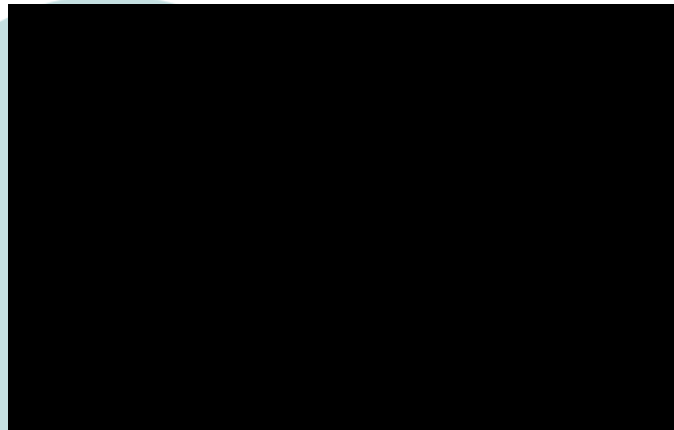
2024.05.13 ㈜글로벌표준인증원 웨비나

Leading Global Trend in Korea, Value beyond the expectation

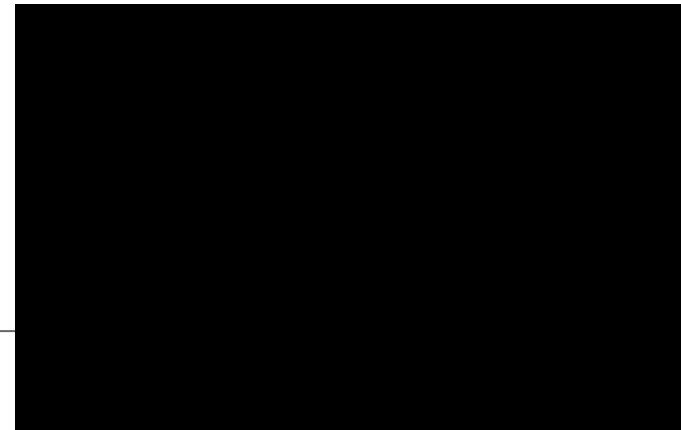
FDA OTC, GMP 공장심사

강사: ㈜글로벌표준인증원 김태경 전문위원 / 전재금 대표



FDA OTC GMP 공장심사

CONTENTS



01

FDA OTC Facility Inspection

FDA OTC 공장심사 개요

- 공장심사 유형
- 공장심사 방식
- 공장심사 범위 및 기준

FDA OTC 공장심사 유형

01

Surveillance Facility Inspection

- 일반적으로 제조시설 등록 이후 1~2년 후(해외제조소 기준) 이루어지는 감사

*지역에 따라 상이

02

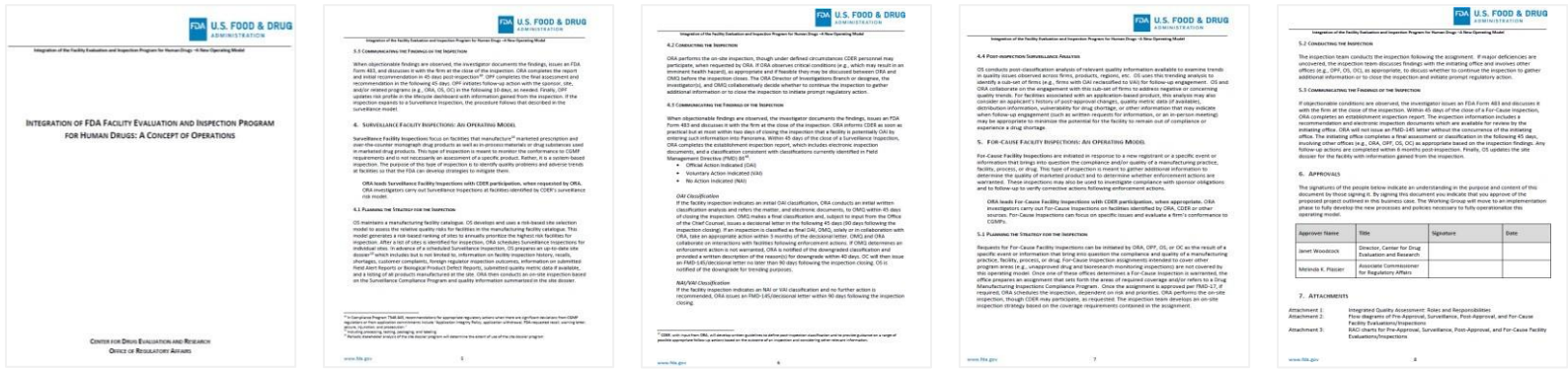
For Cause Facility Inspection

- 의심스러운 점이 있을 경우 이루어지는 감사
- 경쟁사의 폭로 또는 심각한 부작용 보고

03

Post-Inspection

- Surveillance 혹은 For Cause 감사 시 부적합 사항이 있을 경우 이루어지는 감사



출처: 2017, INTEGRATION OF FDA FACILITY EVALUATION AND INSPECTION PROGRAM FOR HUMAN DRUGS: A CONCEPT OF OPERATIONS

FDA OTC 공장심사 방식

[Surveillance Facility Inspection 기준]

FDA ORA(품질정책사무국) 심사원 배정

FDA 482 LETTER 심사통보

심사진행

- FDA 심사관의 이동비용 및 체류비용 부담 및 동의
- FDA 심사관 배정 후 3-5일 간 심사 실시
- USA FDA cGMP 21 CFR Part 210/211에 근거해 심사 실시

주요/중요 발견사항

존재x

필요시, FDA 483문서 발행

존재

심사 중단 후, FDA 483 문서 발행

45일 이내 심사 결과 결정

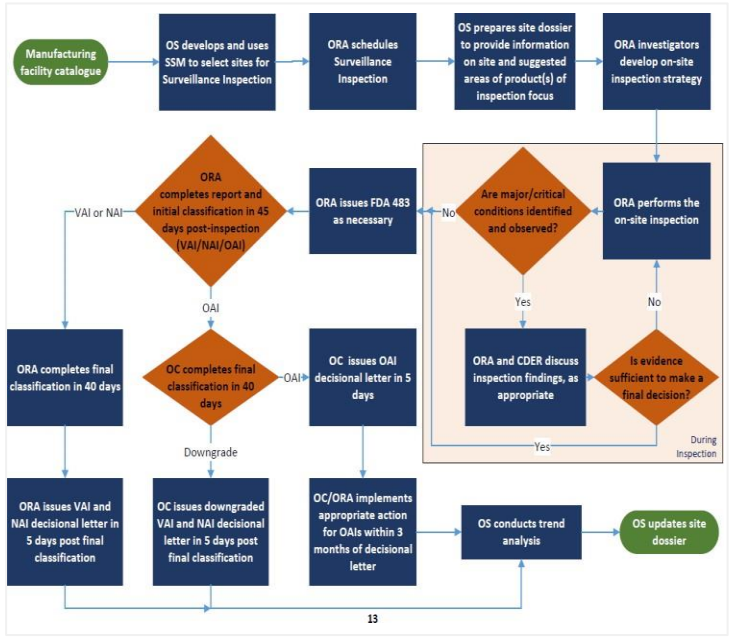
NAI

VAI

OAI

Warning 레터 발행

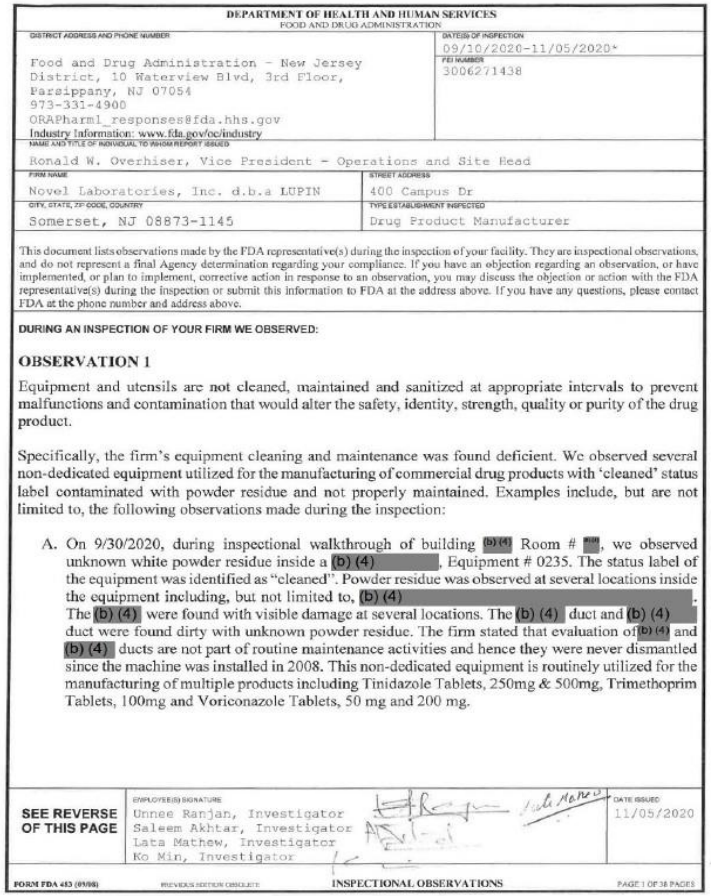
공식적 조치 필요



출처: 2017, INTEGRATION OF FDA FACILITY EVALUATION AND INSPECTION PROGRAM FOR HUMAN DRUGS: A CONCEPT OF OPERATIONS

FDA OTC 공장심사 방식

FDA 483 DOCUMENT



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER
Food and Drug Administration - New Jersey
District, 10 Waterview Blvd, 3rd Floor,
Parsippany, NJ 07054
973-331-4900
ORAPharm1_responses@fda.hhs.gov
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION: 09/30/2020-11/05/2020*
FEI NUMBER: 3006271438

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Ronald W. Overhiser, Vice President - Operations and Site Head

FIRM NAME: Novel Laboratories, Inc. d.b.a LUPIN
STREET ADDRESS: 400 Campus Dr
CITY, STATE, ZIP CODE, COUNTRY: Somerset, NJ 08873-1145
TYPE ESTABLISHMENT INSPECTED: Drug Product Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Equipment and utensils are not cleaned, maintained and sanitized at appropriate intervals to prevent malfunctions and contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, the firm's equipment cleaning and maintenance was found deficient. We observed several non-dedicated equipment utilized for the manufacturing of commercial drug products with 'cleaned' status label contaminated with powder residue and not properly maintained. Examples include, but are not limited to, the following observations made during the inspection:

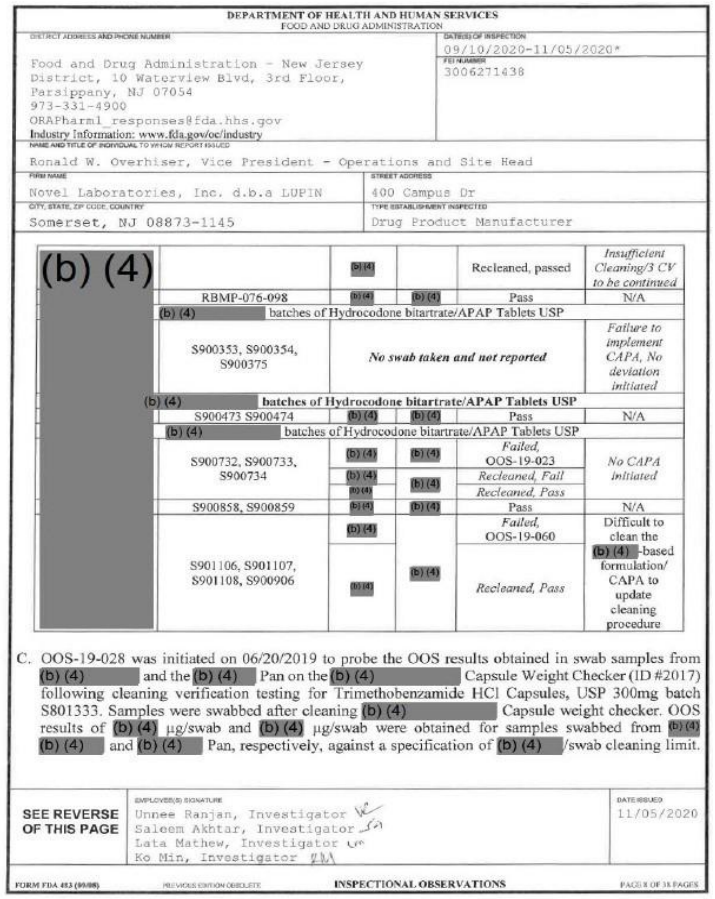
A. On 9/30/2020, during inspectional walkthrough of building (b) (4) Room # [redacted], we observed unknown white powder residue inside a (b) (4). Equipment # 0235. The status label of the equipment was identified as "cleaned". Powder residue was observed at several locations inside the equipment including, but not limited to, (b) (4). The (b) (4) were found with visible damage at several locations. The (b) (4) duct and (b) (4) duct were found dirty with unknown powder residue. The firm stated that evaluation of (b) (4) and (b) (4) ducts are not part of routine maintenance activities and hence they were never dismantled since the machine was installed in 2008. This non-dedicated equipment is routinely utilized for the manufacturing of multiple products including Tinidazole Tablets, 250mg & 500mg, Trimethoprim Tablets, 100mg and Voriconazole Tablets, 50 mg and 200 mg.

SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE
Unnee Ranjan, Investigator
Saleem Akhtar, Investigator
Lata Mathew, Investigator
Ko Min, Investigator

DATE ISSUED: 11/05/2020

FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 1 OF 38 PAGES



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FOOD AND DRUG ADMINISTRATION

Food and Drug Administration - New Jersey
District, 10 Waterview Blvd, 3rd Floor,
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973-331-4900
ORAPharm1_responses@fda.hhs.gov
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION: 09/10/2020-11/05/2020*
FEI NUMBER: 3006271438

Ronald W. Overhiser, Vice President - Operations and Site Head

FIRM NAME: Novel Laboratories, Inc. d.b.a LUPIN
STREET ADDRESS: 400 Campus Dr
CITY, STATE, ZIP CODE, COUNTRY: Somerset, NJ 08873-1145
TYPE ESTABLISHMENT INSPECTED: Drug Product Manufacturer

(b) (4)					
		(b) (4)		Recleaned, passed	*Insufficient Cleaning/3 CV to be continued*
	RBMP-076-098	(b) (4)	(b) (4)	Pass	N/A
	(b) (4) batches of Hydrocodone bitartrate/APAP Tablets USP				
	S900353, S900354, S900375	*No swab taken and not reported*			*Failure to implement CAPA, No deviation initiated*
	(b) (4) batches of Hydrocodone bitartrate/APAP Tablets USP				
	S900473 S900474	(b) (4)	(b) (4)	Pass	N/A
	(b) (4) batches of Hydrocodone bitartrate/APAP Tablets USP				
	S900732, S900733, S900734	(b) (4)	(b) (4)	*Failed,* OOS-19-023	*No CAPA initiated*
		(b) (4)	(b) (4)	*Recleaned, Fail*	
		(b) (4)		*Recleaned, Pass*	
	S900858, S900859	(b) (4)	(b) (4)	Pass	N/A
	S901106, S901107, S901108, S900906	(b) (4)		*Failed,* OOS-19-060	Difficult to clean the (b) (4) -based formulation/ CAPA to update cleaning procedure
		(b) (4)	(b) (4)	*Recleaned, Pass*	

C. OOS-19-028 was initiated on 06/20/2019 to probe the OOS results obtained in swab samples from (b) (4) and the (b) (4) Pan on the (b) (4) Capsule Weight Checker (ID #2017) following cleaning verification testing for Trimethobenzamide HCl Capsules, USP 300mg batch S801333. Samples were swabbed after cleaning (b) (4) Capsule weight checker. OOS results of (b) (4) µg/swab and (b) (4) µg/swab were obtained for samples swabbed from (b) (4) (b) (4) and (b) (4) Pan, respectively, against a specification of (b) (4) /swab cleaning limit.

SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE
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Saleem Akhtar, Investigator
Lata Mathew, Investigator
Ko Min, Investigator

DATE ISSUED: 11/05/2020

FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 8 OF 38 PAGES

FDA OTC ORA

FDA OTC 공장심사 범위 및 기준

01

Hardware

- Lay-Out(OTC 생산 구역) 설계
- 제조현장점검, 제조 및 품질 설비 점검
- 설비에 대한 점검 시 적격성 평가 부분 확인
- 공조 및 정제수 밸리데이션 실시여부 확인 등

02

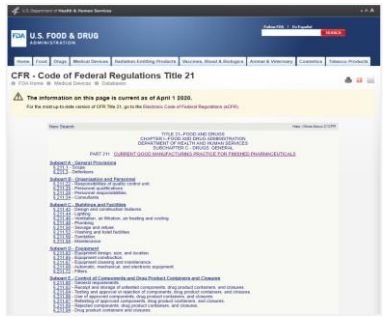
Software

- 해당 제품에 대한 제조 및 품질 기록 점검
- 제품 표준서 및 규격서 점검
- 공정 및 세척 밸리데이션 실시여부 확인
- 시험규격 및 MV(시험법밸리데이션) 실시여부 확인 등

03

21 CFR

- 21 CFR 210 (공장)
- 21 CFR 211 (완제품)



출처: 2020, Electronic Code of Federal Regulations (eCFR)

02

FDA OTC Facility Inspection

FDA OTC 공장심사 대비 고려사항

- 도면설계
- 적격성평가
- 밸리데이션
- 시험규격 재설정
- 시험법 검증
- 제품 및 원료 성분검토

FDA OTC 공장심사 범위 및 기준

Conceptual Design

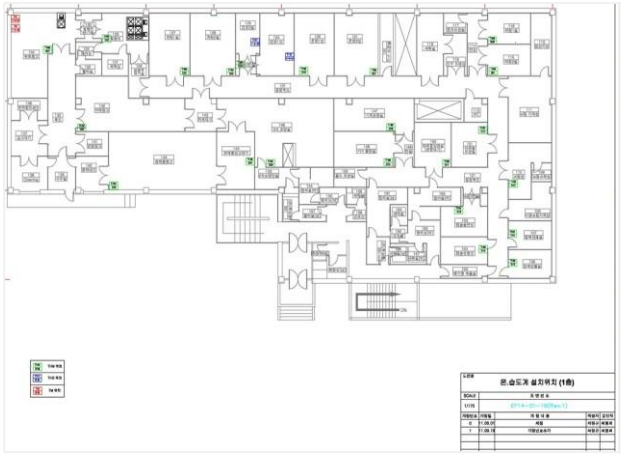
Qualification

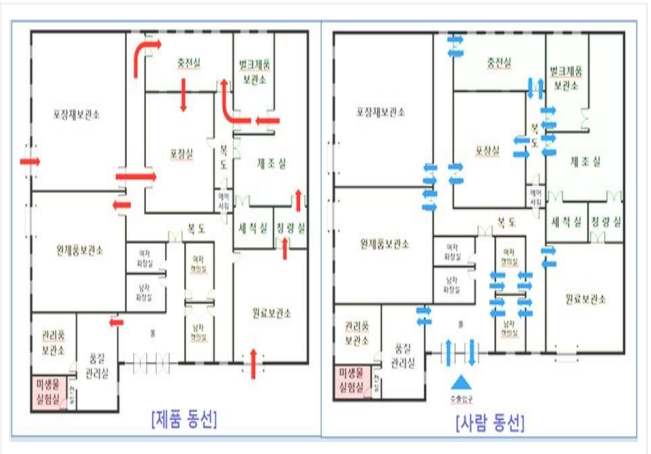
Validation

Laboratory Method

1. 도면설계(Conceptual Design)

- 원칙적으로 화장품 제조 구역과 분리(OTC전용 구역 마련)
  * 단, 제형이 같을 경우 교차오염을 방지하도록 구획
- CGMP승인 업체의 경우 부분 리모델링으로 심사 가능(보완 가능성)
- 청정등급 C grade와 D grade 구역 분리(인동선 구분)
- 물동선의 경우 전실 마련 등

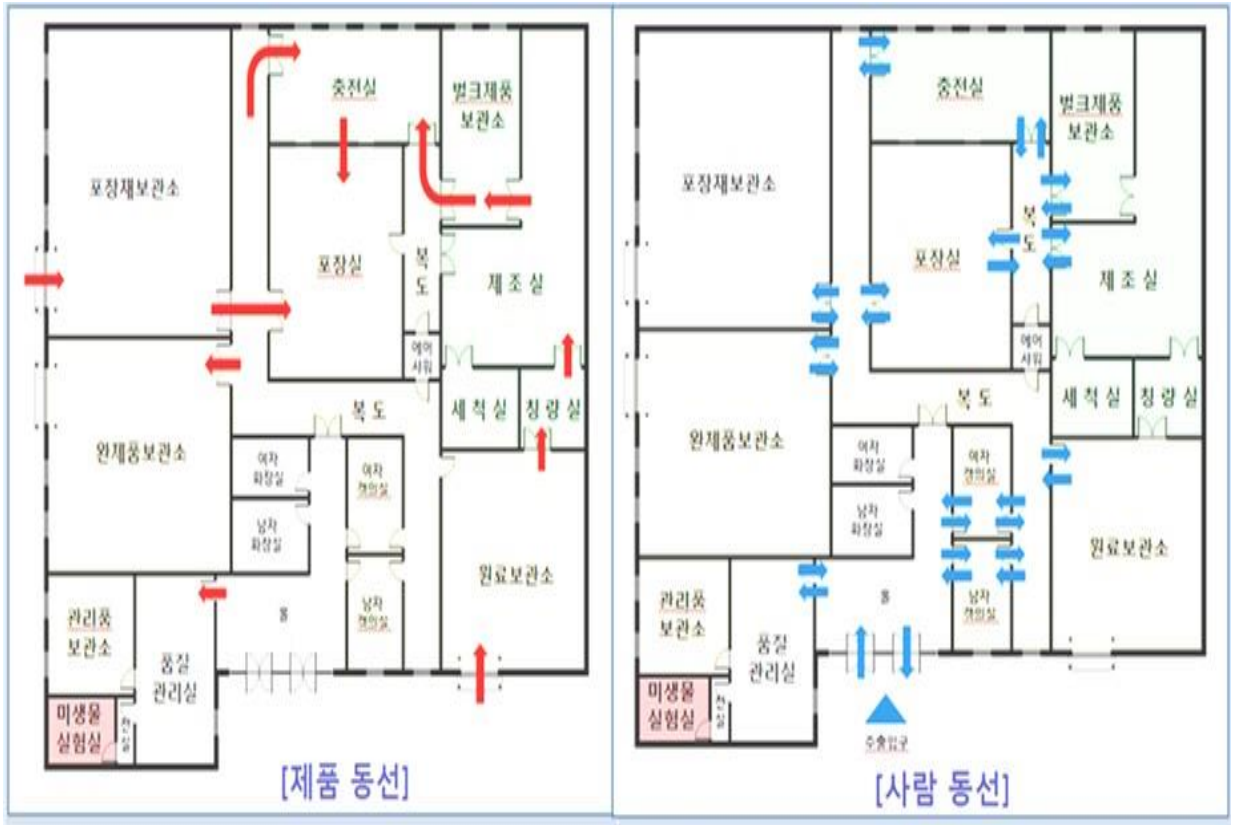




FDA OTC 공장심사 범위 및 기준

- Conceptual Design
- Qualification
- Validation
- Laboratory Method

1. 도면설계(Conceptual Design)



FDA OTC 공장심사 범위 및 기준

Conceptual Design

Qualification

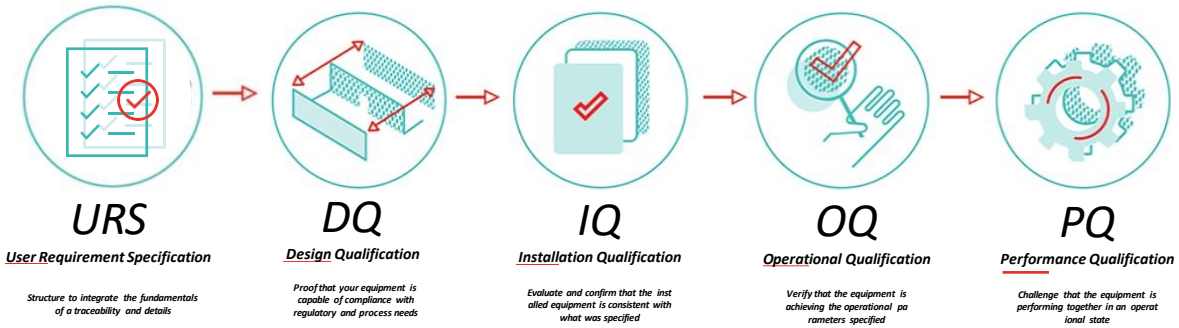
Validation

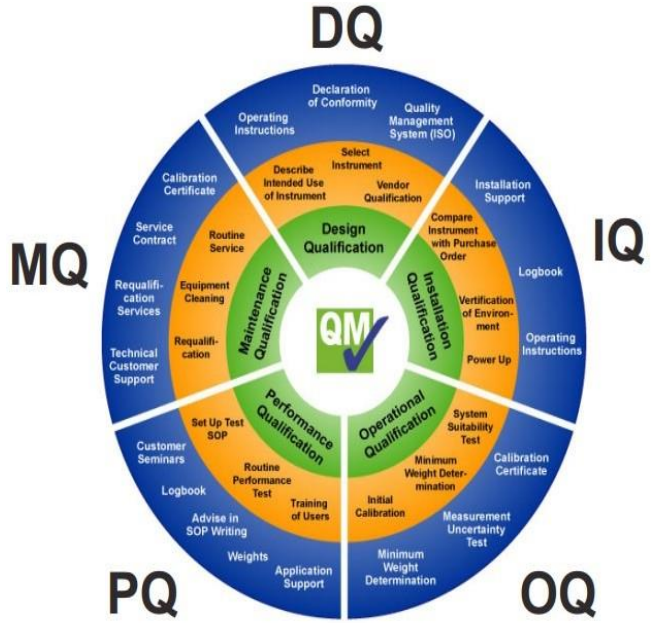
Laboratory Method

2. 적격성평가(Qualification)

- 설비에 대한 적격성 평가(각 설비당 필요)
- URS, DQ, IQ, OQ, PQ로 구분
- 기존설비의 경우 URS, DQ는 제외하여 실시
- 주요 설비

  - 제조설비, 충진설비, 품질분석장비, 공조기, 정제수제조장치 등





FDA OTC 공장심사 범위 및 기준

Conc eptua
De I
sign

Qualifi cation

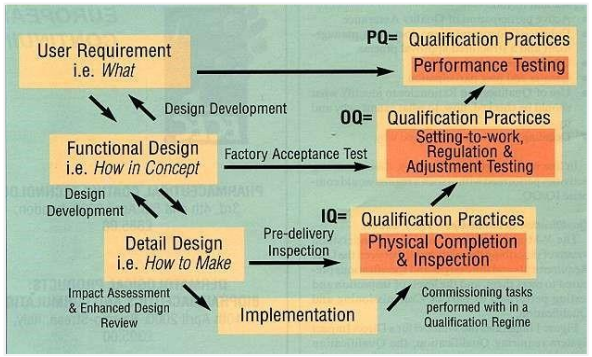
Validation

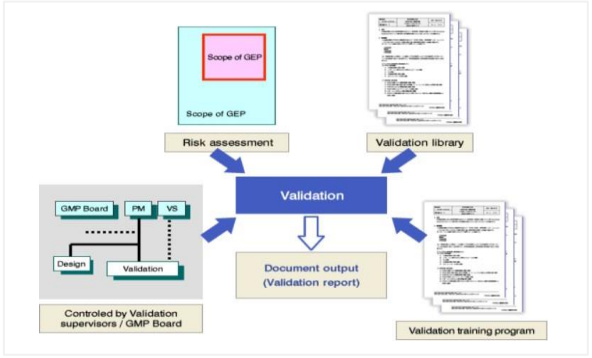
Labor atory
Met hod

3. 밸리데이션(Validation)

Validation 타입

- 세척밸리데이션 (CV)
- 공정밸리데이션 (PV)
- 시험법밸리데이션 (MV)
- 컴퓨터시스템밸리데이션 (CSV)
- 공조밸리데이션 (Phase 2)
- 정제수밸리데이션 (Phase 2)





GSC 글로벌표준인증원

FDA OTC 공장심사 범위 및 기준

Conceptual Design

Qualification

Validation

Laboratory Method

4. 시험규격 재설정(Laboratory Method)

- 원료의 시험 규격 재검토 및 변경
- 완제품 시험에 대한 시험방법 검토 및 검증
- 환경모니터링 규정 검토 및 변경(시험 항목 확대)
- 안정성 시험 관련규정 변경 등(자사 시험 조건 및 기준 허용 안됨)

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C - DRUGS: GENERAL

PART 211 -- CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

Subpart F - Production and Process Controls

Sec. 211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation;

(2) Disintegration time;

(3) Adequacy of mixing to assure uniformity and homogeneity;

(4) Dissolution time and rate;

(5) Clarity, completeness, or pH of solutions.

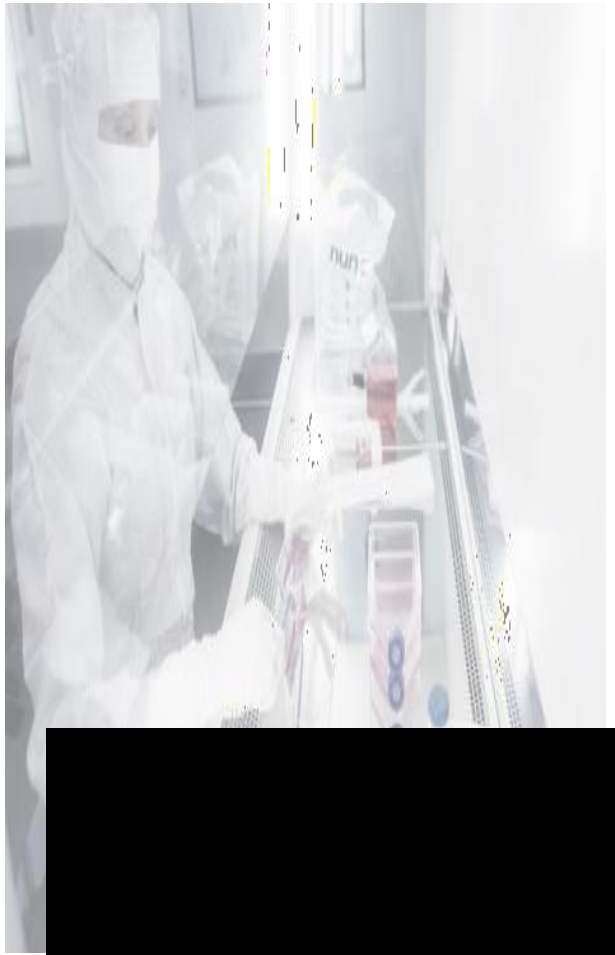
(6) Bioburden testing.

(b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

출처: 2020, Electronic Code of Federal Regulations (eCFR)



FDA OTC 공장심사 범위 및 기준

Conceptual Design

Qualification

Validation

Laboratory Method

5. 시험법 밸리데이션(Method Validation)

- 원료 및 완제품의 시험방법(순도, 함량)에 대한 검증 필요
- 세척 밸리데이션(CV)의 주성분, 세척제에 대한 시험법 검증에 활용
- 특이성, 정확성, 직선성, 반복성, 정밀성, 실험실내 정밀성, 정량한계 검출한계 등의 검증

TITLE 21--FOOD AND DRUGS
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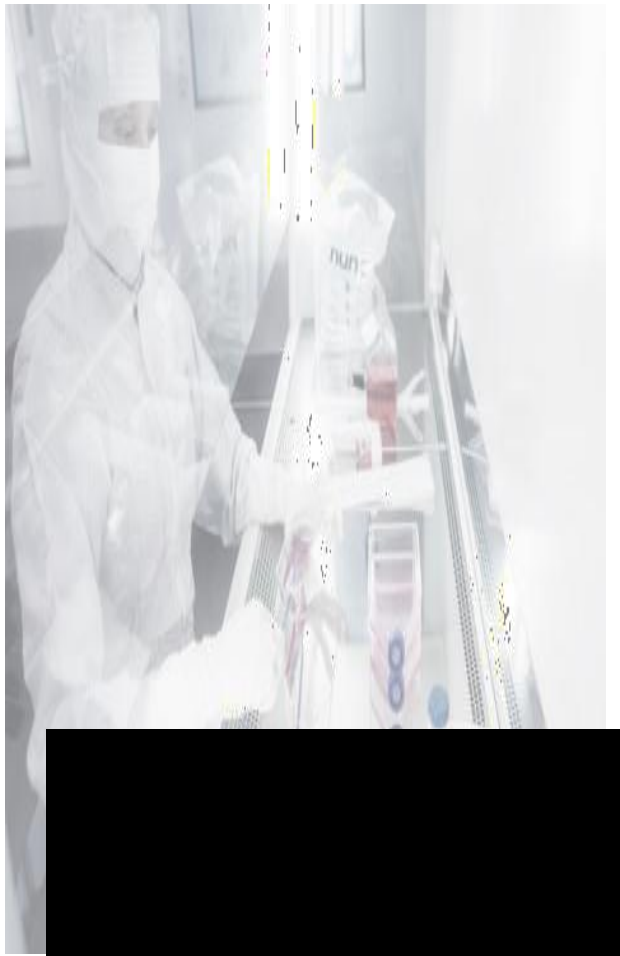

FDA OTC 공장심사 범위 및 기준

Conceptual Design

Qualification

Validation

Laboratory Method

6. 원료 및 제품의 성분검토

- OTC 대상으로 구분되는 원료 및 제품에 대한 성분 검토
- 제품의 수출이력 확인
- 주로 손소독제, 탈모예방 샴푸, 자외선 차단제가 대표적

TITLE 21--FOOD AND DRUGS
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Sec. 211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation;

(2) Disintegration time;

(3) Adequacy of mixing to assure uniformity and homogeneity;

(4) Dissolution time and rate;

(5) Clarity, completeness, or pH of solutions.

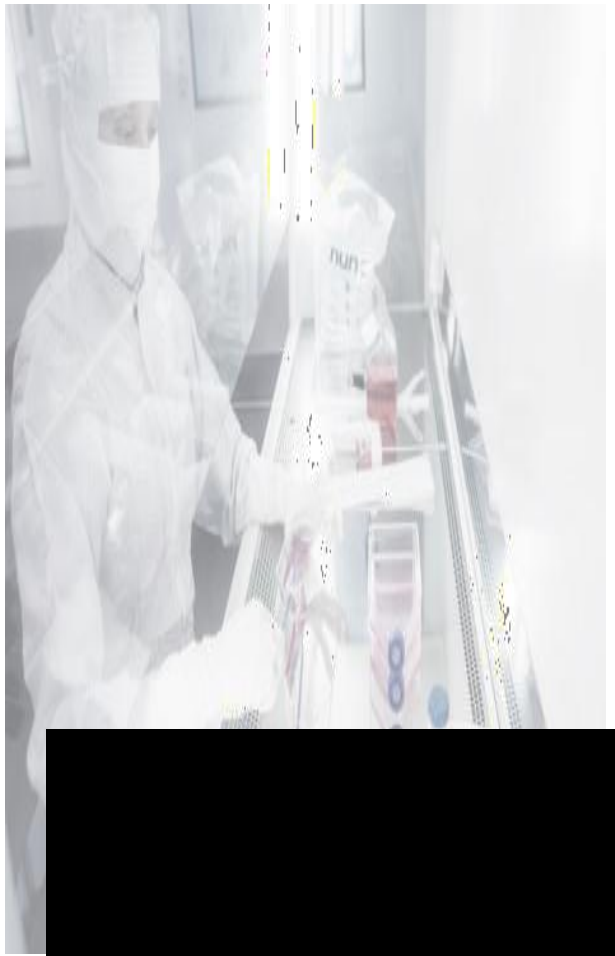
(6) Bioburden testing.

(b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

출처: 2020, Electronic Code of Federal Regulations (eCFR)



03

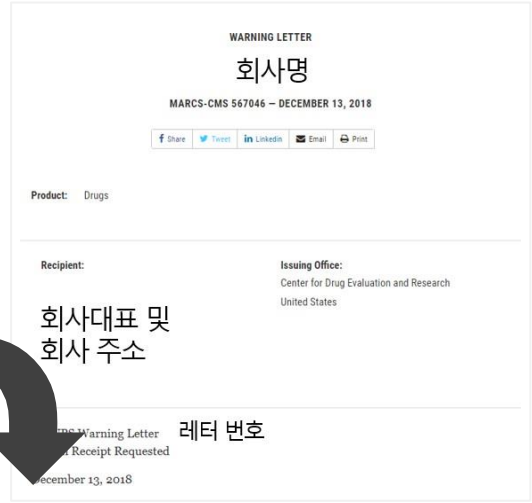
FDA OTC Facility Inspection

FDA OTC 주요 지적사항

- 주요 지적사항

FDA OTC 주요 지적사항

1	적격성평가 미 실시
2	원료 및 완제품에 대한 시험규격 출처 불분명
3	시험법밸리데이션(MV) 미 실시
4	실제 수행된 품질시험이 설정된 시험규격과 상이
5	안정성 시험 미 실시
6	기준일탈의 처리 미흡



WARNING LETTER

회사명

MARCS-CMS 567046 – DECEMBER 13, 2018

Product: Drugs

Recipient:

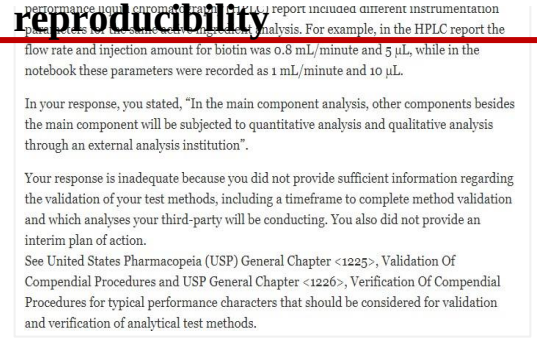
회사대표 및
회사 주소

Issuing Office:
Center for Drug Evaluation and Research
United States

Warning Letter 레터 번호
Receipt Requested
December 13, 2018

Your firm failed to establish an specificity, and reproducibility

d document the accuracy, sensitivity, of its test methods (21 CFR 211.165(e)).



performance ... report included different instrumentation ... analysis. For example, in the HPLC report the flow rate and injection amount for biotin was 0.8 mL/minute and 5 µL, while in the notebook these parameters were recorded as 1 mL/minute and 10 µL.

In your response, you stated, "In the main component analysis, other components besides the main component will be subjected to quantitative analysis and qualitative analysis through an external analysis institution".

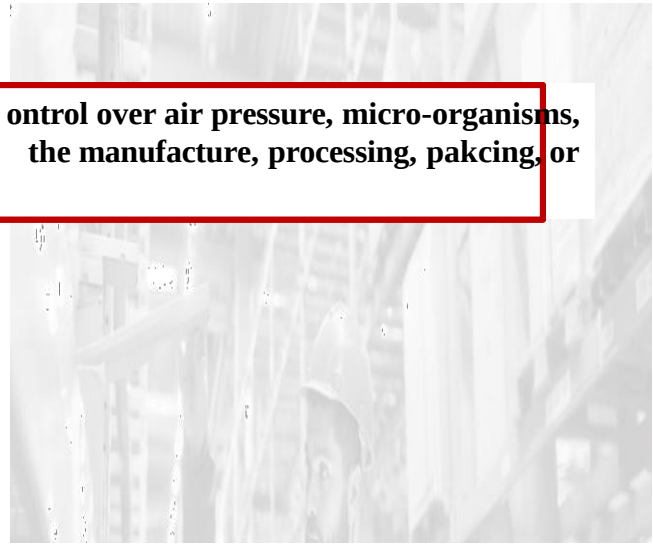
Your response is inadequate because you did not provide sufficient information regarding the validation of your test methods, including a timeframe to complete method validation and which analyses your third-party will be conducting. You also did not provide an interim plan of action.
See United States Pharmacopeia (USP) General Chapter <1225>, Validation Of Compendial Procedures and USP General Chapter <1226>, Verification Of Compendial Procedures for typical performance characters that should be considered for validation and verification of analytical test methods.

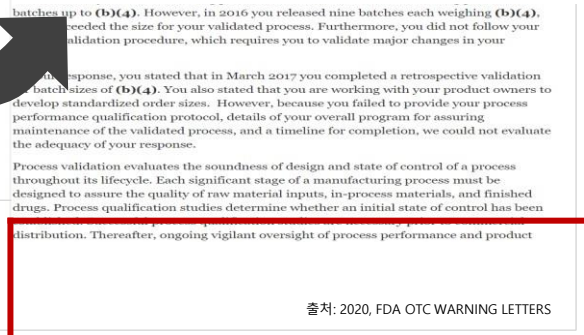
출처: 2020, FDA OTC WARNING LETTERS

FDA OTC 주요 지적사항

7	기준일탈의 처리 미흡
9	보관소에 대한 온·습도 매핑 미 실시
10	공정밸리데이션(PV) 및 세척밸리데이션(CV) 미 실시
8	연간품질평가 및 위험평가 미 실시

Your firm failed to provide equipment for adequate dust, humidty, and temperature when appropriate for holding of a drug product(21 CFR 211.46(b))




batches up to (b)(4). However, in 2016 you released nine batches each weighing (b)(4).
ceeded the size for your validated process. Furthermore, you did not follow your
alidation procedure, which requires you to validate major changes in your

esponse, you stated that in March 2017 you completed a retrospective validation
batch sizes of (b)(4). You also stated that you are working with your product owners to
develop standardized order sizes. However, because you failed to provide your process
performance qualification protocol, details of your overall program for assuring
maintenance of the validated process, and a timeline for completion, we could not evaluate
the adequacy of your response.

Process validation evaluates the soundness of design and state of control of a process
throughout its lifecycle. Each significant stage of a manufacturing process must be
designed to assure the quality of raw material inputs, in-process materials, and finished
drugs. Process qualification studies determine whether an initial state of control has been
distribution. Thereafter, ongoing vigilant oversight of process performance and product

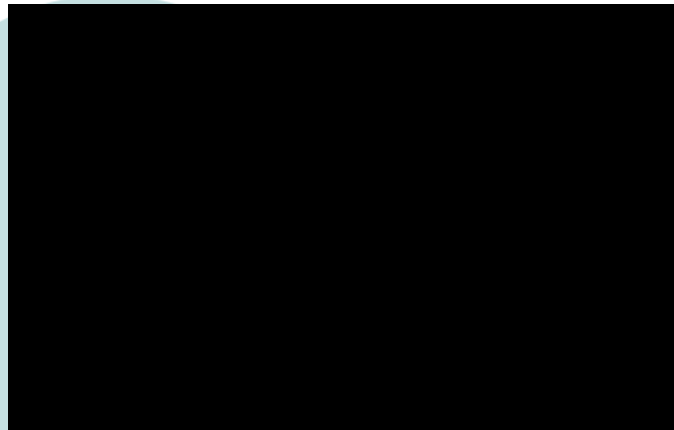
출처: 2020, FDA OTC WARNING LETTERS

2024.05.13 ㈜글로벌표준인증원 웨비나

Leading Global Trend in Korea, Value beyond the expectation

FDA OTC, GMP 심사

강사: ㈜글로벌표준인증원 전재금 대표



GSC 글로벌표준인증원

04

FDA OTC Facility Inspection

FDA OTC 예시사례

- 사례 및 주요 지적사항

1. 21 CFR Part 211 Section 주요 Observations

21 CFR Part 211 Section		주요 Observation 항목	Korea		All Countries	
			%	Rank	%	Rank
B	Organization and Personnel	211.22 품질관리조직의 업무분장 책임 22(d)	15.7%	2	17.7%	1
		211.25 작업자의 적격성 25(a)	11.1%	4		
C	Building and Facilities	211.42 디자인 및 구조 특성 42(c)				
D	Equipment	211.63 설비/장비 적격성 (디자인, 크기 위치 등)	6.5%	10		
		211.67 설비 세척 및 유지관리 67(a), 67(b)	7.8%	6	7.1% 6.6%	7 9
		211.68 전자식 설비나 컴퓨터 또는 관련 시스템 적격성 및 검교정 68(a) Data Integrity 68(b)	8.5%	5		
E	Control of Components and Drug Product Containers and Closures	211.84 원료, 의약품 용기, 마개의 시험과 적합 또는 부적합 판정 84(d)				
F	Production and Process Controls	211.100 생산 및 공정 관리 절차 및 일탈관리 100(a)	11.8%	3	10.0%	5
		211.110 공정 물품과 의약품 검체 채취와 시험 110(a)	7.2%	7	6.4%	10
G	Packaging and Labeling Control					
H	Holding and Distribution	211.142 제품 보관관리 조건 113(b)				
I	Laboratory Controls	211.160 시험 절차 관리 160(b),	17.0%	1	10.9%	4
		211.165 시험과 출하 승인 165(a)	7.2%	9	6.9%	8
		211.166 안전성 시험 166(a)	7.2%	8		
J	Records and Reports	211.188 배치 생산 및 관리 기록서 188(b)				
		211.192 생산 기록서 검토			10.9%	3

출처: 2020, FDA OTC WARNING LETTERS

- **21 CFR Part 211 (148 소 항목 중)**
- **대상 기간 : From 2009 to 2023**

최근 DEG/EG 등 원료의 위해 성분 확인시험 누락으로 Warning Letter 발생 중

2. FDA Drug Inspection 심사결과 및 진행상황

FY2024년 3월까지 (16건)

Legal Name	Inspection date	483발행	Classfication	비고
Outin Futures Corp	03/29/2024	Yes		
SK Biotek Co., Ltd. (Sejong	03/22/2024	No	NAI	
Amorepacific Corporation	03/16/2024	Yes		IA:2023-04-28
Celltrion Inc.	02/27/2024	Yes		
Kolmar Korea Co., Ltd. - Gv	02/16/2024	Yes		
Yuhan Chemical Inc.	01/12/2024	Yes	VAI	
Chemport Inc.	12/14/2023	No	NAI	
CIT Co., Ltd.	12/08/2023	Yes	VAI	
Hanacos Co., Ltd.	12/01/2023	Yes	VAI	
C&T Dream Co., Ltd.	11/10/2023	Yes	OAI	IA: 2024-04-10 WL: 2024-04-11
KONAD Co., Ltd.	11/10/2023	No	NAI	
Imine Co., Ltd.	11/03/2023	No	NAI	
Dong IL Pharm Co., Ltd.	11/03/2023	No	NAI	
FirstCham Co., Ltd.	10/27/2023	Yes	OAI	IA: 2024-03-25 WL: 2024-04-03
Aqualex Co., Ltd.	10/20/2023	Yes	OAI	IA: 2024-02-09 WL: Not Yet
High Tech Pharm Co., Ltd.	10/13/2023	No	NAI	

FY2023년 (14건)

Legal Name	Inspection date	483발행	Classfication	비고
Samsung Biologics Co., Ltd	09/01/2023	Yes	VAI	
Kolmar Korea Co. Ltd. - Gw	07/21/2023	Yes	VAI	
ST Pharm Co., Ltd.	07/14/2023	Yes	VAI	
K.S. PEARL Co., Ltd.	07/07/2023	Yes	VAI	
Raphas Co., Ltd.	06/23/2023	Yes	VAI	
Handock Cosmetics Co., Lt	03/24/2023	Yes	OAI	IA: 2023-07-24 WL: 2023-10-04
JW Pharmaceutical Corpora	03/17/2023	Yes	VAI	
Unimed Pharmaceuticals, Ir	02/14/2023	No	NAI	
Seoul Cosmetics Co., Ltd.	02/03/2023	Yes	OAI	IA: 2023-06-08 WL: 2023-10-02
Hanmi Fine Chemical Co Lt	11/25/2022	No	NAI	
CKD Bio Corporation	11/18/2022	No	NAI	
High Tech Pharm Co., Ltd.	11/11/2022	No	NAI	
Samchundang Pharm Co., L	10/27/2022	Yes	VAI	
Taejoon Pharm Co., Ltd.	10/18/2022	Yes	VAI	

FY2022년 (7건)

Legal Name	Inspection date	483발행	Classfication	비고
Daewoong Pharmaceutical	08/24/2022	Yes	VAI	
Outin Futures Corp	08/12/2022	Yes	OAI	
Kolmar Korea Co., Ltd. - Gv	07/07/2022	Yes	VAI	IA: 2023-05-02
PL Cosmetic	07/01/2022	Yes	VAI	
Celltrion Inc.	06/03/2022	Yes	VAI	
Hanlim Pharm Co., Ltd.	05/31/2022	Yes	VAI	
Mirfeel Korea Co., Ltd				IA: 2022-03-24 WL: 2022-06-22

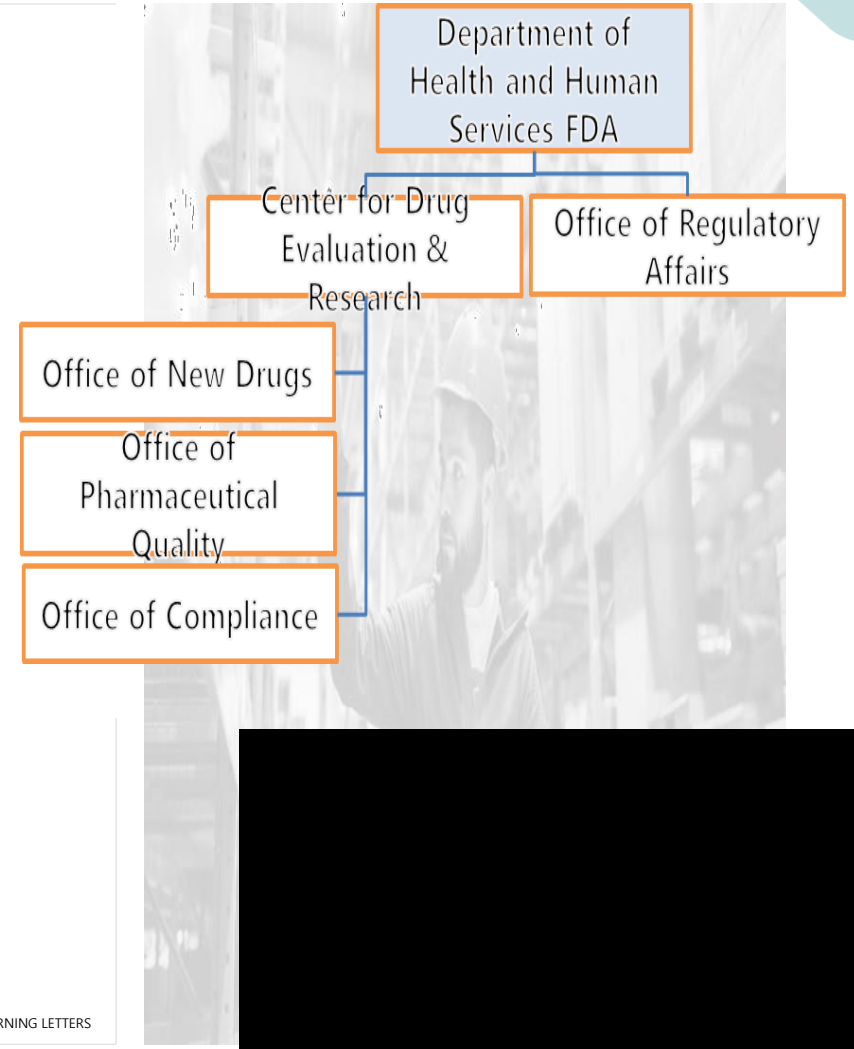
출처: 2020, FDA OTC WARNING LETTERS

- 대상: 의약품 중 임상 제외
- NAI: No Action Indicated
- VAI: Voluntary Action Indicated
- OAI: Official Action Indicated
- IA: Import Alert,
- WL: Warning Letter
- FY: Fiscal Yea

3. FDA 어느 부서에서 심사를 주관할까?

Tasks	OPQ/ OS	ORA/ Pharm	OC/ OMQ	CDER	ORA
Maintain manufacturing facility catalogue	R	C	I	A	
Develop Site Selection Model	R	C	I	A	
Select sites for Surveillance Inspection	R	C	I	A	
Schedule inspection	I	R	I		A
Prepare site dossier	R	C	I	A	
Develop on-site inspection strategy	C	R	I		A
Perform inspection	I	R	I		A
Convene discussion, as appropriate, if major/critical conditions identified	C	R	C		
Issue FDA 483 as necessary	I	R	I		A
Complete report and initial classification in 45 days post-inspection	I	R	I		A
Complete final classification for NAIs and VAIs in 40 days	I	R	I		A
Issue NAI and VAI decisional letter in 5 days post final classification	I	R	I		A
Complete final classification for OAIs and issue OAI decisional letter	C	C	R	A	
If OAI downgraded, issue VAI or NAI decisional letter in 5 days post final classification	I	I	R	A	
Implement appropriate action for OAIs within 3 months of decisional letter	C	C	R	A	
Conduct trend analysis	R	I	I	A	
Update site dossier	R	I	I	A	

출처: 2020, FDA OTC WARNING LETTERS



4-1 FDA Investigator의 조사 운영 매뉴얼 (IOM) 2024년 2월 버전

5.9 화장품 (신규 추가 항목)

1) OTC 심사 시 의약품으로 간주할 수 있는 화장품의 심사 접근

- 현재 색소 첨가제를 제외한, 화장품이나 성분에 대한 FDA 사전 승인은 없지만 화장품 회사는 안전하고 적절한 라벨이 붙은 제품을 마케팅할 책임이 강조

  ✓ 금지된 성분의 사용, 색소 첨가물 관련 요구 사항 미준수, 필요한 경우 변조 방지 포장 요구 사항 미준수, 현장 검사를 반드시 수행하지 않고도 라벨링과 관련된 위반 사항 등을 수집

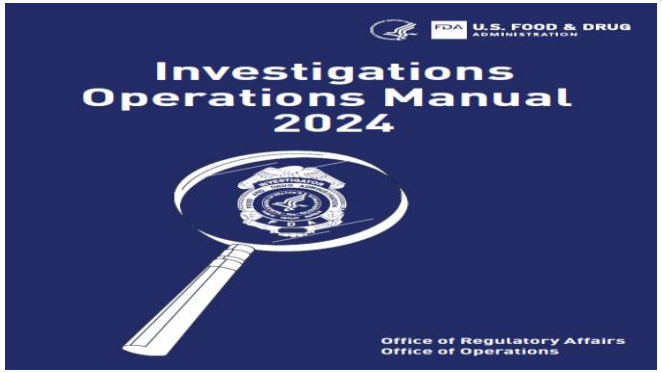
- 엄격하게 화장품으로 판매되지만 의약품에 대한 강조 표시가 있는 제품

  ✓ 모발 성장 촉진, 대머리 예방, 비듬 예방 또는 치료, 속눈썹 성장 강화, 여드름과 같은 피부 질환 치료 등을 주장하는 해당 제품들이 불법적으로 판매되는 의약품으로 간주할 수 있는 증거 수집

- OCAC*가 제품 성분에 대한 우려로 인해 비정상적인 안전 위험을 초래하는 것으로 식별한 특정 화장품들의 무해 증빙 수집

  ✓ "유기농" 또는 "천연"이라고 표시된 성분이나 제품, 전통적인 방부제가 없는 제품, 물티슈 (유아/어린이 및 성인이 사용), 화장품 무알코올 구강 관리 제품, 눈가 제품 등

*OCAC: Office of Compliance and Field Operations



CHAPTER 5 - ESTABLISHMENT INSPECTIONS

SUBCHAPTER 5.1	GENERAL INSPECTION INFORMATION
SUBCHAPTER 5.2	PRE-INSPECTION ACTIVITIES
SUBCHAPTER 5.3	SAFETY DURING INSPECTIONS
SUBCHAPTER 5.4	CONFIDENTIAL SOURCES AND SOURCES
SUBCHAPTER 5.5	INSPECTIONAL ACTIVITIES
SUBCHAPTER 5.6	EVIDENCE DEVLOPEMENT
SUBCHAPTER 5.7	REPORTING
SUBCHAPTER 5.8	HUMAN AND ANIMAL FOODS
SUBCHAPTER 5.9	COSMETICS
SUBCHAPTER 5.10	DRUGS
SUBCHAPTER 5.11	ANIMAL & VETERINARY
SUBCHAPTER 5.12	MEDICAL DEVICE AND ELECTRONIC RADAIATION PRODUCT CONTROL (EPRC)
SUBCHAPTER 5.13	BIOLOGICS
SUBCHAPTER 5.14	BIORESEARCH MONITORING (BIMO)
SUBCHAPTER 5.15	TOBACCO PRODUCTS
SUBCHAPTER 5.16	COMBINATION PRODUCTS

4-2 FDA Investigator의 조사 운영 매뉴얼 (IOM) 2024년 2월 버전

5.10 의약품 (신규 추가 항목)

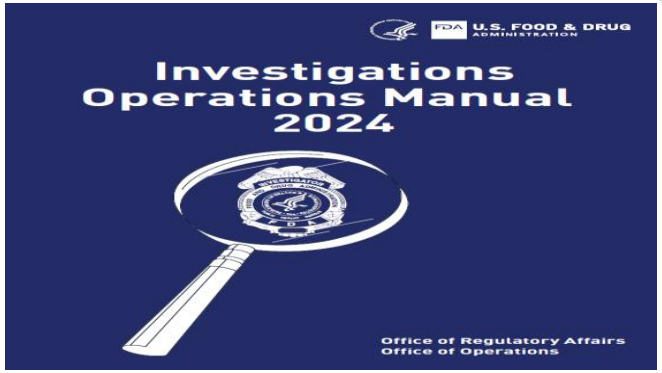
1) 심사 접근법

- 심사 초기에 회사로 접수된 불만 사항들을 검토하여 제품당 불만 사항의 상대적인 수를 결정
- 검역, 반품, 재처리 및/또는 거부된 제품 보관 장소를 검사하여 거부된 제품을 식별
- 가공 추세를 검토하고 21 CFR 211.180(e)에 따라 수행된 검토를 검토하여 공정 관리 문제 및 배치 거부가 있는 제품을 식별
- 실험실 데이터(예: 실험실 통합 문서), OOS 조사 및 실험실 일탈 보고서 요약을 검토

2) 의약품 등록 및 등재

- 시설 실사 중에 의약품 목록이 현재 제품 라인을 정확하게 반영하는지 확인하고 21 CFR 207에 따라 모든 제품 변경, NDC 변경 및 중단을 포함하도록 필요에 따라 목록을 업데이트할 책임을 회사에 상기시켜야 한다.
- 등록 및 목록에 결함이 있는 경우 EIR에 이를 기록하고 문서 샘플을 수집하거나 FDA 감독자에게 문의한다.

*OCAC: Office of Compliance and Field Operations



CHAPTER 5 - ESTABLISHMENT INSPECTIONS

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SUBCHAPTER 5.16	COMBINATION PRODUCTS

5. 글리세린의 DEG 및 EG USP시험이 왜 어려울까?

대한 약전

- 제약사
- ISO17025 인증된 시험기관

USP

- 미국향 OTC(일반의약품) 수출하는 화장품사

DEG와 EG의 KP와 USP 시험 동일

1	크로마토그래피 시스템	Gas Chromatography
2	희석제	메탄올
3	내부표준액	2,2,2-트리클로로에탄올
4	표준액	각 전처리 동일
5	검액	각 전처리 동일
6	조작조건	검출기, 컬럼, 주입기 온도, 검출기 온도, 운반가스, 주입크기, 유량, 주입 유형
7	시스템 적합성	적합성 요구사항
8	분석 규격	0.1% 이하로 검출

<참조>

- 대한 약전 기준으로, 국내 제약사가 국내 인증 시험기관을 통해 시험 사례
- 최근 KOTITI에서 화장품사 의뢰로 글리세린과 프로필렌 글리콜의 DEG/EG USP시험 기준으로 성적서 발행 사례

1. 원료 기준시험의 변경 정보 확인

1) USP and NF Admission And Annotated List update to share

General Notices, Monographs, General Chapters, Reagents, and Tables Affected by Changes Appearing in *USP-NF*

Official on	USP Admission List	USP Annotated List	NF Admission List	NF Annotated List
20231201			no new articles	
20240501		<232> ELEMENTAL IMPURITIES -LIMITS <1059> Excipient Performance <Excipients for changes>		
20240801		<541> Titrimetry <791> pH <Excipients for changes>	no new articles	Deletion: Carbomer 934, Carbomer 934P, Carbomer 940, Carbomer 941, Carbomer 1342

2) USP Newsletters & Updates 구독

To receive timely email updates on new Official Text (USP activities, products, and services), sign up for the free Compendial Updates service go.usp.org/newsletter-subscriber

3) Publication Announcements / Revision Bulletins

To track the general announcement for publication Notices, such as reference changes, redesigned monographs, and USP–NF Online https://www.uspnf.com/notices/gen-announcements or https://www.uspnf.com/official-text/revision-bulletins (변경될 대상만 알 수 있음, 상세 내용은 USP-NF On line 구독자를 통해 확인 필요)

4) Search for FDA Guidance Documents

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

5-1 원료 기준시험의 변경 정보 확인

Official on	USP Admission List	USP Annotated List	NF Admission List	NF Annotated List
20231201			no new articles	
20240501		<232> ELEMENTAL IMPURITIES -LIMITS <1059> Excipient Performance <Excipients for changes>		
20240801		<541> Titrimetry <791> pH <Excipients for changes>	no new articles	Deletion: Carbomer 934, Carbomer 934P, Carbomer 940, Carbomer 941, Carbomer 1342

출처: 2020, FDA OTC WARNING LETTERS

5-2 원료의 중요 품질 불순물시험

Impurities		Elemental Impurities		Others	
General Chapter	Official on	General Chapter	Official on	General Chapter	Official on
〈466〉 Ordinary Impurities	20181001	<232> Limits	20211201 => 20240501	〈3〉 Topical and Transdermal Drug Products	20231201
〈476〉 Control of Organic Impurities in Drug Substances and Drug Products	20210501	<233> Procedures	20180501	〈467〉 Residual Solvents	20220901
〈1086〉 Impurities in Drug Substances and Drug Products	20210501				

출처: 2020, FDA OTC WARNING LETTERS

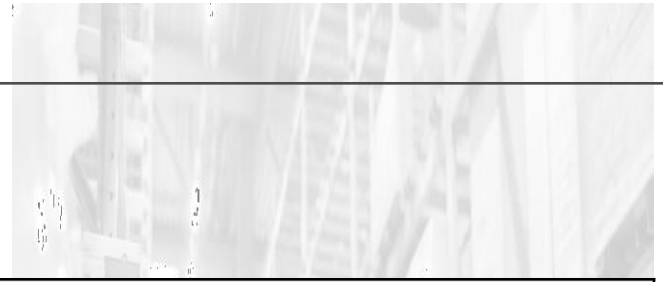
5-3 원료의 중요 품질 불순물시험

출처: 2020, FDA OTC WARNING LETTERS

예) Carbomer Impurities for LIMIT OF BENZENE

2022-05-01	2023-12-27	2026-08-01
Benzene Acceptance criteria: • Carbomer 934 NMT 5000ppm • Carbomer 934P NMT 1000ppm • Carbomer 940 NMT 5000ppm • Carbomer 941 NMT 5000ppm • Carbomer 1342 NMT 2000ppm	***immediate implementation*** • **2018 ICH Q3C 지침에 따라 벤젠 2ppm이하 권장사항** • **벤젠을 사용하지 않은 대체 등급의 카보머 권장** 30P Reformulating Products That co.pdf	Deletion: USP-NF Carbomer 934, Carbomer 934P, Carbomer 940, Carbomer 941, Carbomer 1342

5-4 부형제의 중요 품질 특성시험



출처: 2020, FDA OTC WARNING LETTERS

예) 부형제 Talc Test 변경

2022-05-01	2025-12-01
IDENTIFICATION • 〈1901〉 Theory and practice of asbestos detection in pharmaceutical talc	• Talc containing (detectable) asbestos is not pharmaceutical grade. • IMPURITIES: - LIMIT OF CALCIUM Test - 〈901〉 Detection of Asbestos in Pharmaceutical Talc • SPECIFIC TESTS - MICROBIAL ENUMERATIC FOR SPECIFIED MICROOR for topical administratior • ADDITIONAL REQUIREMENT - LABELing

5-5 부형제의 중요 품질 특성시험

출처: 2020, FDA OTC WARNING LETTERS

CDER Small Business and Industry Assistance (SBIA) Learn Highlight

2) USP Newsletters & Updates 구독

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3) Publication Announcements / Revision Bulletins

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4) Search for FDA Guidance Documents

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

GSC의 컨설팅 영역

GSC 서비스 범위

Mock Inspection	Data Integrity	QMS	Qualification (제조/지원/분석)	Validation (MV/PV/CV)	FDA Pre-Correspondence	FDA Site-Inspection (5 Days)	CAPA Response to FDA (3Months)

- AS-IS vs. TO-BE (21CFR211)
- ANSI 455-3 vs. 455-4

- 21 CFR 211 기준, QMS 구축
- Site Master File 수립
- Validation Master Plan 수행

FDA Field 심사
- Form4003 기반 문서 제출 지원
- 심사 시연 대비 사전 준비 지원
- FDA Investigator의 과거 심사 이력 및 심사원 성향 분석
- FDA Field Audit Coordinatorr & 5일회의록
- Form483 Response 작성 지원
- CAPA 컨설팅
- 2차례 CAPA Report 작성 지원
- 재심사 요청 (필요 시)

데이터 무결성 (12MD)
- **Pre-Audit 및 프로젝트 구축**
- **절차서 구축**
- **8H 교육 수료증 발행**
- **Audit Trail DB 분석 (에러 /경고 점검 일지)**
- **1개월 운영의 기록 점검 지원**
- **Post-Audit 및 CAPA 수립**

출처: 2020, FDA OTC WARNING LETTERS

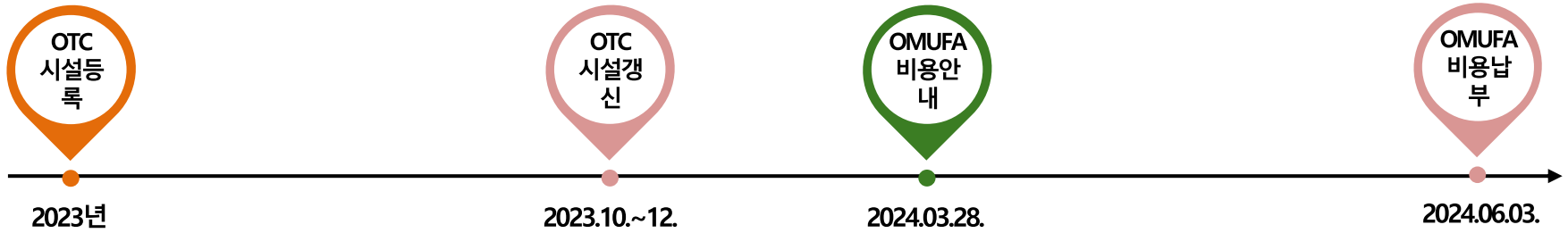
05

FDA OTC Facility Inspection

OMUFA 안내

- OMUFA 타임라인

OMUFA 타임라인



1) OMUFA FY 2024는 2023년도 내 OTC 시설등록 된 업체에 청구되는 비용입니다.
2) 각 시설에 해당하는 비용을 user fee 포탈을 통해 납부해야 합니다.
3) 극단적인 예시로 2024년 9월 31일에 시설등록을 한 A업체는 갱신기간 전에 등록을 했으므로 다음 년도 FY 2025 비용을 납부하여야 합니다.

FDA MoCRA 임상시험 안내

1) FDA의 Good Clinical Practice: Integrated Addendum to ICH Guidance for Industry에 따라 임상시험의 기준이 나와있습니다.

- 중요예시. 시험책임자는 시험 착수를 위한 교육을 충분히 받아야 하며 시험은 반드시 IRB/IEC 혹은 국제적인 규정 (regulatory authorities)에 따라야 합니다.

2) 즉, 반드시 미국의 FDA에서 인정하는 기관이 없으며 규정에 맞는 기관의 영문보고서에 따라 화장품에 맞는 Claim을 사용할 수 있습니다.

Q&A

*인증 관련 자세한 문의는 ㈜글로벌표준인증원으로 주세요 ^^*

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· GSC 상담 전화 : 02-899-4265(4268)
· GSC 대표 메일 : office@gsckorea.co.kr

GSC 블로그

GSC 유튜브

THANK YOU

GSC 블로그

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