MERCK MILLIPORE

See more. Worry less.

Successfully navigate regulatory challenges.

Merck Millipore is a division of MERCK

Navigating the complicated world of global approvals

Bringing a new drug to market – and keeping it there – can be a long and complicated journey. The manner in which companies navigate regulatory challenges can mean the difference between first-to-market success and cost overruns. We have been setting standards in regulatory services for many years and understand the responsibilities you face.

We've bundled our extensive regulatory know-how together with our chemical and pharmaceutical expertise to create a comprehensive range of APIs, excipients, and services that help you get your product to market more quickly.

With Merck Millipore's worldwide presence and dedicated teams, we constantly review regulatory developments in all the relevant markets to keep you one step ahead – today and tomorrow.

Merck Millipore's regulatory competence lets you:

- Speed approval preparation and extend compliance
- Simplify your qualification processes and reduce stress
- Increase supply-chain transparency and reliability

The EMPROVE® qualified process for ready-to-use regulatory documentation

Creating in-house documentation for pharmaceutical raw materials on your own can be costly, risky, and time-consuming. We have been setting standards for raw materials in the industry with our EMPROVE® dossiers since 2004. Designed to make your job easier by providing a thorough and seamless material qualification trail, our EMPROVE® product lines include excipients, APIs, and products for biopharmaceutical production. For the EMPROVE® apis, we provide access to DMFs, CEP or ASMF instead of the EMPROVE® dossier. EMPROVE® products allow you to simplify your processes to demonstrate GMP compliance and ease your marketing authorization. Our comprehensive, ready-to-use documentation is tailor-made to fulfill the latest regulatory requirements – saving you time and money.

The EMPROVE® dossiers, which include about 400 products, are much more than just raw materials and documentation. They are the result of a transparent qualification process and supply chain. The dossiers are based on the globally accepted CTD format and contain detailed usage-specific documentation that includes information on manufacturing, test methods, and purity as well as stability data.

Visit www.merckmillipore.com/emprove for more information.

EXCiPACT™-certified: Keeping you on the safe side

Merck Millipore is one of the first companies to successfully complete a comprehensive EXCiPACT™ audit (GMP and GDP) – helping to further increase supply-chain reliability while reducing costs. This new, voluntary certification scheme for pharmaceutical excipients grants independent approval by especially qualified third-party auditors. Compliance to GMP and GDP standards is certified by the scheme, providing you with time- and cost-savings when you use Merck Millipore excipients in your products.

The EXCiPACT™ certificate demonstrates compliance to the EXCiPACT™ standard which includes raw material sourcing, manufacturing, testing, packaging, storage, and release for the 400 products of the EMPROVE® exp and EMPROVE® bio lines: e.g., organic and inorganic salts, polyols, acids, bases, solvents, and aqueous solutions.

Visit www.merckmillipore.com/excipact or www.excipact.org for more information.

GDUFA-registered to speed access

The Generic Drug User Fee Amendment (GDUFA) is a 5-year program initiated by the FDA. Designed to speed access to safe and effective generic drugs and reduce drug costs, it was signed into law in July of 2012. Merck Millipore has been on board from the very beginning: all our API production sites have been self-identified and related facility fees have been paid. Where applicable, associated DMF fees have been paid for our APIs. And despite its impact on manufacturers' bottom lines, the new program ultimately supports faster access to safer drugs – a goal Merck Millipore strives to excel at every day.

Visit www.merckmillipore.com/gdufa or www.fda.gov for more information.

July 2012
GDUFA registration

2004
First EMPROVE® dossier

Staying compliant with the new elemental impurities standards

New elemental impurities standards are confronting the pharmaceutical and chemical industry with new challenges, requiring a shift in industry practices for compliance. At Merck Millipore, we are prepared to meet tomorrow's challenges today. Not only do we offer you a range of products that are compliant with current and upcoming regulations – our regulatory and analytical expertise can help ensure that your products stay compliant as new guidelines are implemented.

The ICH Q3D Guideline

Designed to provide a global policy for limiting elemental impurities in drug products, this guideline includes – unlike the existing EMA guideline – not only elements added intentionally (reagents, catalysts), but also elemental impurities that occur naturally or have been introduced by interaction (e.g., manufacturing equipment). The consultation period is closed and ICH is working to prepare the final guideline. It's finalization is expected in 2014. Merck Millipore already provides proper analytical and regulatory support to achieve compliance for the respective pharmaceutical substances.

US Pharmacopeia

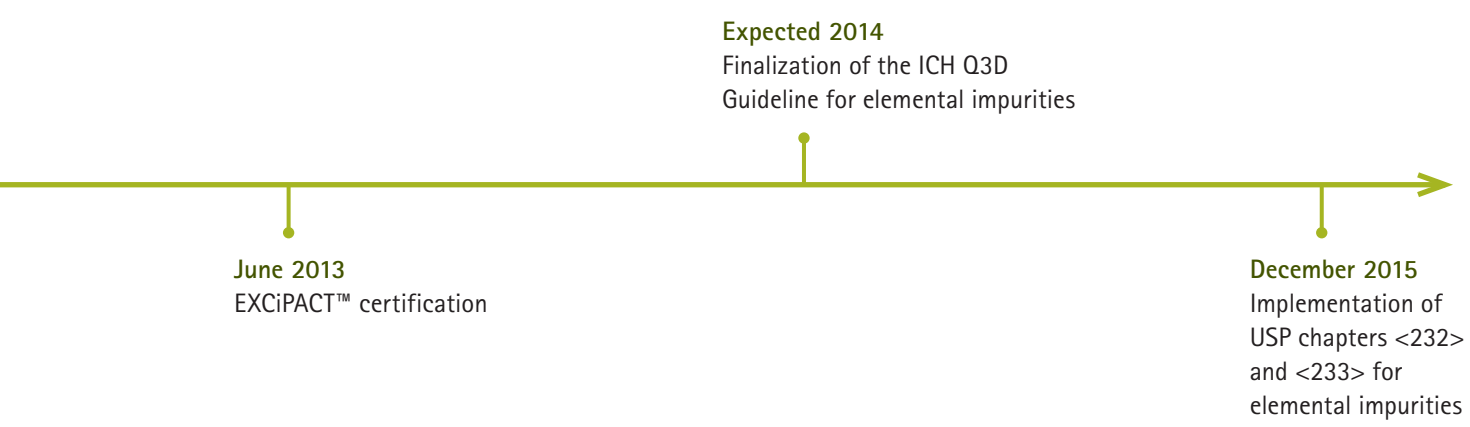
US Pharmacopeia implementation of the USP general chapters on Elemental Impurities was deferred in May 2013 as work continues together with ICH Q3D to align their activities. In March 2014 the latest drafts of USP general chapters were published. Merck Millipore is committed to following the EMA guideline, given that it remains effective for new drugs. The new implementation date for USP chapters <232> und <233> is to be announced in December 2015.

We understand the importance of being compliant with all these existing and upcoming regulations and are closely following developments around the world in order to provide you with the best possible solutions.

Visit www.ich.org for more information.

The EMA Metal Guideline

Already officially effective for new drug products at this time, there has been a recent deferment in order to allow time for better harmonization with the impending ICH requirements. This will only affect existing drugs that have not had to meet these requirements before.



Glossary

ASMF – Active Substance Master File
The European version of the Drug Master File.

CEP – Certificate of suitability to the European Pharmacopeia
Certification granted to individual manufacturers by the EDQM (European Directorate for the Quality of Medicines & HealthCare) to demonstrate compliance with the Ph Eur monograph (substance or herbal drug) or general chapter on minimizing TSE (Transmissible Spongiform Encephalopathy) risks. The CEP for chemical purity is an alternative procedure to the ASMF for all APIs and excipients with monographs in the Ph Eur.

DMF – Drug Master File
Detailed information concerning a specific facility, process, or product submitted to the US FDA intended for incorporation by reference into an NDA (New Drug Application), abbreviated NDA, supplemental NDA, IND (Investigational New Drug), or biological license application.

EMA – European Medicines Agency
The European Medicines Agency is a centralized agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union.

EXCiPACT™ – International Excipient Certification
EXCiPACT™ is a voluntary international scheme to provide independent third-party certification of manufacturers, suppliers, and distributors of pharmaceutical excipients.

FDA – Food and Drug Administration
Regulatory Authority for the United States of America. This US Authority is responsible for the protection of public health by helping safe and effective products (food and medical products) reach the market and monitoring such products for continued safety after they are in use.

GDP – Good Distribution Practice
Good Distribution Practice ensures that the level of quality determined by GMP is maintained throughout the distribution network, so that authorized medicines are distributed to retail pharmacists and others selling medicines to the general public without any alteration of their properties. The principles of GDP for medicinal products are stated in Directive 2003/94/EC.

GDUFA – Generic Drug User Fee Amendment
The Generic Drug User Fee Amendment is designed to speed access to safe and effective generic drugs to the public and reduce costs for the industry. The law requires industry to pay user fees to supplement the costs of reviewing generic drug applications and inspecting facilities. Additional resources will enable the Agency to reduce a current backlog of pending applications, cut the average time required to review generic drug applications for safety, and increase risk-based inspections.

GMP – Good Manufacturing Practice
Good Manufacturing Practice ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. GMP guidelines provide guidance for manufacturing, testing, and quality assurance in order to ensure that the drug product is of suitable quality for human consumption.

ICH – International Conference on Harmonization
The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use is unique in bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan, and the US to discuss scientific and technical aspects of drug registration. It makes recommendations towards achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.

ICH Q3D – Guideline for Elemental Impurities
This new guideline is proposed to provide a global policy for limiting metal impurities qualitatively and quantitatively in drug products.

USP – The United States Pharmacopoeia
The US Pharmacopoeial Convention is a scientific non-profit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed, and consumed worldwide. USP's drug standards are enforceable in the United States by the Food and Drug Administration, and these standards are used in more than 140 countries.

The typical technical data above serve to generally characterize the product. These values are not meant as specifications and they do not have binding character. The product specification is available separately, from the website: www.merckmillipore.com

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.

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www.merckmillipore.com/regulatoryroadmap

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