INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

API GMP 가이드

(GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS)

Current Step 4 version
dated 10 November 2000

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 10 November 2000, this guideline is recommended for adoption to the three regulatory parties to ICH

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1. 서론(INTRODUCTION)

1.1 목적(Objective)

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

이 문서(가이드)는 적절한 품질 경영 시스템에서 활성 제약 성분(API)을 제조하기 위한 GMP 관련 가이드라인을 제공하기 위한 것이다. 또한 목표로 하거나 보유하는 것으로 표시된 품질과 순도 기준에 부합하는 API의 제조를 지원하기 위한 것이다.

In this Guide "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls. In this Guide the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this Guide, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent. The Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

이 가이드에서 "제조"라 함은 물품의 인수, API의 생산, 포장, 재포장, 표시, 재표시, 품질 관리, 출하 승인, 보관, 유통 및 관련 관리 활동 모두를 포함한다. 이 가이드에서 "should"는 적용 대상이 아니거나 적어도 동등한 수준의 품질 보증을 제공하는 것으로 증명된 다른 방법으로 대체된 상황이 아닌 경우에 적용해야 하는 권고 기준을 의미한다. 이 가이드에서 "CGMP(Current Good Manufacturing Practices)"와 "GMP(Good Manufacturing Practices)"는 동등한 것이다. 전체적으로 이 가이드는 제조 작업자의 안전 문제나 환경 보호 부분을 다루지 않는다. 이러한 부분은 제조업체의 고유한 책임이며 국가별 관련 법규에 따라 규제된다.

This Guide is not intended to define registration/filing requirements or modify pharmacopoeial requirements. This Guide does not affect the ability of the

responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents must be met.
이 가이드는 등록/신고 기준을 규정하거나 약전 기준을 변형하기 위한 것이 아니다. 이 가이드는 판매/제조 허가나 의약품 신청과 관련하여 API에 관한 구체적인 등록/신고 기준을 설정하는 해당 규제 기관의 권한에 영향을 주지 않는다. 등록/신고 문서에 기술된 모든 것을 준수해야 한다.

1.2 법적 적용(Regulatory Applicability)

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this Guide.
법적으로 API로 분류되는 물품은 국가에 따라 다를 수 있다. 어떤 물품이 제조된 지역이나 국가 또는 그 물품이 의약품 생산에 사용된 지역이나 국가에서 그 물품을 API로 분류한다면, 이 가이드에 따라 제조되어야 한다.

1.3 적용범위(Scope)

This Guide applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidelines for drug (medicinal) products as defined by local authorities.
이 가이드는 사람 의약품 제조에 사용되는 API의 제조에 적용된다. 무균 API 제조인 경우에는 API를 무균 상태로 만들기 직전까지 적용된다. 무균 API의 멸균 및 무균 공정은 이 가이드의 대상이 아니며, 규제 기관이 정한 의약품 GMP 가이드라인을 따라야 한다.

This Guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section 18.

이 가이드는 화학적 합성, 추출, 세포 배양/발효, 또는 천연물로부터 회수, 또는 이들 공정의 조합으로 제조되는 API를 대상으로 한다. 세포 배양/발효 공정으로 제조되는 API에 대한 구체적인 가이드라인은 18항에서 다룬다.

This Guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this Guide. In addition, the Guide does not apply to medical gases, bulk-packaged drug (medicinal) products, and manufacturing/control aspects specific to radiopharmaceuticals.
모든 백신, 전세포, 전혈 및 혈장, 혈액 및 혈장 유래 제품(혈장 분획), 유전자 치료제 API는 이 가이드의 적용 대상에서 제외된다. 하지만 혈액 또는 혈장을 원료로 사용해 생산되는 API는 적용 대상에 포함된다. 세포 기질(포유류, 식물, 곤충 또는 미생물 세포, 조직 또는 형질 전환 동물을 포함한 동물 유래)과 초기 공정 단계에 GMP가 적용될 수 있으나 이 가이드의 대상은 아니다. 이외에도 의료용 가스, 벌크 포장 의약품, 방사성 의약품 관련 제조/관리에 이 가이드가 적용되지 않는다.

Section 19 contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicnal products).
19항에는 특히 임상 시험을 위한 의약품(임상 시험 의약품)의 생산에 사용되는 API의 제조와 관련된 가이드라인이 기술되어 있다.

An "API Starting Material" is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structure.
"API 출발 물질"은 API 생산에 사용되고 중요한 구조적 부분으로 API 구조에 통합되는 원료, 중간 제품 또는 API를 의미한다. API 출발 물질을 시중에서 구입하거나 계약 또는 합의에 따라 하나 이상의 공급업체로부터 구입하거나

자체적으로 생산할 수 있다. 일반적으로 API 출발 물질의 화학적 특징과 구조가 규명되어 있어야 한다.

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API Starting Material is normally introduced into the process.
업체는 API 생산이 시작되는 부분을 정하고 근거를 문서화해야 한다. 합성 공정인 경우에 이 부분은 "API 출발 물질"이 공정에 도입되는 지점에 해당된다. 다른 공정(예, 발효, 추출, 정제 등)인 경우에는 상황별로 근거를 설정한다. 일반적으로 API 출발 물질이 공정에 도입되는 지점에 관한 가이드라인이 표 1에 정리되어 있다.

From this point on, appropriate GMP as defined in this Guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.
이 지점부터 이 가이드에 규정된 적절한 GMP 기준을 중간 제품 및/또는 API 제조 단계에 적용한다. API의 품질에 영향을 주는 것으로 확인된 중요 공정 단계의 밸리데이션도 실시한다. 그러나 특정 공정 단계를 밸리데이션하기로 결정했다고 해서, 그 공정 단계가 반드시 중요한 단계라는 의미는 아니다.

The guidance in this document would normally be applied to the steps shown in gray in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronizing), should be conducted at least to the standards of this Guide.
이 문서의 가이드라인은 일반적으로 표 1에 회색으로 표시된 단계에 적용된다. 그렇다고 이 표의 모든 단계를 실시해야 한다는 의미는 아니다. 공정이 초기 단계에서 정제 및 포장 등 마지막 단계로 갈수록, API 제조에 적용되는 GMP 수준을 더욱 강화한다. 과립, 코팅 또는 입자 크기의 물리적 조작(예, 밀링, 마이크로나이징) 같은 API의 물리적 공정을 적어도 이 가이드의 기준에 따라 실시한다.

This GMP Guide does not apply to steps prior to the introduction of the defined "API Starting Material".

이 GMP 가이드는 지정 "API 출발 물질"의 투입 이전 단계에 적용되지 않는다.

Table 1: Application of this Guide to API Manufacturing

Type of Manufacturing	Application of this Guide to steps used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Biotech/ fermentation cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging

→ **GMP 기준 적용 강화** →