Historic Events and Milestones in the Development of GMP

Year	Event
1937	The Massengill disaster, also referred to as the sulfanilamide disaster, occurred in the US in 1937, when 107 people, including many children, died after taking Elixir Sulfanilamide, a cough medicine. The syrup, which was easy to ingest and tasted good, was developed, in particular, as a cough syrup for children. The cause of the poisoning was the sweet, alcoholic compound diethylene glycol, which was used as a solvent with the addition of raspberry-flavored antibiotic syrup. [8] US law in 1937 did not require a comprehensive review of toxicity before bringing a drug product to market. As a result, it was initially unclear whether sulfanilamide or the additives in it were responsible for the poisonings that occurred. It was only later, following research by Dr. Frances Oldham Kelsey (who years later, in her role as an FDA employee doggedly and successfully opposed the application for approval of a sleep aid that contained thalidomide: Contergan) that the high level of toxicity of diethylene glycol was discovered. The pharmaceutical company S. E. Massengill Co. was fined USD 26,000, an amount that now seems remarkably low. The sulfanilamide disaster became a milestone in the history of consumer protection and is therefore important for the development of uniform guidelines and laws – the precursors to the later GMP rules. [9]
1938	In 1938, the US Congress passed the Federal Food, Drug, and Cosmetic Act following the tragic sulfanilamide disaster. This resulted in the creation of the FDA. [8]
1957–1963	One of the largest disasters involving a drug product in the Federal Republic of Germany occurred in the 1960s: the Contergan disaster. The medication, which was produced by Grünenthal GmbH and contained thalidomide (Contergan), was intended to help with nausea and insomnia. However, harmful side effects resulted in a number of children being born with serious deformities. Put simply, a medication that had not been tested for all possible risks and side effects was brought to market in a number of countries. As result, some 10,000 children around the world were born with congenital defects. The number of fetuses who died during pregnancy is unknown. [10] Interestingly, the US remained largely unaffected, as the FDA did not allow the medication to be imported. As a result, there are only 17 known cases in the US involving harm caused by the drug.
1962	In 1962, the US Congress passed the Kefauver Harris Drug Amendment. This amendment not only increased safety requirements, it also required proof of a medication's effectiveness for the first time – retroactively for all prescribed products approved since 1938. This laid the foundation for the statutory regulation of clinical studies along the lines of regulatory approval procedures and quality assurance measures involved in the development of drug products. [11]
1969	Based on events and pressure from the FDA, the WHO formulated the first guidelines for the production of pharmaceutical products – the first GMP guidelines – with the goal of ensuring the traceability of the production process.
1970	The Pharmaceutical Inspection Convention (PIC) was founded in Europe; it subsequently issued guidelines for appropriate testing of drug products. [13]
1972	In the US, a manufacturer's intravenous therapies were recalled from the market due to stability problems. The manufacturer was unable to reliably demonstrate the quality of its product through testing. [14]
1978	In the US, GMP was set down in the form of a regulation in the US Code of Federal Regulations (CFR) under 21 CFR 210 and 21 CFR 211. Other sections of the CFR were also relevant for GMP (including 21 CFR 11 and 21 CFR 820). [12]
1978	In Germany, the Medicinal Products Act (*Arzneimittelgesetz* – AMG) entered into force, serving as the statutory basis for protecting public health, in particular based on high requirements for the careful handling of drug products by the pharmaceutical industry, pharmacists, and doctors. It required a multistage approval process, thus revolutionizing the German market for drug products. [15]
1982	Consumers who took Tylenol (acetaminophen) died as a result of cyanide poisoning. An unknown person intentionally laced the drug with cyanide during the production process. It was thus a willful act of sabotage. The

	FDA subsequently issued new rules to prevent such acts. [16]
1985	In Germany, the new Pharmaceutical Company Ordinance (*Pharmabetriebsverordnung*) defined appropriate regulations in line with European law for the production of drug products from tissue preparations (known as tissue engineering). [17]
1989	The main GMP document of the European Union (EU), the EU GMP guidelines, were published for the first time. They are based on Council Directive 89/341/EEC of May 3, 1989. This directive requires all EU Member States to comply uniformly with GMP standards during the industrial production of drug products, and thus serves as the basis for two separate sets of GMP guidelines issued by the Commission. [18]
1989/ 1990	The generic drug scandal: several manufacturers of generic drugs fraudulently submitted products made by other companies (including some made by the original manufacturers) as their own products.
1990	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (also known as the International Conference on Harmonization, ICH) is established by the FDA, the European Commission together with the European Medicines Agency (EMA; formerly known as the European Medicines Evaluation Agency, EMEA), the Japanese Ministry for Health, Labor, and Welfare (MHLW), and the trade groups the Pharmaceutical Research and Manufacturers of America (PhRMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), and the Japan Pharmaceutical Manufacturers Association (JPMA). [15]
1993	The Barr ruling: this ruling played a key role in fomenting discussion within the pharmaceutical industry about the GMP-compliant handling of out-of-specification analysis results (testing until the results coincide with the specifications, also known as testing into compliance). This is not permitted and is prohibited under GMP. [19]
1995	The European Medicines Agency (formerly known as EMEA and now known as EMA) was founded as an agency of the EU with its headquarters in London. It is responsible for assessing and monitoring drug products. Its task is to maintain and promote public health in the EU by coordinating the ongoing assessment and monitoring of all human and animal drug products. It therefore plays a key role in the authorization of drug products in the EU and the states of the European Economic Area. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) was also established in 1995. [15]
2002	*GMP for the 21st Century: A Risk-Based Approach* was put forward for discussion and published in the US. However, this report was only later published as a binding requirement. [15] US pharmaceutical group Schering-Plough Corp., based in Kenilworth, New Jersey, accepted a fine of USD 500 million imposed by the FDA for violating quality standards. As a result, Schering-Plough, known in the US for allergy medications Claritin and Clarinex, lowered its profit forecast for 2002. Specifically, the case involved production facilities in Puerto Rico and New Jersey. The company wanted to temporarily suspend production of the criticized products (asthma inhalers that contained no active substances). Schering-Plough had had production problems in Puerto Rico and New Jersey for years. In mid-February 2002, the company announced that the FDA had filed complaints about defective quality at four plants. The company's share price fell by nearly 50 percent. [20]
2004	Tests showed that the pain reliever Vioxx, produced by Merck & Co., Inc., doing business in Germany as MSD Sharp & Dohme GmbH, increased the risk of heart attack. This finding resulted in the largest voluntary recall campaign in the pharmaceutical industry to date, with the company paying USD 950 million in fines and civil claims. [21]
2006	In Europe, the EU GMP guidelines were restructured. At the same time, in Germany the Pharmaceutical Company Ordinance (Pharmabetriebsverordnung) was replaced with the Ordinance on the Manufacture of Medicinal Products and Active Ingredients (Arzneimittel- und Wirkstoffherstellungsverordnung – AMWHV). The AMWHV is the ordinance governing the application of GMP when producing drug products and active substances. As a national legal framework, it thus forms the binding statutory basis for companies that wish to produce, test, store, or sell drug products and active substances. [15] The AMWHV implements the principles and guidelines defined in Parts I and II of the EU GMP guidelines in respect of medicinal products for human use and veterinary medicinal products.
2007/ 2008	The heparin scandal: the anticoagulant produced in China was connected with 82 confirmed deaths in the US and a number of serious allergic reactions – including 27 serious reactions following administration via injection in Germany. The company Baxter AG recalled all batches distributed in the US by the Chinese manufacturer. In Germany, the company Rotexmedica GmbH was forced to remove its unfractionated heparin from the market due to the complications. Subsequently, manufacturers, including Sanofi Aventis, in other European countries, such as Sweden and England, as well as Australia, followed suit and also removed batches from the market. The cause was a substance (oversulfated chondroitin sulfate) that was evidently added to the raw heparin intentionally in order to reduce

	costs, as it offers an enormous savings potential. The raw heparin that was used by all manufacturers came from China, where, according to experts, 70 percent of the global market is sourced. Experts believed that the reason for the failure to identify the quality flaws was excessive demands placed on the authorities tasked with oversight because of the dramatic increase in the overseas production of starting materials and finished drug products. [22]
2009	A total of 84 children killed by teething medicine: from November 2008 to February 2009, 84 children in Nigeria died after taking pain medication; another 111 children became ill. The medication was supposed to relieve pain caused by teething. The medication, which was apparently not tested sufficiently for interactions, caused kidney failure. It had to be recalled from the market. [23]
2010	The Duogynon case – a less publicized drug scandal: hormonal preparation Duogynon was long used as a pregnancy test. The compound was suspected of causing deformities in children. [24]
2011	Revision of EU GMP guidelines, Chapter 4: Documentation (valid from June 30, 2011) 2011, Part III of the EU GMP guidelines (GMP-related documents): Site Master File, Pharmaceutical Quality System, Quality Risk Management, MRA Batch Certificate 2012, Part III of the EU GMP guidelines: *Template for the "written confirmation" for active substances exported to the European Union for medicinal products for human use*, 2013, revised Chapter 1 (Pharmaceutical Quality System) and Chapter 7 (Outsourced Activities), valid from January 31, 2013.
2012	Major raid conducted against a Chinese drug counterfeiter: the Chinese authorities arrested 2,000 people suspected of counterfeiting drug products. The products were worth USD 180 million. [25]
2014	Chapters 2 (Personnel) and 6 (Quality Control) of the EU GMP guidelines were revised.
2015	Thousands of deformities as a result of a Sanofi medication: an anticonvulsant led to serious deformities. Thousands of children were affected. [26]
2015	Chapters 3 (Premises and Equipment), 5 (Production), and 8 (Complaints and Product Recall) of the EU GMP guidelines were revised. Revision of Annex 15 (Qualification and Validation) of the EU GMP guidelines.
2016	Revision of Annex 16 (Certification by a Qualified Person and Batch Release) of the EU GMP guidelines.
2017	Cancer drug scandal because of a medication diluted by a pharmacist: a pharmacist in Bottrop, located in west-central Germany, diluted cytotoxic agents and earned an amount of EUR 56 million. [27]
2017	A new Part IV (GMP requirements for Advanced Therapy Medicinal Products) of the EU GMP guidelines was published, which had to be implemented by May 22, 2018. Annex 13 (Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No. 536/2014) was published.
2018	Annex 2 (Manufacture of Biological active substances and Medicinal Products for Human Use) of the EU GMP guidelines was revised. Annex 17 (Real Time Release Testing and Parametric Release) of the EU GMP guidelines entered into force.

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