organizations or were corrective actions implemented after a failure that led to injuries or deaths.

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As you may have noticed, the regulatory agencies and standard organizations all have similar functions. Even though they won't admit it, each probably watch the others and adopt concepts or standards that work to ensure that medical products are safe and effective.