MINISTRY OF
FOOD AND DRUG SAFETY

Implementation of ICH Q3D guideline in Korea

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Ministry of Food & Drug Safety(MFDS)

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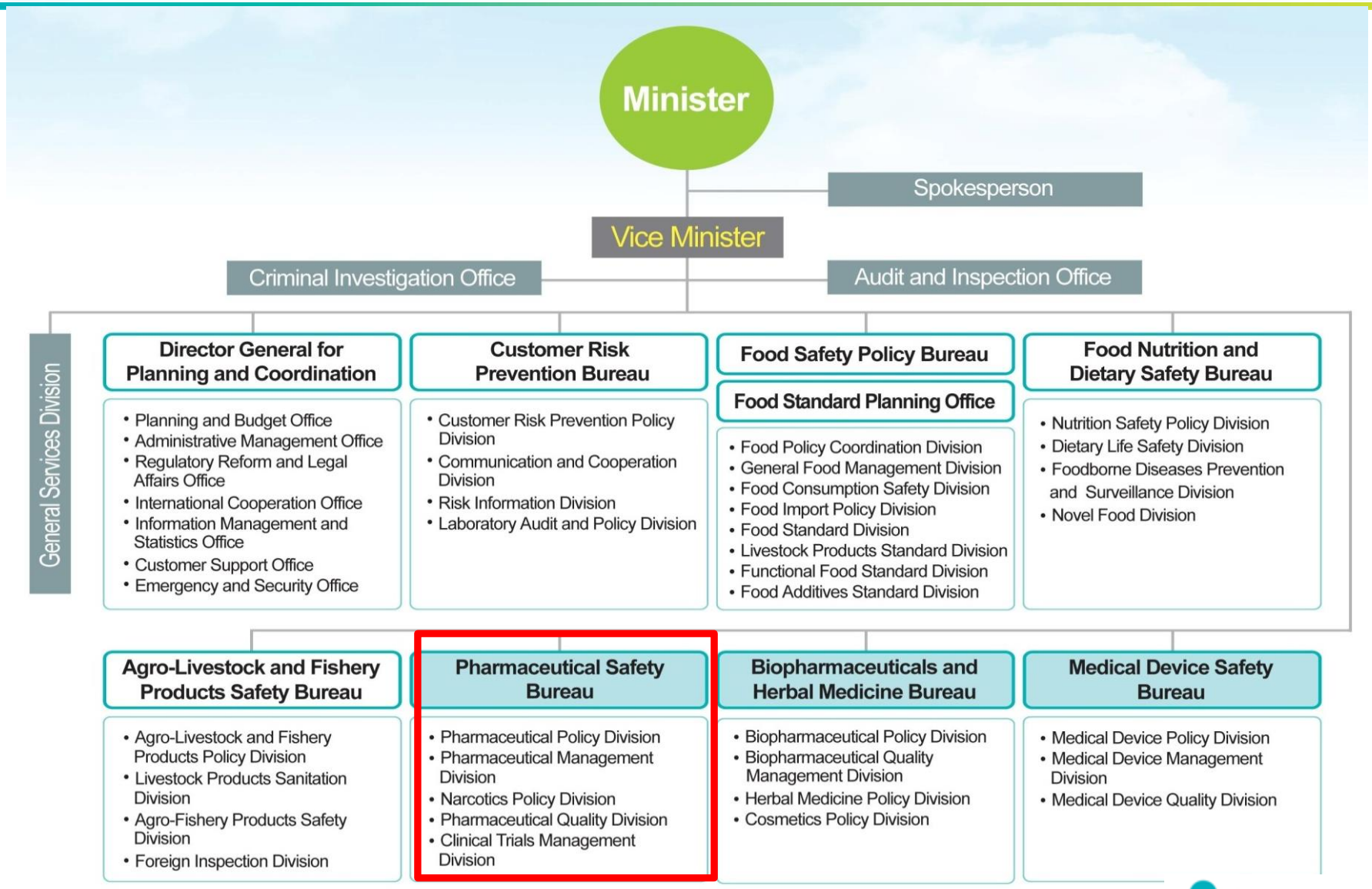
Organization of MFDS

MFDS Headquarters



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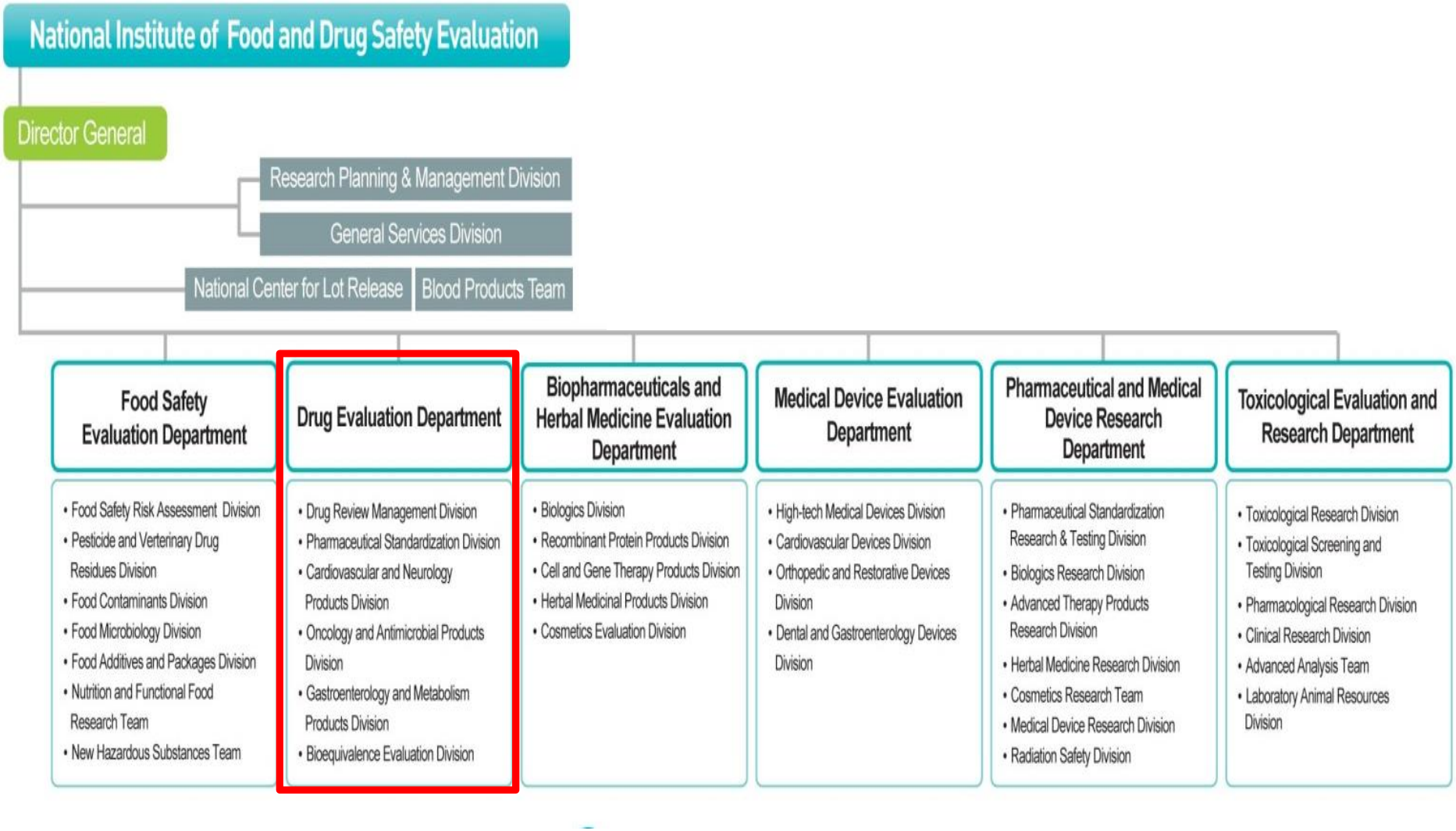
NIFDS(Affiliated agency)



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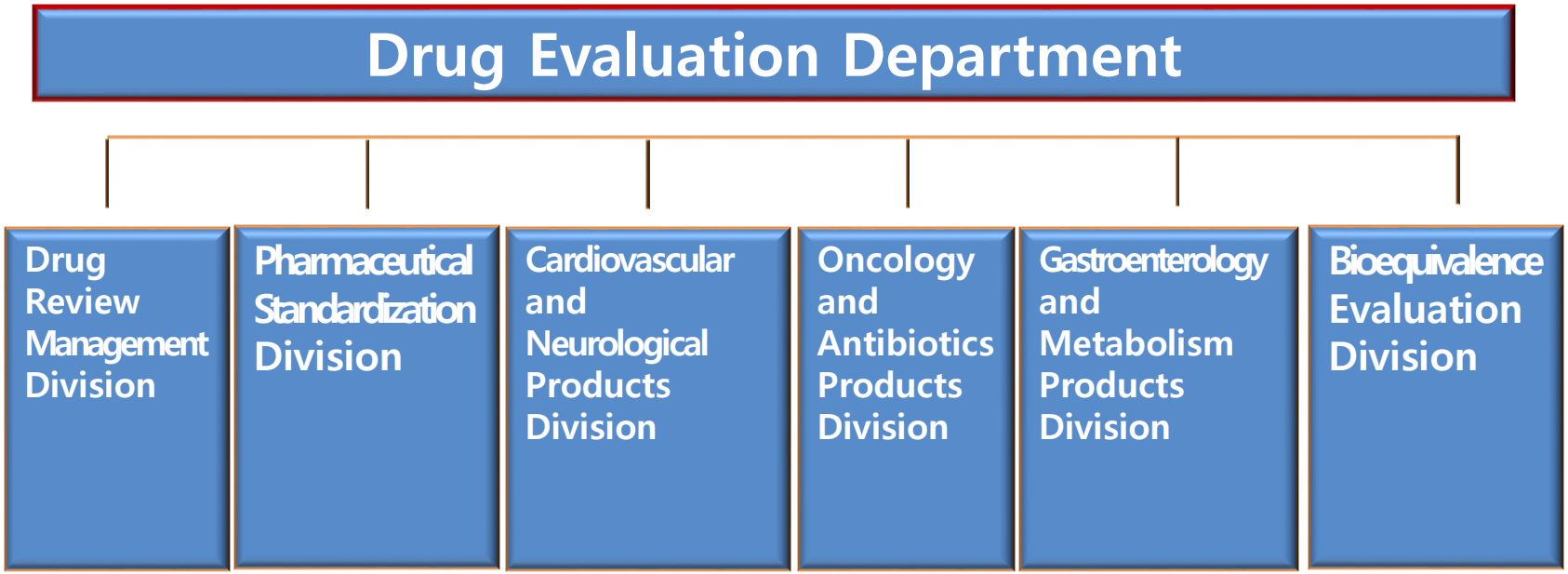
NIFDS-Drug Evaluation Department



- ✓ 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

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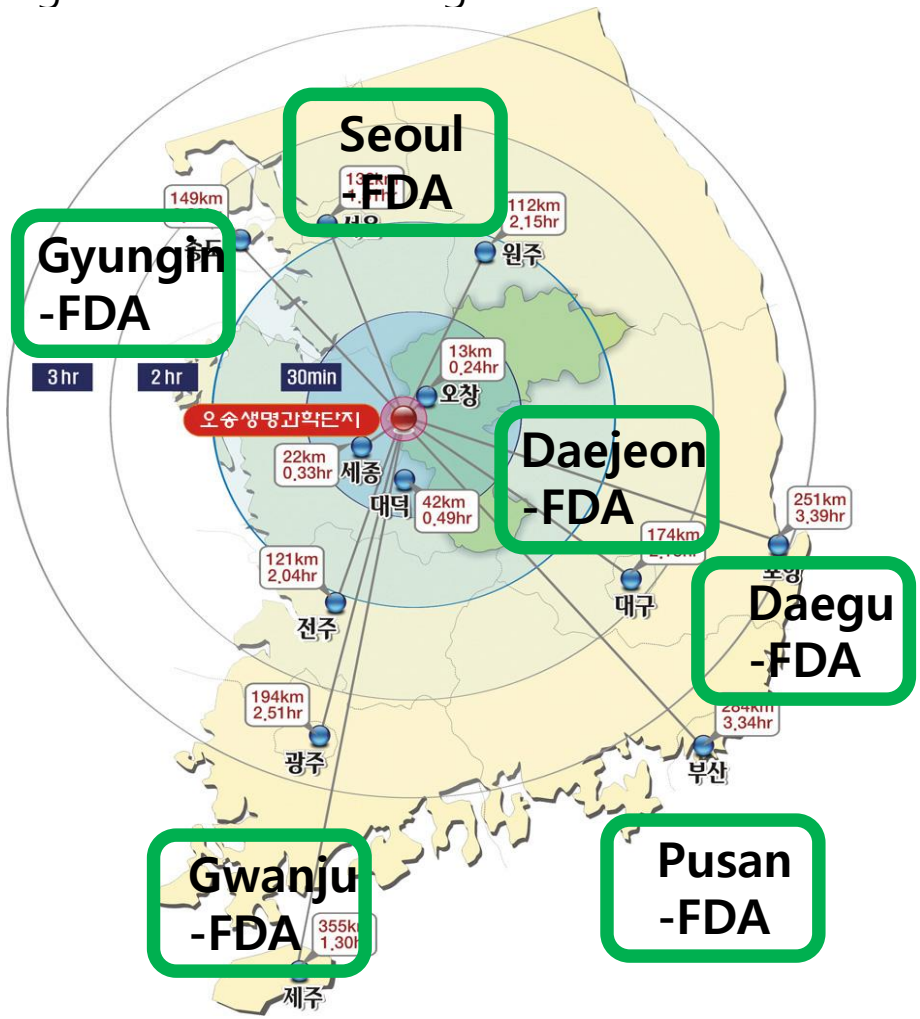
Regional-FDA

6 Regional Food and Drug Administration



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ICH Q3D guideline application in Korea

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

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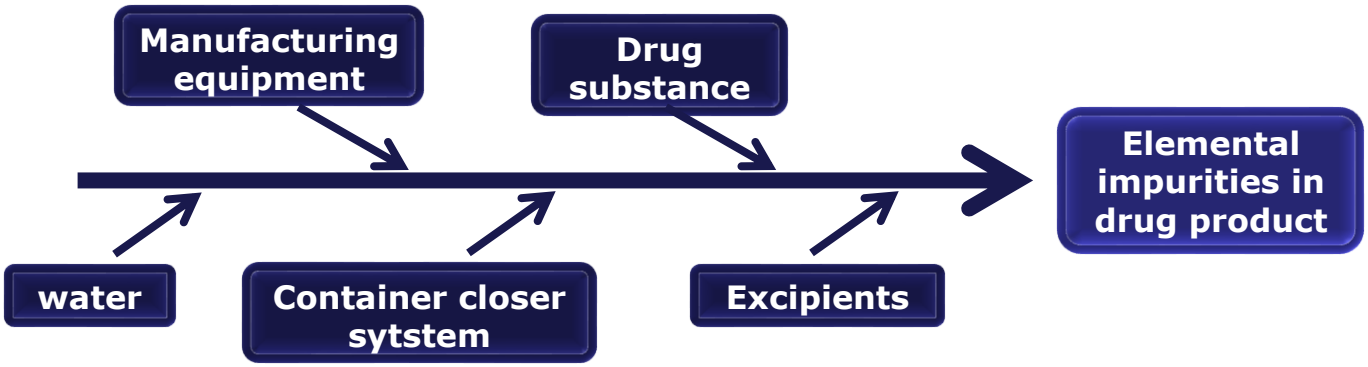
In the Drug Products

- **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>

➡ ***Implemented in July of 2002***

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DMF Introduction and Expansion

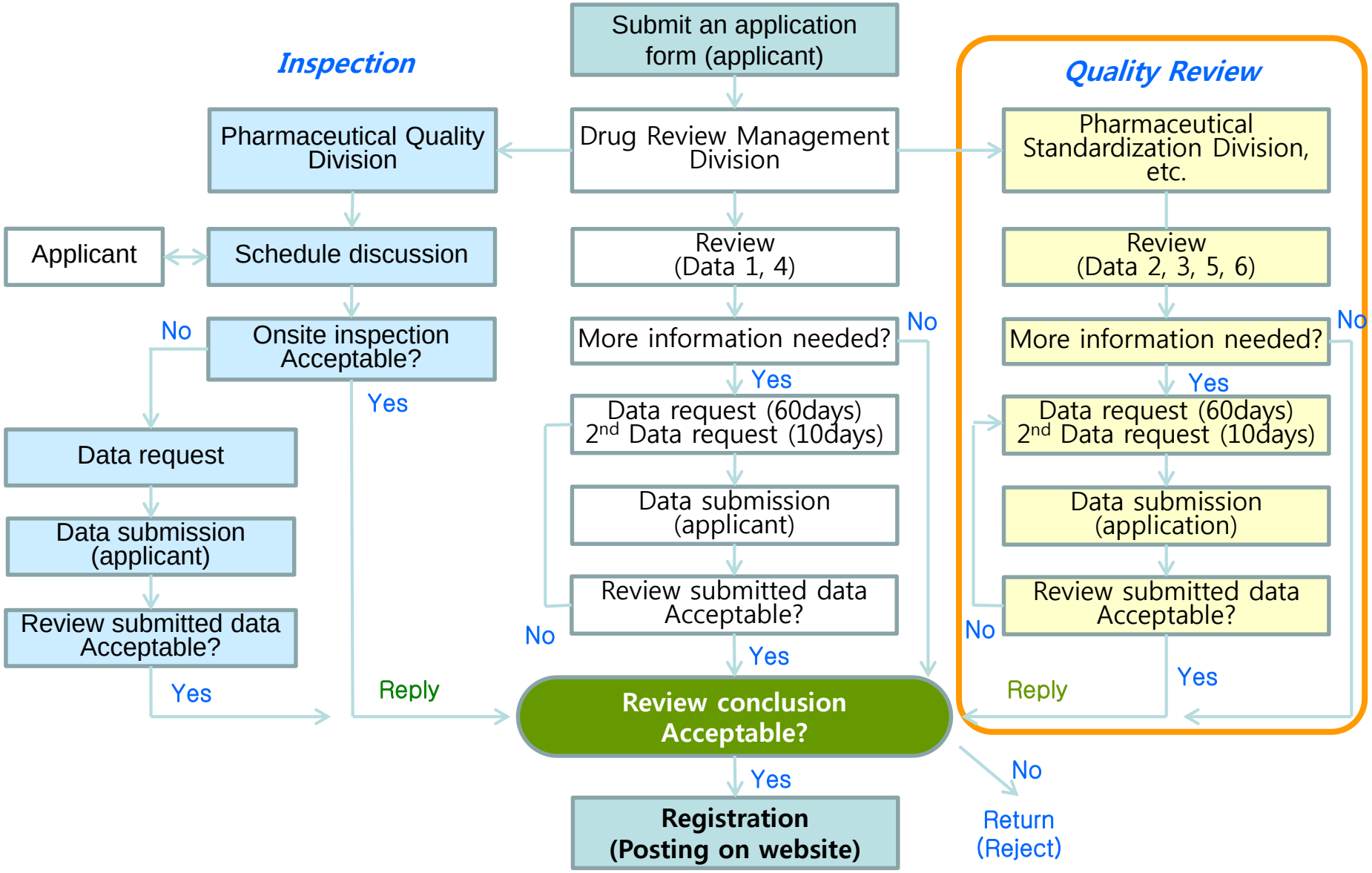
- Introduction of drug substance registration system (DMF)
  - July 1 of 2002, active drug substance for new drug

- Expansion of its subjects step by step
  - Since 2005, annually expanded step by step to much-used 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 (www.mfds.go.kr) *(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)

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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
1. 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 · organic impurities · inorganic impurities (elemental impurities) · residual impurities (3) Domestic/ foreign patent information	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 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 ㎥	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 ㎥	HC-22	C, S, Cr, Ni, Mn, Si, Mo, Fe, P, V, W, Co

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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

Element	Class	1	2	3	4	5	6	7
		Intentionally 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
Co	2A	No	Yes	No	No	N/A	1.50μg/g	Needed management
V	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
Tl	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)

Element	Class	1	2	3	4	5	6	7
		Intentionally 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
Ba	3	No	No	No	No	N/A	N/A	Not needed management
Mo	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
		ppm(μg/g)
Cd	1	0.5
Pb	1	0.5
As	1	1.5
Hg	1	3
Co	2A	5
V	2A	10
Ni	2A	20
Se	2B	15
Li	3	55
Mo	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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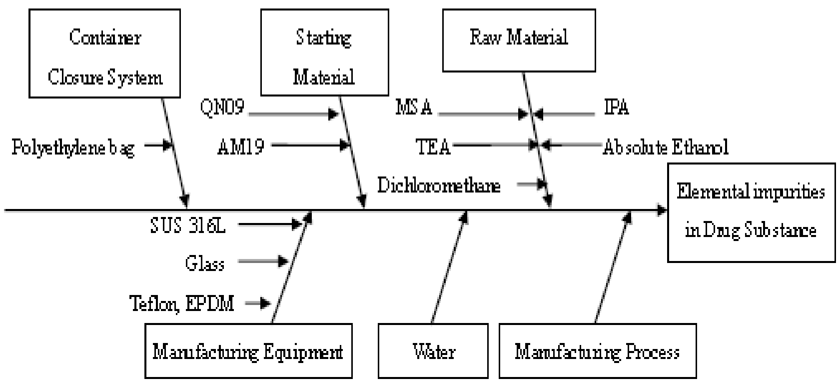

구분	자재명	제조사	Potentially present?	Intentionally added	비고
Staring Material	QN09 (... -pyl- 6-... hydro-4- ox... -3- ...) [illegible]	[illegible]	No	No	N/A
	AM19 (... amino- ...) [illegible]	J... P... cos	No	Pd	[illegible] 사 비중발이나 [illegible] 사와 공정 유사하므로 동일하게 평가 진행함
Raw Material	MSA [illegible]	[illegible] mio	Pb (<5 ug/g)	No	AAS 로 1종 분석(Pb)
	TEA [illegible]	BASF	No	No	업체 자료 및 구두 답변 참고함
	Dichloromethane [illegible]	[illegible]	No	No	ICP-OES 로 3종 분석(Cd, Hg, Pd)
	Absolute Ethanol [illegible]	[illegible]	No	No	ICP-MS 로 16종 분석(Cd, Pb, As, Co, V, Ni, Tl, Au, Ag, Li, Sb, Ba, Mo, Cu, Sn, Cr)
	IPA (Isopropyl ...) [illegible]	[illegible] Che... (...)	No	No	N/A

구분	자재명	제조사	Potentially present?	Intentionally added	비고
Container Closure System	Polyethylene bag (PE bag)		No	No	AAS 로 4종 분석(Pb, Cd, Hg, Cr). RoHS approved

재질(Material)	해당 설비 및 부속품	Composition	용제의 용출 불순물
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, Mn, Si, P, S	Cr, Ni, Mo
Teflon	가스켓 (예, 배관재질부위, Filter housing 재질부위)	C, F	N/A
Glass	F/D Sight Glass	Si, Na, Ba, Zr, B, Ca	N/A
EPDM	[illegible] Sheet	C	N/A
Polypropylene	Filter (예, 용매 여과)	C	N/A
Nylon66	Filter (예, 흡습)	C, O, N	N/A

* Comment : Fe, B, Al, W, Zn, K, Ca, Na, Mn, Mg 등과 같은 금속불순물은 ICH Q3D 가이드에 따라 위해평가 수행 해당 사항 없음.

구분	시험명	시험기준		비고
주간시험 (Weekly test)	TOC(ppb)	Alert level	200 이하	USP, EP 시험항목
		Action level	Alert Level 재초과시	
		Guideline reference level	500 이하	
	전도도(μs/cm)	Alert level	25 ℃: 1.1 이하	
		Action level	Alert Level 재초과시	
		Guideline reference level	25 ℃: 1.3 이하	
	일반세균 (CFU/200mL)*	Alert level	4 이하	
		Action level	10 이하	
		Guideline reference level	20 이하	
	엔도톡신 (EU/mL)	Alert level	0.03 이하	
		Action level	0.06 이하	
		Guideline reference level	0.25 이하	
분기시험 (Quarterly test)	Appearance	무색 투명 투피의 불순 없		EP 시험 항목
	Nitrates	적합(0.2ppm 이하)		
	Heavy metal	적합(0.1ppm 이하)		

구분	공정명	공정조건 (Min~Max ℃)	설비 재질	재질 내구성	금속불순물 유출 가능성
EF01	Coupling 반응	0~26℃	Glass Lined Mild Steel	≤50℃에서 내구성 문제 없음 in NaOH, NH3	유출 가능성 없음
	진공 건조	65~75℃	SUS 316L	≤420℃에서 내구성 문제 없음	유출 가능성 없음
EF02	Saltformation 반응	30~35℃	Glass Lined Mild Steel	≤110℃에서 내구성 문제 없음 in HCl, H2SO4	유출 가능성 없음
	진공 건조	50℃	SUS 316L	≤420℃에서 내구성 문제 없음	유출 가능성 없음
EF03	Recrystallization 반응	0~55℃	SUS 316L	≤420℃에서 내구성 문제 없음	유출 가능성 없음
	진공 건조	55℃	SUS 316L	≤420℃에서 내구성 문제 없음	유출 가능성 없음

구분	공정명	공정조건 (Min~Max ℃)	설비 재질	재질 내구성	금속불순물 유출 가능성
EF01	Coupling 반응	0~26℃	Glass Lined Mild Steel	≤50℃에서 내구성 문제 없음 in NaOH, NH3	유출 가능성 없음
	진공 건조	65~75℃	SUS 316L	≤420℃에서 내구성 문제 없음	유출 가능성 없음
EF02	Saltformation 반응	30~35℃	Glass Lined Mild Steel	≤110℃에서 내구성 문제 없음 in HCl, H2SO4	유출 가능성 없음
	진공 건조	50℃	SUS 316L	≤420℃에서 내구성 문제 없음	유출 가능성 없음
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	진공 건조	55℃	SUS 316L	≤420℃에서 내구성 문제 없음	유출 가능성 없음

Element	Class	Potential elemental impurity derived from
Cd (Cadmium)	1	For reference
Pb (Lead)	1	Raw materials (MSA)
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 (Molybdenum)	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 (Mercury)	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 (Molybdenum)	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 (ppb)	*Result of Analysis(ppb) QUB17013		*Result of Analysis(ppb) QUB17014		*Result of Analysis(ppb) QUB17015		Site
					결과	판정	결과	판정	결과	판정	
Cd (Cadmium)	1	≤0.2	≤200	≤60	반도이하	적합	반도이하	적합	반도이하	적합	의산 ICP-OES
Pb (Lead)	1	≤0.5	≤500	≤150	반도이하	적합	반도이하	적합	반도이하	적합	연구소 ICP-MS
As (Arsenic)	1	≤1.5	≤1500	≤450	반도이하	적합	반도이하	적합	반도이하	적합	연구소 ICP-MS
Hg (Mercury)	1	≤0.3	≤300	≤90	반도이하	적합	반도이하	적합	반도이하	적합	연구소 ICP-MS
Co (Cobalt)	2A	≤0.5	≤500	≤150	반도이하	적합	반도이하	적합	반도이하	적합	의산 ICP-OES
V (Vanadium)	2A	≤1	≤1000	≤300	반도이하	적합	반도이하	적합	반도이하	적합	연구소 ICP-MS
Ni (Nickel)	2A	≤2	≤2000	≤600	반도이하	적합	반도이하	적합	반도이하	적합	의산 ICP-OES
Pd (Palladium)	2B	≤1	≤1000	≤300	반도이하	적합	반도이하	적합	반도이하	적합	연구소 ICP-MS
Li (Lithium)	3	≤25	≤25000	≤7500	반도이하	적합	반도이하	적합	반도이하	적합	의산 ICP-OES
Sb (Antimony)	3	≤9	≤9000	≤2700	반도이하	적합	반도이하	적합	반도이하	적합	의산 ICP-OES
Mo (Molybdenum)	3	≤150	≤150000	≤45000	반도이하	적합	반도이하	적합	반도이하	적합	의산 ICP-OES
Cu (Copper)	3	30	≤30000	≤9000	반도이하	적합	반도이하	적합	반도이하	적합	의산 ICP-OES
Cr (Chromium)	3	110	≤110000	≤33000	반도이하	적합	반도이하	적합	반도이하	적합	의산 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)

MINISTRY OF FOOD AND DRUG SAFETY

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

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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

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Thank You

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