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Current Approach for Control of Nitrosamine Impurities in Japan

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Daito Pharmaceutical Co.,Ltd.
Quality & Regulatory Affairs
Regulatory Affairs
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Today's Topics

- Company Profile (Daito Pharmaceutical Co.,Ltd.)
- Outline for Control of Nitrosamine Impurities
- Actions for Control of Nitrosamine Impurities at Daito
- Draft Guideline for Nitrosamine Impurities in Japan

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Company Profile
(Daito Pharmaceutical Co.,Ltd.)

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Company Profile

Established : June, 1942

Location : Toyama-City, Toyama Pref.

Representative : OTSUGA Yasunobu, CEO

Capital : JPY 5.37 billion

Sales : JPY 44.99 billion (as of May, 2020)

Employees : 624 (as of May, 2020)

Business Activities :

Manufacture, sales, and Import/Export of Pharmaceutical Products (FDFs) and APIs

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Outline for Control of Nitrosamine Impurities

Cases of Nitrosamine contamination

Period	Product (API)	Contaminated Nitrosamine	Contamination Route
Jul., 2018	Valsartan	NDMA	Manufacturing Process
Sep., 2018	Irbesartan	NDEA	Manufacturing Process
Mar., 2019	Losartan Potassium	NMBA	Manufacturing Process
Sep., 2019	Ranitidine Hydrochloride	NDMA	Degradation
Sep.,2019	Nizatidine	NDMA	Degradation

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Requirements for Control of Nitrosamine

Several guidelines were published by the agencies

- **Information on nitrosamines for marketing authorization holders (EMA/189634/2019)**
- **Questions and answers on “Information on nitrosamines for marketing authorization holders” (EMA/CHMP/428592/2019 Rev.1)**
- **Control of Nitrosamine Impurities in Human Drugs(U.S.FDA Guidance for Industry 2020.09) etc.**

Major Nitrosamines and each allowable limit are shown in the guidelines

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Major Nitrosamines and Proposed Limits

Compound name	Abbreviation	Allowable limit value(ng/Day)*	
		EMA	FDA
N-Nitrosodimethylamine	NDMA	96.0	96
N-Nitrosodiethylamine	NDEA	26.5	26.5
N-Nitrosodiisopropylamine	NDIPA	26.5	26.5
N-Nitrosodi-n-butylamine	NDBA	26.5	26.5
N-Nitrosoethylisopropylamine	NEIPA	26.5	26.5
N-Nitrosopiperidine	NPPR	26.5	-
N-Nitrosomethylphenylamine	NMPA	26.5	26.5
N-Nitroso-N-methyl-4-aminobutyric acid	NMBA	96.0	96

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Requirement for Control in Japan

In Japan・・・

「Control for Genotoxic Impurities in Sartan Products」 (Office Memorandum on Nov. 14, 2018)

The following results for Sartan FDFs were reported.

① Risk evaluation for generation of NDMA/NDEA

② Measurement results of all API lots used for the Sartan FDFs within the effective period

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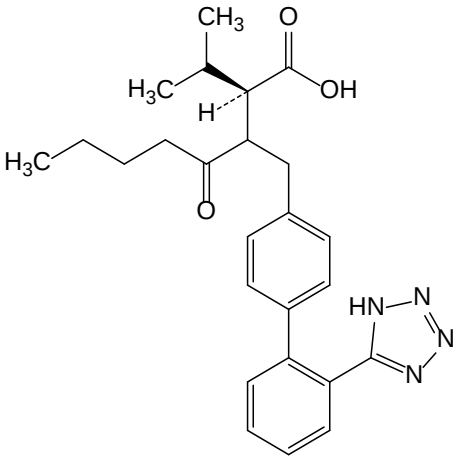
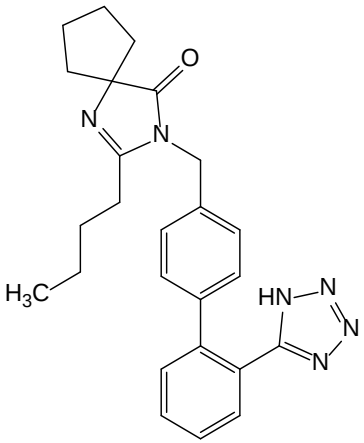
Actions for Control of Nitrosamine Impurities at Daito

Sartan Products manufactured by Daito

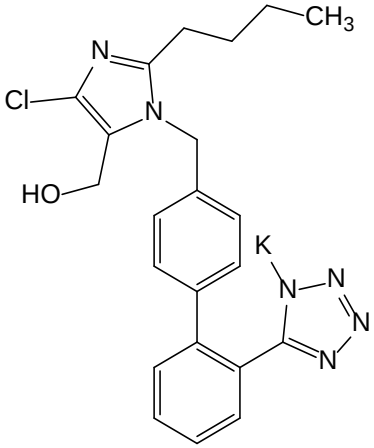
Product Name	FDF	API
Valsartan	In-house	In-house
Irbesartan	In-house	In-house
Losartan Potassium	In-house	In-house
Olmesartan Medoxomil	N/A (Only for API sales)	In-house



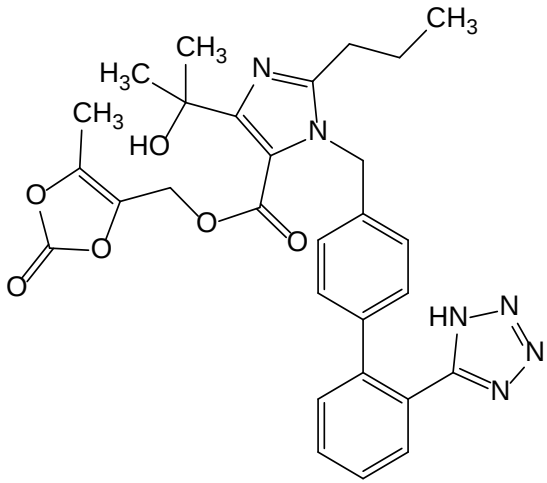
Valsartan



Irbesartan



Losartan potassium



Olmesartan Medoxomil

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Investigation for Nitrosamins in Sartan APIs

1. Valsartan

Manufacturing Site	DMF	Step	Usage of nitrosating agents	Usage of Amines	Generation of Nitrosamines
Mfg. Site A (Starting Material)	No	Step-1	○	○	Yes (NDEA)
		Step-2	×	○	No
		Step-3	×	×	No
Mfg. Site B (Intermediate)	Yes	Step-4	×	○	No
		Step-5	×	×	No
		Step-6	×	○	No
		Step-7	×	×	No
Daito (API)		Step-8	×	×	No
		Step-9	×	×	No
		Step-10	×	×	No

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Investigation for Nitrosamins in Sartan APIs

2. Irbesartan

Manufacturing Site	DMF	Step	Usage of nitrosating agents	Usage of Amines	Generation of Nitrosamines
Mfg. Site A (Intermediate①)	Yes	Step-1	○	○	Yes (NDEA)
		Step-2	×	○	No
		Step-3	×	×	No
Mfg. Site B (Intermediate②)		Step-4	×	○	No
		Step-5	×	×	No
		Step-6	×	○	No
		Step-7	×	×	No
Daito (API)		Step-8	×	×	No

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Investigation for Nitrosamins in Sartan APIs

3. Losartan Potassium

Manufacturing Site	DMF	Step	Usage of nitrosating agents	Usage of Amines	Generation of Nitrosamines
Mfg. Site A (Starting Material)	No	Step-1	○	○	Yes (NDEA)
		Step-2	×	○	No
		Step-3	×	×	No
Mfg. Site B (Intermediate)	Yes	Step-4	×	○	No
		Step-5	×	×	No
		Step-6	×	○	No
		Step-7	×	×	No
Daito (API)		Step-8	×	×	No
		Step-9	×	×	No

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Investigation for Nitrosamins in Sartan APIs

4. Olmesartan Medoxomil

Manufacturing Site	DMF	Step	Usage of nitrosating agents	Usage of Amines	Generation of Nitrosamines
Mfg. Site A Mfg. Site B (Starting material)	No	Step-1	Site A : ○	○	Yes (NDEA)
			Site B : ×	○	No
		Step-2	×	○	No
		Step-3	×	○	No
		Step-4	×	×	No
Mfg. Site C (Intermediate)	Yes	Step-5	×	×	No
		Step-6	×	○	No
		Step-7	×	×	No
Daito (API)		Step-8	×	×	No
		Step-9	×	×	No

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Summary of Investigation

Results for Nitrosamines contamination risk

Product Name	Risk Evaluation for Nitrosamine Contamination			
	Risk	Risk Process	Type of Nitrosamine	MF
Valsartan	Yes	Most upstream (Step-1)	NDEA	No
Irbesartan	Yes	Most upstream (Step-1)	NDEA	Yes
Losartan Potassium	Yes	Most upstream (Step-1)	NDEA	No
Olmesartan Medoxomil	Yes	Most upstream (Step-1)	NDEA	No

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Control of Nitrosamine in Sartan API①

Discussion for Control of Nitrosamine (as of 2019)

◆ Daito

- No analytical instrument (LC-MS, GC-MS, etc.) was installed.
- Spike study of upstream process was considered to understand fate factor in the processes; however, the spike study could not be executed because Daito had no experience for manufacturing of the upstream processes.

Control of Nitrosamine in Sartan API①

Discussion for Control of Nitrosamine (as of 2019)

◆ Manufacturing Site for SM/Intermediates

- No analytical instrument (LC-Ms, GC-MS, etc.) was installed.
- Execution of spike study was requested to the sites; however, the study was not performed since the sites did not understand the necessity of the study.

  Valsartan/Losartan/Olmesartan

  ＞Because the process is out of the DMF

  Irbesartan

  ＞The site agreed to conduct spike study because the process is within the DMF; however, there were difficulties in scheduling.

It was decided to conduct measurement of API, and the measurement was contracted to external analytical laboratories.

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Control of Nitrosamine in Sartan API①

API Name	No. of Lots	NDMA*	NDEA
Valsartan	99	N.D.（12）	N.D.
Irbesartan	30	N.D.（14）	N.D.
Losartan Potassium	284	N.D.（14）	N.D.
Olmesartan Medoxomil	38	N.D.（20）	N.D.

Quantitative limit : NDMA 0.1ppm, NDEA 0.1ppm

＊as of Apr. 2019

＊It was concluded that there was no risk of NDMA contamination; however, measurements were conducted according to the office memorandum

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Control of Nitrosamine in Sartan API②

The following actions were decided as next step.

◆ **Valsartan/Losartan/Olmesartan**

➡ **Continue the measurement for NDEA of API (Limit: Not detected)**

◆ **Irbesartan (As response to DMF inquiries in 2019)**

➡ **Spike study for NDEA was executed (to confirm fate factor)**

Material	NDEA result	Set limit
Intermediate①	2,000 ppm (Spiked volume)	0.133 ppm*
Intermediate②	0.32 ppm	0.02 ppm
API	-	Not detected

＊Allowable limit of NDEA in guidelines

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Control of Nitrosamine in Sartan API③

Issues and Measures for Risk Reduction

◆ **Issues**

- Understanding for mfg. process was insufficient.
- Too much spiked volume (insufficient evidence for fate)
- LOQ of analytical method is too high (insufficient accuracy).

◆ **Measures for risk reduction**

- Analytical method development (LOQ : NMT0.03 ppm)
- Discontinuation of usage of recovered solvents in the process in which Nitrosamine is generated.
- Control of Nitrosamines for other products

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Current Activities at Daito

Preparation of Risk Assessment Protocol

Subjected product : Own product (API:49, FDF:122)

Risk based Assessment

- Generation in Mfg. processes
- Contamination from raw materials
  (Raw materials, additives, water, recovered solvent)
- Contamination from primary packaging material
- Cross contamination from Equipment shared products
- Degradation during storage

If assessed as “Risk”. . .

Measurement is conducted to evaluate the contamination level

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Nitrosamine Contamination Risk Assessment

◆ Generation by reaction (Mfg. Process, etc.)

Nitrosamines are generated by reaction of nitrosating agents and amino compounds

→ Evaluation was conducted if the following conditions were applicable

- Nitrosation of amines (secondary or tertiary) or its salts
- Chemoselective nitrosation of amines (secondary or tertiary) under mild or heterogeneous conditions.
- Photo-oxidation of formamides followed by degradation of formed intermediates.
- Conversion to thionitrile by sulphurisation / nitrosation of thiol
- Biological catalysis of amines
- Oxidation of alkylhydrazines by oxidizing agents such as Ozone, exygen etc.
- Nitrosation of alkylhydrazine derivatives.
- Reaction of Nitrosamine compound precursors and mono / dichloramines.

＊Refer to Appendix for the details

Nitrosamine Contamination Risk Assessment

◆ Contamination from Used Materials

Questionnaire was requested to all manufacturers of purchased raw materials / packaging materials

→ Nitrosamine contamination risk is under assessment according to the responses.

Type of Material	No. of requests	No. of responses
Raw Material (API)	220	214
Raw Material (FDF)	335	326
Primary packaging material	771	759
Total	1326	1299

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Nitrosamine Contamination Risk Assessment

◆ Cross Contamination from Equipment shared Products

Equipment usage list was prepared

→ Presence/absence of equipment share with “Risk” products

Product	Risk of Nitrosamines	Used Equipment						Cross contamination risk
		Reactor 1	Reactor 2	Centrifuge 1	Centrifuge 2	Dryer 1	Dryer 2	
A	Yes	-	○	○	-	-	○	Yes
B	No	○	-	-	○	○	-	No
C	No	-	○	-	○	○	-	Yes
D	No	○	-	-	○	-	○	Yes

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Issues for Risk Assessment

- Since all materials should be investigated, thousands of questionnaires are needed.
- It is difficult to collect the questionnaires from the manufacturers who have less understanding for Japanese requirement (especially foreign/chemical manufacturer)
- In case the purchased volume is small, it might be difficult to have cooperation by the manufacturer

So many resources are needed to collect the information for materials

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Issues for Risk Assessment

- Knowledge and understanding for chemical reaction are needed for principle of Nitorosamine generation during mfg. processes and storaging.
- For the Nitrosamines which are known that carcinogenic risk is very low, there is room to study for treatment of such Nitrosamines in case they are assessed as "Risk" (N-Nitrosomethyl-t-butylamine, N-Nitrosoproline, etc.)

Decision based on knowledge of organic chemistry/toxicity is needed

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Issues for Risk Assessment

- **Basically, the manufacturing of generic products (APIs and FDFs) is conducted with shared equipment. Therefore, volume of investigation of cross contamination risk from equipment shared product become big.**

Evaluation of cleaning confirmation, equipment usage, control of mfg. schedule, etc. became too complicated to consider the risk reduction

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Issues for Risk Assessment

- The specific analytical instrument is required due to very low allowable limit.
- Establishment of analytical method might be difficult due to generation of degradation impurities.

- Due to many products, it might take lots of resources for establishment of analytical method.
- Limited analysts can perform the measurement since it needs special instrument

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Draft Guideline for Nitrosamine Impurities in Japan

Draft Guideline for Nitrosamines ①

(Issues under discussion)

1. Applicable range for risk assessment

(whether to include Biological product)

→ FDA : All products manufactured by chemical synthesis
EMA : Biological product is also included

2. Procedure of risk assessment

(Cause of contamination, risk assessment method, analytical method, etc.)

→ Which guidance (FDA, EMA) shall be followed (or both)?

*MHLW: Ministry of Health, Labour and Welfare
*FPMAJ: Federation of Pharmaceutical Manufacturer's Association of Japan

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Draft Guideline for Nitrosamines ②

3. Allowable limit for known Nitrosamines

→ Judgement for Nitrosamines, the limits of which are different between the guidelines of FDA and EMA

4. Timelines for implementing changes for risk evaluation, measurement, and risk reduction

Risk Evaluation :

In the initial guidance timeline was within 6 months for both of FDA, EMA.
After that,
EMA extended the timeline to March, 2021
(18 months from initial guidance), and
FDA extended the timeline to March,2021
(7 months from initial guidance)

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Draft Guideline for Nitrosamines ③

4. Timelines for implementing changes for risk evaluation, measurement, and risk reduction (cont.)

Changes for risk reduction :

Limit date of confirmation study is within 3 years from the initial guidance for both of EMA/FDA. (EMA : Aug., 2022, FDA : Jul., 2023)

Regulatory submission :

EMA : Product which uses chemical synthesis API is within 3 years from the initial guidance (by Aug. 2022)
Product which uses non-chemical synthesis API (including biological product) (by Jul. 2023)

FDA : Within 3 years from the initial guidance (by Jul. 2023)

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Mt. Tateyama at Toyama in April or May