Top 12 Recent Global API Regulatory Developments

WITH DALTON

Peter Pekos

Company Vision

"To make the impossible possible, Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

Disclaimer

This technical report is intended to provide information to quality and regulatory correspondents on the 2020 revisions of *Annex 1: Manufacture of Sterile Medicinal Products*. This technical report should be read in conjunction with the relevant laws, regulations, and guidance's that apply to your situation.

FDA inspected, HC approved, & MRA with EMA

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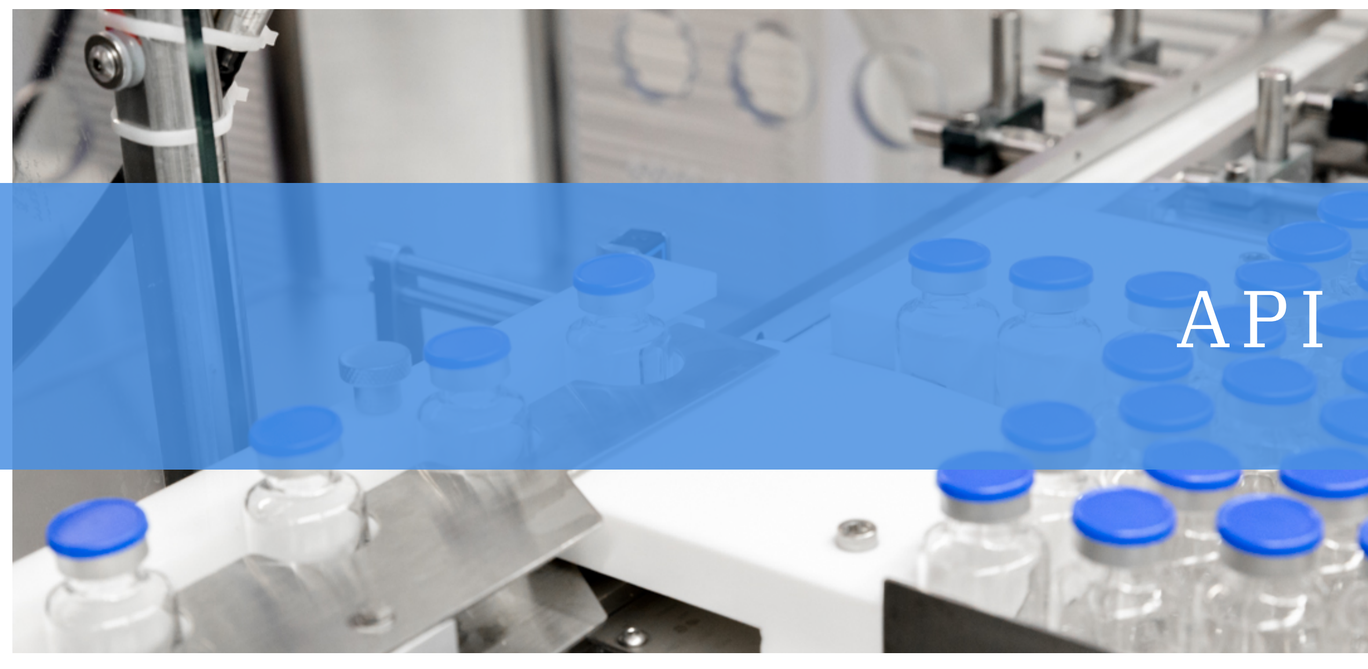


API

What is An Active Pharmaceutical Ingredient?

Any substance or mixture of substances intended to be used as an active ingredient in the manufacture of a medicinal drug product. Such substances are intended to provide a pharmacological action or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. An example of an API is the acetaminophen contained in a pain relief tablet.

API Relevent Documents

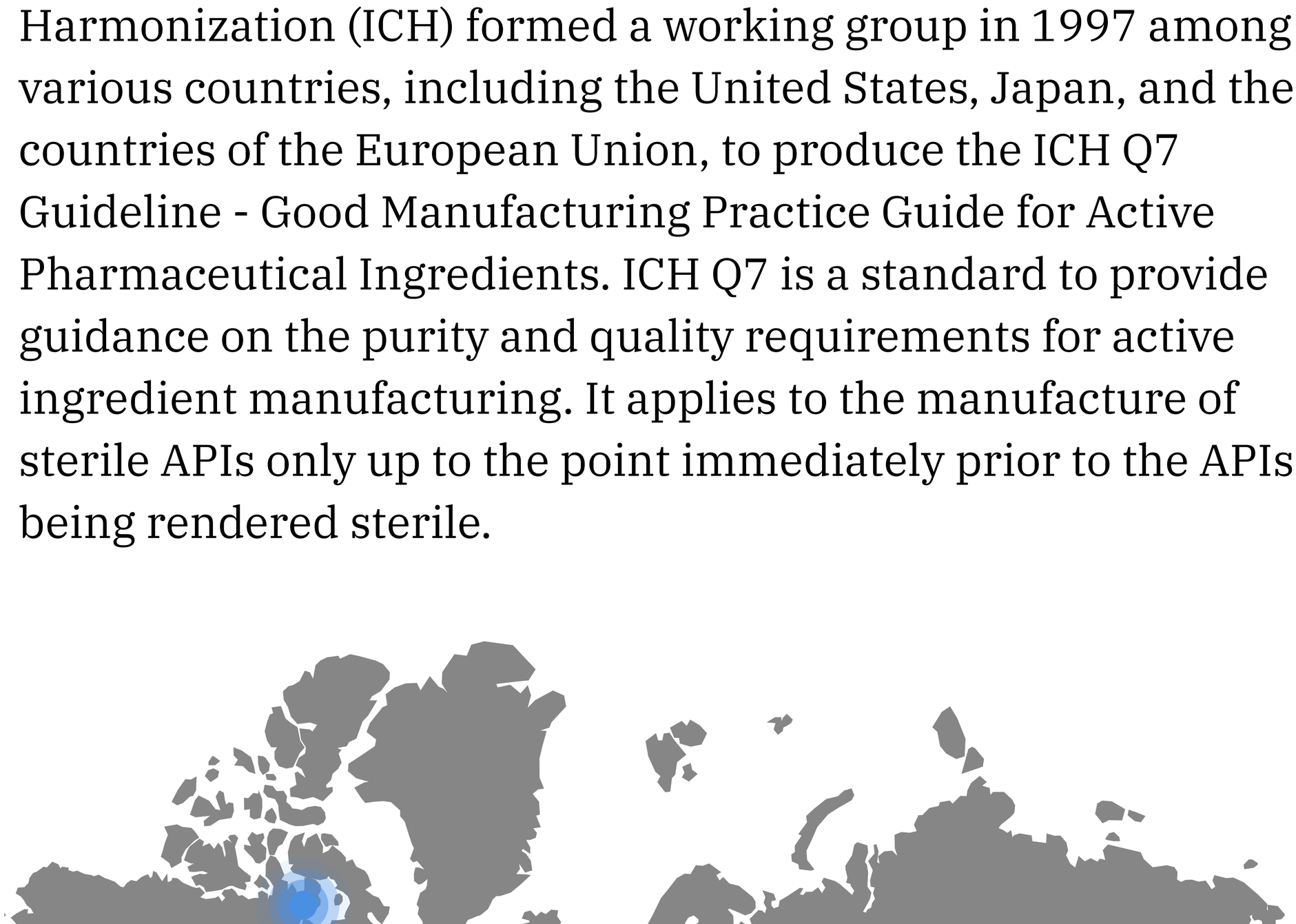
In recent years, guidelines and supplementary documents have been published by many regulatory organizations across the globe that deal with the topic of active substances, amongst which are:

- Control of Nitrosamine Impurities in Human Drugs
- Pharmacopoeia Monograph
- Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants
- 10th Edition of The International Pharmacopoeia
- APIC - GMPs for APIs: "How to do" Document - Interpretation of the ICH Q7 Guide Version 15
- Health Canada’s Good manufacturing practices guidelines for active pharmaceutical ingredients (GUI-0104) 2022
- ANVISA: Version 2 of the CADIFA Manual for APIs

API Regulations

Why Regulate Active Ingredients?

The quality of a drug's Active Pharmaceutical Ingredients (APIs) has a direct impact on the overall safety and efficacy of the marketed drug product. Over the past years, a number of negative health incidents have been linked to poorly manufactured and contaminated active ingredients. As a result, the majority of governments around the world have recognised the importance of regulating active ingredients in their jurisdiction. In addition, The International Conference on Harmonization (ICH) formed a working group in 1997 among various countries, including the United States, Japan, and the countries of the European Union, to produce the ICH Q7 Guideline - Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. ICH Q7 is a standard to provide guidance on the purity and quality requirements for active ingredient manufacturing. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile.



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Recent API Regulatory Changes: Timeline

Sep 2020

FDA Guidance on Nitrosamine Impurities in Medicinal Products and APIs

The FDA introduces a new Industry Guidance after a detailed risk assessment on the nitrososamine incident. This guidance reflects the current state of knowledge concerning nitrosamine impurities. This FDA guidance highlights the significance of precise understanding of the supply chain and control over suppliers and transport routes. It also states the requirement to prioritize risk assessments based on the guidelines from ICH Q9 and the following criteria:

- Maximum daily dose - Daily dose limits are given for six nitrosamine species commonly found in pharmaceutical preparations (highest limit of 96 ng/day for NDMA, lowest limit of 26.5 ng/day for NDEA, NMPA, NIPEA, and NDIPA)
- Treatment duration
- Therapeutic indication
- Number of patients treated

The FDA guidance also provides sets out a clear framework on the communication and reporting obligations of Drug Master File holders in cases of forced changes in the manufacturing process due to contamination. Furthermore, deadlines are defined for risk assessment, confirmatory testing, and submission of changes.

Jan 2021

Health Canada Introduces Temporary Establishment Licensing Requirements for Atypical Active Pharmaceutical Ingredients

Health Canada releases an interim method to implementing Drug Establishment Licensing requirements for certain Active Pharmaceutical Ingredients (APIs) used in the manufacture of human and veterinary pharmaceutical drugs that are also used outside of the pharmaceutical sector. Health Canada defines atypical APIs as ingredients used as pharmaceutical excipients, or as ingredients in natural health products (NHPs), veterinary health products (VHPs), foods, cosmetics and that meet recognised standards other than Good Manufacturing Practices (GMPs).

Feb 2021

EMA Outlines GMP Criteria for Herbal Substances For Use as APIs

EMA sets forth clarification on GMP classification requirements. Reference should be made to the table in EU GMP Guide Annex 7 (Manufacture of Herbal Medicinal Products) illustrating the application of GACP (Good Agricultural and Collection Practice) and GMP (Good Manufacturing Practice) to the manufacture of herbal medicinal products (HMPs).

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Mar 2021

European Pharmacopoeial Monographs for Sartan Preparations Updated

After learning of nitrosamine impurities in sartan formulations, the European Pharmacopoeia Commission updated two general chapters and five API monographs (angiotensin II receptor antagonists with a tetrazole ring). The following sartan APIs are involved:

- Candesartan cilexetil
- Irbesartan
- Losartan potassium
- Olmesartan medoxomil
- Valsartan

Apr 2021

APIC Updates the "Cleaning Validation" Guide for APIs

The relevant task force of APIC's Quality Working Group - a sector group of the European Chemical Industry Council (CEFIC) - has primarily added and updated chapters (4) Acceptance Criteria and (9) Cleaning Validation Protocol

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Jun 2021

ANVISA Introduces Version 2 of the CADIFA Manual for APIs

The second version of the Brazilian Health Regulatory Agency's (Anvisa) "CADIFA Manual for Administrative Procedures" was issued and must be followed for API dossiers. The Active Pharmaceutical Ingredient dossier (DIFA) must be submitted to the agency by the DIFA holder to receive a CADIFA (letter of the suitability of the active pharmaceutical ingredient). The majority of the updates and modifications in the current version of the handbook are contained in chapter "III Before Submission."

Jul 2021

Release of The International Pharmacopoeia (Ph. Int.) 10th Edition

The 10th Edition of the International Pharmacopoeia (Ph. Int.) is published and includes suggested processes for analysis and specifications for pharmaceutical substances (active pharmaceutical ingredients, APIs) and dosage forms.

Jul 2021

The EDQM will include Real-Time Remote Inspections (RTEMIS) into its system for monitoring active substance manufacturing.

The European Directorate for the Quality of Medicines (EDQM) has determined that Real-Time Remote Inspections (RTEMIS) are ready to become an "integral feature" of its system for monitoring active substance manufacturers. EDQM began piloting RTEMIS in November 2020 in response to the pandemic.

FUN Fact!

Aug 2021

Implementing Regulation (EU) 2021/1280: GDP for APIs used as Starting Materials in Veterinary Medicinal Products

The Commission Implementing Regulation (EU) 2021/1280 specifies the good distribution practices for active substances used as starting materials in veterinary medicinal products. It concerns importers, distributors, and manufacturers. The Regulation is directly applicable in all Member States and is strongly based on the principles of Good Distribution Practice of active ingredients for medicinal pharmaceuticals for human use.

Oct 2021

Pharma Sets a Foundation for Greener API Manufacturing

The IQ Green Chemistry Working Group adopts the Green Aspirational Level (GAL)— as a standardized green efficiency objective for API manufacturing processes that takes into account the complexity of the synthetic pathway.

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Dec 2021

APIC - GMPs for APIs: "How to do" Document - Interpretation of the ICH Q7 Guide Version 15

Uppdates to the following chapters

- In Chapter (7), only the last section on highly toxic raw materials has been updated.
- Chapter (8) "Production and In-Process Controls" comprises revisions principally in sections 8.1, 8.3, and 8.5 which contains revisions in two parts (8.51 and 8.52) that cite the most recent ISPE Guideline information for APIs. The method for regular deviations, for example, has been incorporated in paragraph 8.15, and improvements may also be found in paragraphs 8.10, 8.12, and 8.13.
- In chapter (11) "Laboratory Controls," the statement "There should be SOPs (authorised by the Quality Unit)..." has been added.
- Updates in Chapter (14) "Rejection and Reuse of Materials" address the issue of nitrosamine contamination.

Feb 2022

Health Canada Revises the Good manufacturing practices guidelines for active pharmaceutical ingredients (GUI-0104).

These guidelines apply to non-sterile APIs and their intermediates for use in human and veterinary drugs and replaces: Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (API), Version 1 (December 6, 2013)

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Dalton's Services

We bring over 30 years of experience developing products for our clients that are compliant, transferable, and scalable.

Dalton is a leader in the development and manufacturing of complex cGMP APIs. Our skilled scientists can support your drug discovery process through API Synthesis for all stages of pre-clinical and clinical trials as well as small scale commercial manufacturing. We provide integrated process development, API manufacturing and finished dose manufacturing at a single location with the expertise required for developing a process that is robust, transferable, and scalable to meet your requirements.

Our API development services include:

- Lead identification
- Synthetic route development
- Feasibility studies & tech transfer
- Process optimization & scale-up
- Scale-up troubleshooting
- Engineering batches
- cGMP API manufacturing

Dalton is Health Canada licensed to manufacture, test, and package complex pharmaceutical products for global markets. US FDA inspected; Dalton manufactures commercial products for the USA. The MRA (Mutual Recognition Agreement), recognizes Health Canada Licensed facilities in seven countries.

For more information on services we provide, visit our website.

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