

Implementation of ICH Q3D guideline in Korea

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Pharmaceutical Standardization Division

Drug Evaluation Department

National Institute of Food & Drug Safety Evaluation(NIFDS)

Ministry of Food & Drug Safety(MFDS)

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Organization of MFDS

Minister

Spokesperson

Vice Minister

Criminal Investigation Office

Audit and Inspection Office

Director General for Planning and Coordination

- Planning and Budget Office
- Administrative Management Office
- Regulatory Reform and Legal Affairs Office
- International Cooperation Office
- · Information Management and Statistics Office
- Customer Support Office
- · Emergency and Security Office

Customer Risk Prevention Bureau

- Customer Risk Prevention Policy Division
- Communication and Cooperation Division
- · Risk Information Division
- Laboratory Audit and Policy Division

Food Safety Policy Bureau

Food Standard Planning Office

- · Food Policy Coordination Division
- · General Food Management Division
- · Food Consumption Safety Division
- Food Import Policy Division · Food Standard Division
- Livestock Products Standard Division Functional Food Standard Division
- Food Additives Standard Division

Food Nutrition and **Dietary Safety Bureau**

- · Nutrition Safety Policy Division
- · Dietary Life Safety Division
- Foodborne Diseases Prevention and Surveillance Division
- · Novel Food Division

Agro-Livestock and Fishery Products Safety Bureau

- Agro-Livestock and Fishery **Products Policy Division**
- Livestock Products Sanitation Division
- Agro-Fishery Products Safety Division
- Foreign Inspection Division

Pharmaceutical Safety Bureau

- Pharmaceutical Policy Division
- Pharmaceutical Management Division
- · Narcotics Policy Division
- · Pharmaceutical Quality Division
- Clinical Trials Management Division

Biopharmaceuticals and Herbal Medicine Bureau

- Biopharmaceutical Policy Division
- Biopharmaceutical Quality Management Division
- Herbal Medicine Policy Division
- Cosmetics Policy Division

Medical Device Safety Bureau

- Medical Device Policy Division
- Medical Device Management Division
- Medical Device Quality Division



NIFDS(Affiliated agency)



Food Safety Evaluation Department

- · Food Safety Risk Assessment Division
- Pesticide and Verterinary Drug Residues Division
- Food Contaminants Division
- · Food Microbiology Division
- · Food Additives and Packages Division
- Nutrition and Functional Food Research Team
- New Hazardous Substances Team

Drug Evaluation Department

- Drug Review Management Division
- Pharmaceutical Standardization Division
- Cardiovascular and Neurology Products Division
- Oncology and Antimicrobial Products
 Division
- Gastroenterology and Metabolism
 Products Division
- Bioequivalence Evaluation Division

Biopharmaceuticals and Herbal Medicine Evaluation Department

- Biologics Division
- · Recombinant Protein Products Division
- · Cell and Gene Therapy Products Division
- · Herbal Medicinal Products Division
- Cosmetics Evaluation Division

Medical Device Evaluation Department

- High-tech Medical Devices Division
- · Cardiovascular Devices Division
- Orthopedic and Restorative Devices
 Division
- Dental and Gastroenterology Devices
 Division

Pharmaceutical and Medical Device Research Department

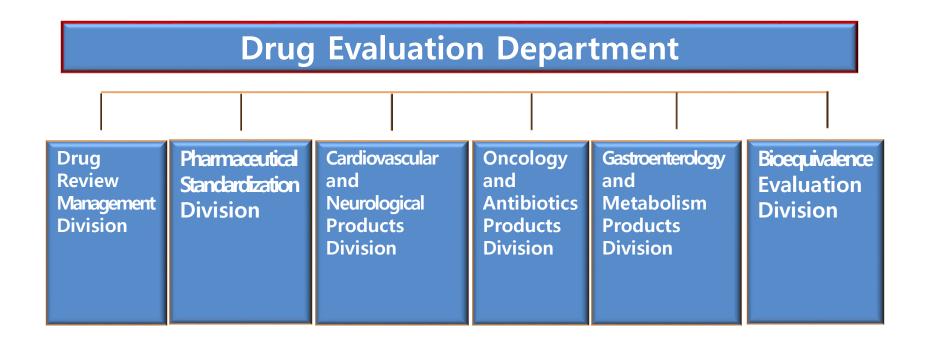
- Pharmaceutical Standardization Research & Testing Division
- Biologics Research Division
- Advanced Therapy Products Research Division
- · Herbal Medicine Research Division
- · Cosmetics Research Team
- Medical Device Research Division
- · Radiation Safety Division

Toxicological Evaluation and Research Department

- Toxicological Research Division
- Toxicological Screening and Testing Division
- Pharmacological Research Division
- · Clinical Research Division
- · Advanced Analysis Team
- Laboratory Animal Resources
 Division



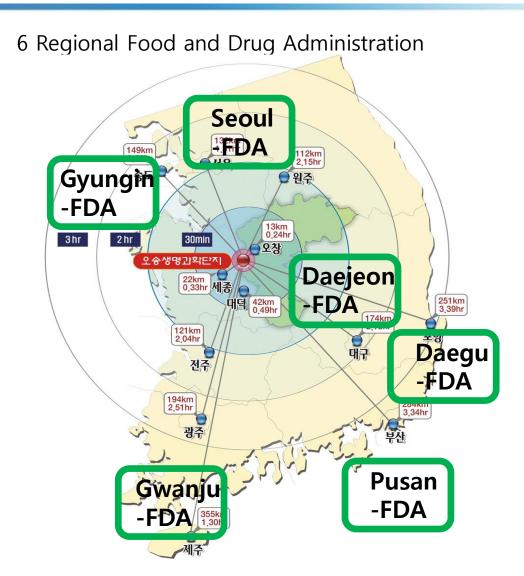
NIFDS-Drug Evaluation Department



- ✓ 3 NDA Review Division
- ✓ 1 ANDA(Bioequivalence) Review Division
- ✓ 1 ANDA(Quality) and DMF Review Division
- √ 1 Drug Approval and Review Management Division
 - → DMF registration



Regional-FDA







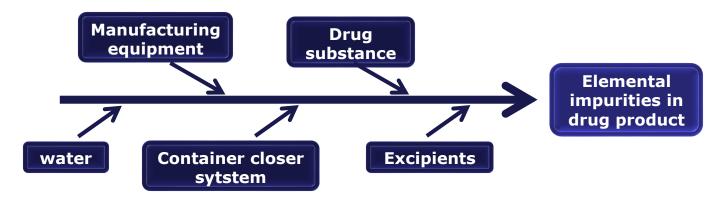
ICH Q3D guideline Application in Korea

- Establishment of Guidelines for the assessment and management of metal impurities in pharmaceuticals('17.4)
 - based on ICH Q3D ,not mandatory but only for recommendation.
- Revision of Regulation for Pharmaceutical Approvals, Notification and Reviews (MFDS Notification) ('19.5(?) → one year grace → '20. 5(?))
 - To mendatory the filing of safety data on elemental impurities in finished drug products (for all NDA, ANDA and generics)
 - drug substance should be screened for elemental impurities during the purity test and set criteria when necessary.
- Korean pharmacopoeia is not yet implemented the Q3D guideline
 - will be revised in a few years



In the Drug Products

- Risk assessment based control of elemental impurities
 - identify known or potential sources of elemental impurities in the drug products



- evaluate the presence of particular elemental impurites in the drug product
 - → determine the observed or predicted level of the impurity
 - → compare it with the established PDE.



- Summary of risk assessment process and control of elemental impurities
 - ✓ if the level of elemental impurity is less than control threshold
 (30% of PDE) → no additional controls are needed

The level and the Variability of an elemental impurity can be established by providing datas from three representative production scale lot or 6 representative pilot scale lots of the components

- ✓ if the level is more than the control threshold → additional controls are needed
 - modification of the manufacturing process
 - ▶ implementation of in-process or upstream controls
 - establishment of specific limits for excipients or materials
 - establishment of specification limit for the drug product
 - selection of appropriate container closer system

In the Drug Substances

Drug Master File (DMF)

- Submit detailed information about chemistry, manufacturing, and controls (CMC) of drug substances(APIs) to MFDS
 - including facilities, manufacturing process, material management, impurities, packaging, stability, etc.
- Evaluate submitted documents and register eligible drug substances
 - through technical document review and onsite Inspection
- Only registered drug substances can be used for manufacturing and selling pharmaceutical products

<Pharmaceutical Affairs Act, Para 2, Art. 31>





DMF Introduction and Expansion

- Introduction of drug substance registration system (DMF)
 - July 1 of 2002, active drug substance for new drug
- Expansion of its subjects step by step
 - Since 2005, annually expanded step by step to muchused drug substances by its effectiveness
 - Today, 211 materials and their salts and hydrates
 - Will be expanded to ALL DRUG SUBSTANCES

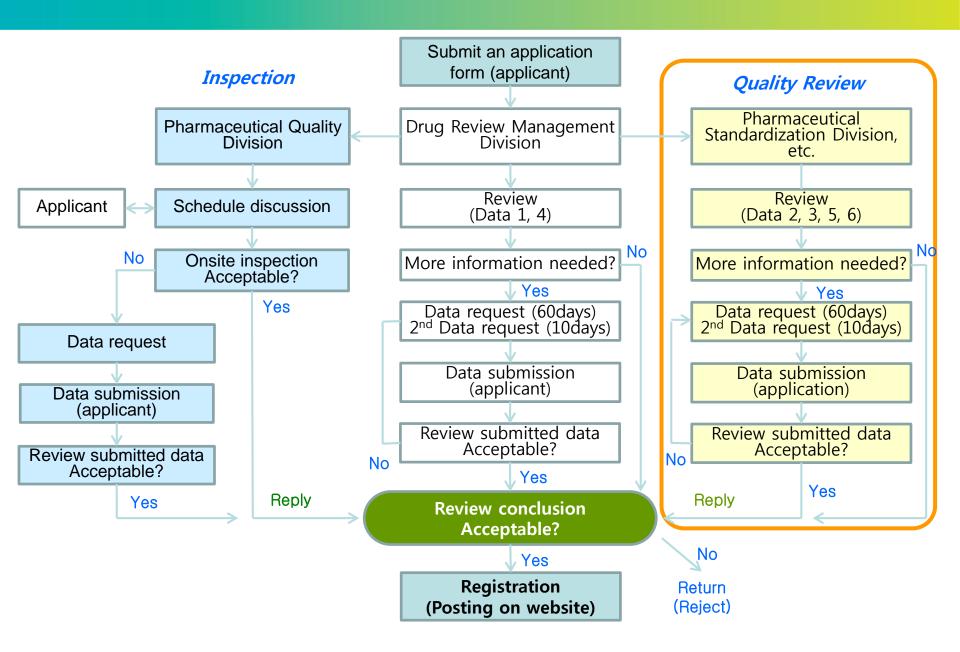


Laws and Regulations

- The Pharmaceutical Affairs Act
 - Para. 2, Art. 31, Art. 42
- Regulation for drug substance registration (MFDS Notification)
 - ✓ The scope of drug substances to register
 - ✓ How to prepare the data
 - ✓ The scope of the data
 - ✓ The requirement of the data to be submitted
 - ✓ The exemption from submission
 - ✓ The process of the application and registration, etc.



Process of the DMF



Registration and Notification

- Issue a registration certificate
 - in case data review and onsite inspection for a drug substance are appropriate
- Post information of a drug substance on website
 - MFDS website (<u>www.mfds.go.kr</u>) (Korean)
 - Relevant information in public
 - ✓ Category of a drug substance (API of new drug/ Drug substance indicated in Annex 1)
 - ✓ Registration number and date
 - ✓ Name of register (DMF holder)
 - ✓ Name of drug substance
 - ✓ Name of manufacturer and its address, country
 - ✓ Other remark (as necessary)



Documents for the DMF

- Regulation for drug substance registration, Art. 3
 - ✓ How to prepare data
 - Fill in an application form for registration of drug substance
 - Following data should be included in conformity with Regulation, Art. 4
 - 1) Data on facility for manufacture and quality management
 - 2) Data on physicochemical properties and stability
 - 3) Data on manufacturing process, packaging, container, cautions in storage and handling, etc.
 - 4) Data proving the eligibility of the substance (equivalent to KGMP or above the level of KGMP)
 - 5) Data including batch analysis, analytical procedures, used solvent of drug substance
 - 6) Sample drug substance for test
 - ✓ Limited to the case needs quality test permitted by the Minister of MFDS
 - Data can be submitted using the Common Technical Document (CTD)

Comparison of DMF and CTD; about elemental impurities

KDMF	CTD
Data on facility for manufacture and quality management	1.7.3. GMP documents for manufacturing and quality management of pharmaceuticals
 2. Data on physicochemical properties and stability a. Physicochemical properties (1) Developmental history (2) Structure elucidation, physicochemical properties and biological properties - Impurities 	 3.2.S.1. General information 3.2.S.1.1. Nomenclature 3.2.S.1.2. Structure 3.2.S.1.3. General properties 3.2.S.2. Manufacture 3.2.S.2.6. Manufacturing process development 3.2.S.3. Characterization
 organic impurities inorganic impurities (elemental impurities) residual impurities (3) Domestic/ foreign patent information 	 3.2.S.3.1. Elucidation of structure and other characteristics 3.2.S.3.2. Impurities organic impurities inorganic impurities (elemental impurities)

Example of data submission on elemental impurities in drug substances

Elemental impurity component composition according to the reactor equipment materials

< EZT 반응기 장비 재질에 따른 구성성분 분석표 >

R-521	CPS200904045	반응용	5 m'	HC-22	C, S, Cr, Ni, Mn, Si, Mo, Fe, P, V, W, Co
R-522	CPS200904046	반응용(공정연구실)	500ℓ	HC-22	C, S, Cr, Ni, Mn, Si, Mo, Fe, P, V, W, Co
R-523	CPS201102002	반응용	10 m'	HC-22	C, S, Cr, Ni, Mn, Si, Mo, Fe, P, V, W, Co



Example of data submission on elemental impurities in drug substance – risk assessment

4. Risk Assessment.

-Perform the risk assessment followed the below table, and attach the related documents.

Table A. Elemental Impurities Risk Assessment

		1	2	3	4	5	6	7
Element	Class	Intentionall y added (if used in the process)	Elemental impurities with a relatively high abundance and/or are impurities in excipients	Manufacturing equipment	Leached from container closure systems	Acceptable variability of elemental impurity contribution	Control threshold (30%)	Action
Cd	1	No	Yes	No	No	N/A	0.15µg/g	Needed management
Pb	1	No	Yes	No	No	N/A	0.15μg/g	Needed management
As	1	No	Yes	No	No	N/A	0.45μg/g	Needed management
Hg	1	No	Yes	No	No	N/A	0.90μg/g	Needed management
Со	2A	No	Yes	No	No	N/A	1.50µg/g	Needed management
~	2A	No	Yes	No	No	N/A	3.00µg/g	Needed management
Ni	2A	No	Yes	No	No	N/A	6.00µg/g	Needed management
TI	2B	No	No	No	No	N/A	N/A	Not needed management
Au	2B	No	No	No	No	N/A	N/A	Not needed management
Pd	2B	No	No	No	No	N/A	N/A	Not needed management
Ir	2B	No	No	No	No	N/A	N/A	Not needed management
Os	2B	No	No	No	No	N/A	N/A	Not needed management
Rh	2B	No	No	No	No	N/A	N/A	Not needed management
Ru	2B	No	No	No	No	N/A	N/A	Not needed management
Se	2B	No	No	No	No	Possible to come from	4.50µg/g	Needed management

4. Risk Assessment. (Continued)

Table A. Elemental Impurities Risk Assessment (Continued)

			disk Assessment (Continued)					
	1		2	3	4	5	6	7
Element	Class	Intentionall y added (if used in the process)	Elemental impurities with a relatively high abundance and/or are impurities in excipients	Manufacturing equipment	Leached from container closure systems	Acceptable variability of elemental impurity contribution	Control threshold (30%)	Action
Ag	2B	No	No	No	No	N/A	N/A	Not needed management
Pt	2B	No	No	No	No	N/A	N/A	Not needed management
Li	3	Yes	No	No	No	N/A	16.5µg/g	Needed management
Sb	3	No	No	No	No	N/A	N/A	Not needed management
Ва	3	No	No	No	No	N/A	N/A	Not needed management
Мо	3	No	No	Yes	No	N/A	90.0μg/g	Needed management
Cu	3	No	No	No	No	N/A	N/A	Not needed management
Sn	3	No	No	No	No	N/A	N/A	Not needed management
Cr	3	No	No	Yes	No	N/A	330μg/g	Needed management

5. Acceptance criteria and class of elemental impurities.

Element	Class	Acceptance criteria
Element	Class	ppm(μg/g)
Cd	1	0.5
Pb	1	0.5
As	1	1.5
Hg	1	3
Со	2A	5
٧	2A	10
Ni	2A	20
Se	2B	15
Li	3	55
Мо	3	300
Cr	3	1100

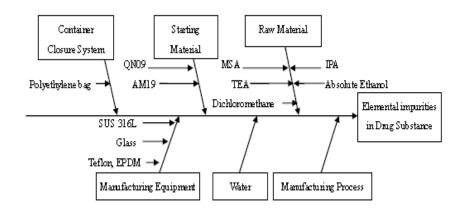
6. Evaluation and Conclusion.

As the final risk assessment, Class1 (Cd, Pb, As, Hg), Class2A (Co, V, Ni), Class2B (Se) and Class3 (Li, Mo, Cr) was classified as detectable elemental impurities. Based on the above data, perform the Analytical Method validation (AMV). If the result of test is less than 30%, manage the elemental impurities followed the SOP No. QC 220"Elemental Impurities Control Program".

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구분	자기미	계조사	Potentially present?	Intentionally added	NД
Staring Material	(?	, ,	No	No	N/A
	ne mo	J P. 708	No	Pd	· 사 비송날이나 '사와 공개 유자학으로 동일하게 평가 관계를
	(lv	i mo	Pb (<5 ug/g)	No	ааs д 1 ಕ್ 44 (Рь)
	1 E-A	ESF	No	No	일계 자르 및 구두 답변 참조함
Raw			No	No	ICP-OES I 3 F #4 (Cd, Hg, Pd)
Material	Australe 2	 	No	No	ICP-MS ≥ 16 ♣ ≧4 (Cd, Pb, As, Co, V, Ni, Tl, Au, Ag, Li, Sb, Ba, Mo, Cu, Sn, Cr)
	(150 ,	1 3 Che:	No	No	N/A

구는	자기 명	对些牛	Potentially present?	Intentionally added	刷江
Container Closure System	Polyethylene bag (PE bag)		No	No	AAS 로 4 중 분석 (Pb, Cd, Hg, Cr). RoHS approved

지점(Material)	해당 설비 및 부속품	Composition	설치의 중축 봉순물
Glass Lined Mild Steel	RE-S-001, RE-S-002, TK-S-003(MSA)	Si, Na, Ba, Zr, B, Ca	N/A
SUS 316L	RE-S-003, RE-S-004, FD-S-001, FD-S-002, FD-S-003, FD-S-004, TK-S-001, PK-S-001, PK-S-002, PK-S-003, SR-S-001, TK-S-006, HO-S-001, HO-S-002, HO-S-003	Fe, C, Cr, Ni, Mo, Mr, Si, P, S	Cr, Ni, Mo
Teflon	가스켓 (세, 제관제계부위) Filter housing 세계부위)	C, F	N/A
Glass	F/D Sight Glass	Si, Na, Ba, Zr, B, Ca	N/A
EPDM	≢ ≛ Sheet	С	N/A
Polypropylene	Filter(예, 용제 역과)	С	N/A
Nylonéé	Filter(4 ,各合)	C,O,N	N/A

^{*}Comment :Fe, B, Al, W, Zn, K, Cn, Na, Min, Mg 등과 같은 금속불순물은 ICHQ3D 가이드에 따라 위해생가 수행 해당 사람 없음.

구분	시험별	시험기	ग्र	
		Alert level	200 이라	
	TOC(ppb)	Action level	Alert Level 계초화시	
		Guideline reference level	500 이라	
		Alert level	25 ˚C: 1.1 이라	USP, EP
구초시험 (Weekly test)	정도도 (µs/cm)	Action level	Alert Level 기초하시	
		Guideline reference level	25 ˚C: 1.3 이라	₩
	일반4군 (CFU/200mL)*	Alert level	4 이라	1
		Action level	10 이약	1
		Guideline reference level	20 이약	
		Alert level	0.03 이하]
	센도국신	Action level	0.06 이목]
	(EU/mL)	Guideline reference level	0.25 이욱	
분기시험	Appearance	平线 平明 平平	1의 화손 의	EP
(Quarterly	Nitrates	격탁(0.2ppm 이라)		시험 항목
test)	Heavy metal	격함 (0.1pp	(4 M 3 4	

중지대	공치조건 (Min~Max C)	설비 치 <u>계</u>	기점 내무실	공속분순물 수술 가능성
Coupling 44	0~26°C	Glass Lined Mild Steel	≤50 6세계 내 구설 문제 없음 in NaOH, NH3	수울 가능성 없습
지장 건츠	65~75°C	SUS 316L	≤420℃ 위시 내 구성 문제 없습	4 출 가능성 없습
Saltformation 🕏	30~35°C	Glass Lined Mild Steel	≤110 0세시 내 구설 문제 없음 in HCl, H2SO4	4 출 가능성 없음
지장 건물	2002	SUS 316L	≤420℃ 위시 내구성 문제 없습	4 출 가능성 없습
Recrystallization	0~SS©	SUS 316L	≤420℃ 에서 내 구성 문제 없음	◆◆ 八七仏 似 ◆
관광 전조	5570	SUS 316L	≤420℃ 에서 내구성 문제 없음	유출 가능성 없음
	Coupling 변용 전략 전후 Saltformation 변용 전략 전후	(Min-Max C) Coupling 社会 0~26℃ 和書 対本 65~75℃ Saltformation 社会 30~35℃ 和書 対本 50℃ Recrystallization 0~55℃	Min-Max C MM	Minr-Max C

구는	중지대	공정조건 (Min~Max C)	설비 기본	지점 내구성	공 속본순 물 송술 가능성
EF01	Coupling 📆	0~26°C	Glass Lined Mild Steel	≤50 C에서 내 구설 문제 없음 in NaOH, NH3	수술 가능성 없는
	건강 건츠	65~75°C	SUS 316L	≤420℃ 위시 내구성 문제 없습	수축 가능성 없는
EF02	Saltformation 🕏	30~35°C	Glass Lined Mild Steel	≤110 ℃에서 내 구설 문제 없음 in HCl, H2SO4	수출 가능성 없음
	김종 건조	2000	SUS 316L		수출 가능성 없습
EF03	Recrystallization	0~55°C	SUS 316L		↑ 출 가능성 없습
Er 00	관광 건조	35°C	SUS 316L	≤420℃ 에서 내 구성 문제 없음	유승 가능성 없는

Element	Class	Potential elemental impurity derived from		
Cd (Cadmium)	1	For reference		
Pb (Lead)	1	Raw materials (MS A)		
As (Arsenic)	1	For reference		
Hg (Mercury)	1	For reference		
Co (Cobalt)	2A	Manufacturing equipment		
V (Vanadium)	2A	For reference		
Ni (Nickel)	2A	Manufacturing equipment		
Pd (Palladium)	2B	Starting materials (AM19)		
Li (Lithium)	3	For reference		
Sb (Antimony)	3	For reference		
Mo (Molybdenim)	3	Manufacturing equipment		
Cu (Copper)	3	For reference		
Cr (Chromium)	3	Manufacturing equipment		

Element	Class	Oral Concentration (µg/g)	Parenteral Concentration (µg/g)	Potential elemental impurity derived from
Cd (Cadmium)	1	0.5	0.2	For reference
Pb (Lead)	1	0.5	0.5	Raw materials (MSA)
As (Arsenic)	1	1.5	1.5	For reference
Hg (Mexury)	1	3	0.3	For reference
Co (Cobalt)	2A	5	0.5	Manufacturing equipment
V (Vanadium)	2A	10	1	For reference
Ni (Nickel)	2A	20	2	Manufacturing equipment
Pd (Palladium)	2B	10	1	Starting materials (AM19)
Li (Lithium)	3	55	25	For reference
Sb (Antimony)	3	120	9	For reference

Element	Class	Oral Concentration (µg/g)	Parenteral Concentration (µg/g)	Potential elemental impurity derived from	
Mo (Molybdenim)	3	300	150	Manufacturing equipment	
Cu (Copper)	3	300	30	For reference	
Cr (Chromium)	3	1100	110	Manufacturing equipment	

Element	Class	Acceptance Criteria (µg/g)	Acceptance Criteria (ppb)	30% of Acceptance Criteria	*Result of Analysis(ppb) QUB17013		*Result of Analysis(ppb) QUB17014		*Result of Analysis(ppb) QUB17015		Site
		(48/87)	(550)	(ppb)	결과	판정	결과	판정	결과	판정	
Cd (Cadmium)	1	≤0.2	≤200	≤ 60	한도이하	격함	한도이하	저함	한도이하	격람	判社 ICP-OES
Pb (Lead)	1	≤0.5	≤500	≤150	한도이하	격활	한도이하	神聖	한도이하	격탈	웹구소 ICP-MS
As (Arsenic)	1	≤1.5	≤1500	≤450	반도이라	적합	반도이라	적합	판도이라	격합	연구소 ICP-MS
Hg (Mercury)	1	≤0.3	≤300	≤90	반도이하	격합	반도이하	격장	판도이하	격합	연구소 ICP-MS
Co (Cobalt)	2 A	≤0.5	≤500	≤150	한도이하	격합	한도이하	격함	한도이하	격합	의社 ICP-OES
V (Vanadium)	2 A	≤1	≤1000	≤300	한도이하	격찾	한도이하	격합	한도이하	격합	영구소 ICP-MS
Ni (Nickel)	2 A	≤2	≤2000	≤600	반도이하	격합	반도이라	격함	한도이라	격합	의산 ICP-OES
Pd (Palladium)	2B	≤1	≤1000	≤300	반도이하	적합	반도이하	적합	반도이하	격합	연구소 ICP-MS
Li (Lithium)	3	≤ 25	≤ 25000	≤7500	한도이하	凋蟄	한도이하	湖擊	한도이하	凋蟄	判社 ICP-OES
Sb (Antimony)	3	≤9	≤9000	≤2700	한도이하	격합	한도이라	调整	한도이하	격합	역산 ICP-OES
Mo (Molybdemim)	3	≤ 150	≤ 150000	≤45000	한도이하	격합	한도이하	격함	한도이하	격합	单社 ICP-OES
Cu (Copper)	3	30	≤ 30000	≤9000	한도이하	계합	한도이하	격함	한도이하	격इ	判社 ICP-OES
Cr(Chromium)	3	110	≤ 110000	≤33000	한도이하	격합	한도이하	격함	한도이하	격합	司任 ICP-OES

*각 배치에 대한 분석결과는 MV 에서 검증된 최소 측정 수준인 정량한계 이하로 검출되었으며 정량한계는 각각

Cd 40ppb, Pb 150ppb, As 450ppb, Hg 90 ppb, Co 100ppb, V 300 ppb, Ni 100 ppb , Pd 300 ppb, Li 7500 ppb, Sb 2700 ppb, Mo 45000 ppb, Cu 9000 ppb, Cr 33000 ppb **이다**.

Changes to a Registered DMF and Elemental impurities

✓ DMF should be up-to-date!

Major changes

- ✓ synthetic route change, batch size change more than 10 times
- ✓ changes in catalyst and reagents used in the critical synthesis process
 - ✓ changing the source of starting materials and critical intermediates

Risk assessment of elemental impurities should be undertaken

Follow official process of the DMF (Application, review, and approval of changes)



Elemental impurities in the Korean Pharmacopoeia

- The Korean Pharamcopoiea full revision is scheduled in 2019
 - but, is not yet revised reflecting elemental impurities
 - will be revised in few years including general chapters and monographs



Summary

- ICH Q3D is about to be implemented in Korea by
 - establishment of guideline
 - revision of MFDS notification (revision of regulation for drug substance)
 - The Korean Pharmacopoiea is not yet revised reflecting elemental impurities but is planned to be revised in a few years
- drug substances are been regulated by DMF registration
 - Including elemental impurities in impurity test
- MFDS will help and lead our local drug subtance suppliers to implement Q3D guideline on their quality approval system



Thank You

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