



Hamari Chemicals Ltd.

“Technology for life”

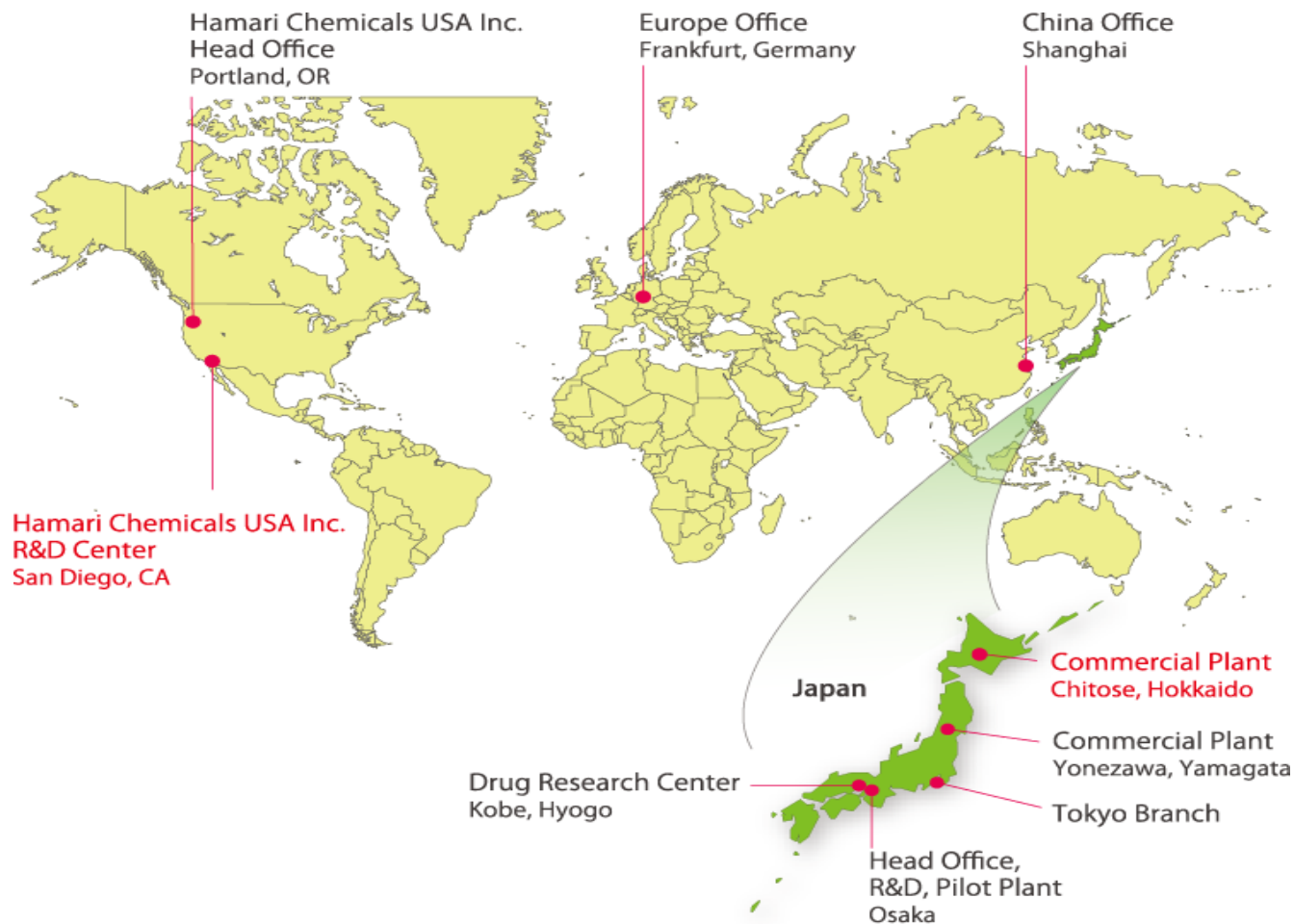


Who are we?

- **Global supplier of custom manufactured API's and Intermediates**
- **Established in 1948**
- **Turnover: 5.6B Yen (USD ~70M) [2010]**



Locations



Custom Chemical Manufacturing Technology

More than 60 different synthesis reactions on a commercial scale

Strengths: **Amino acid derivatives**
 Oligopeptides
 Optically active compounds



A look back to the beginning...

- 1948 Hamari's first product: **Saccharin**
- 1950 first API: **Quinine Ethylcarbonate**
- 1957 first custom synthesis: **Orotic acid**
- 1961 first Amino acid: **DL-Methionin**
- 1962 first Amino acid derivative: **Methyl Methionine Sulfonium Chloride**
- 1966 first peptide in laboratory: **L-Leucil L-Leucine**
- 1968 first peptide on commercial scale: **L-Glycil L-Glycine**
- 1970 first peptide on a multi-ton scale: **β -Alanyl L-Histidine**



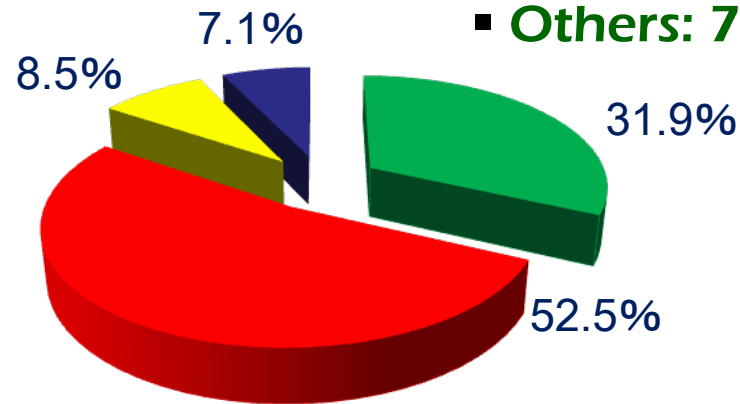
- 1970 first contract manufacturing: protected Amino Acids
- 1976 first contract manufacturing with multi-step synthesis
- 1985 first FDA approved product: **Ibuprofen**
- 1997 FDA inspection of the Yonezawa facility
- 2001 ISO 14001 Certification of the Yonezawa facility
- 2002 launch Zinc Carnosine in US marketplace
- 2006 two Separate FDA inspections of the Yonezawa facility
- 2008 establishment of a high-potency laboratory and a kilo-scale laboratory in
the Osaka facility
- 2008 establishment of the Kobe laboratory



Sales in 2011

▪ Sales volume: 71 million USD (Fiscal 2011)

- Intermediates: 31.9%
- API: 52.5%
- Nutritional Ingredients: 8.5%
- Others: 7.1%

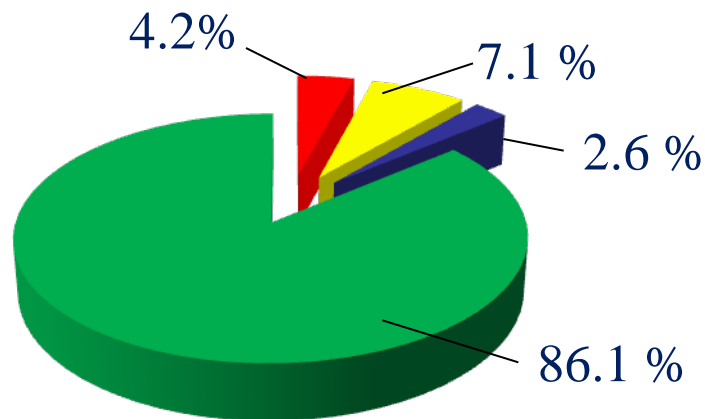


■ Intermediates ■ API ■ Nutritional Ingredients ■ Others



Our customers by region

- Europe: 7.1 %
- Japan: 86.1%
- America: 4.2 %
- Others: 2.6 %



■ America ■ Europe ■ Others ■ Japan



API Examples (Commercial Products)




| Product Name | Manufacturing Site | Annual Production Amount | Delivery Location |
|------------------------------|--------------------|--------------------------|---------------------|
| Polaprezinc / Zinc Carnosine | Yonezawa | 11 t | Domestic and USA |
| Benfotiamine | Yonezawa | 50 t | Domestic and Europe |
| Tamsulosin HCl | Osaka | 26 kg | Domestic |

* Final intermediate



Food Supplement Products Sold in the US

Hamari has been supplying food supplement ingredients to the US market for over than 20 years.

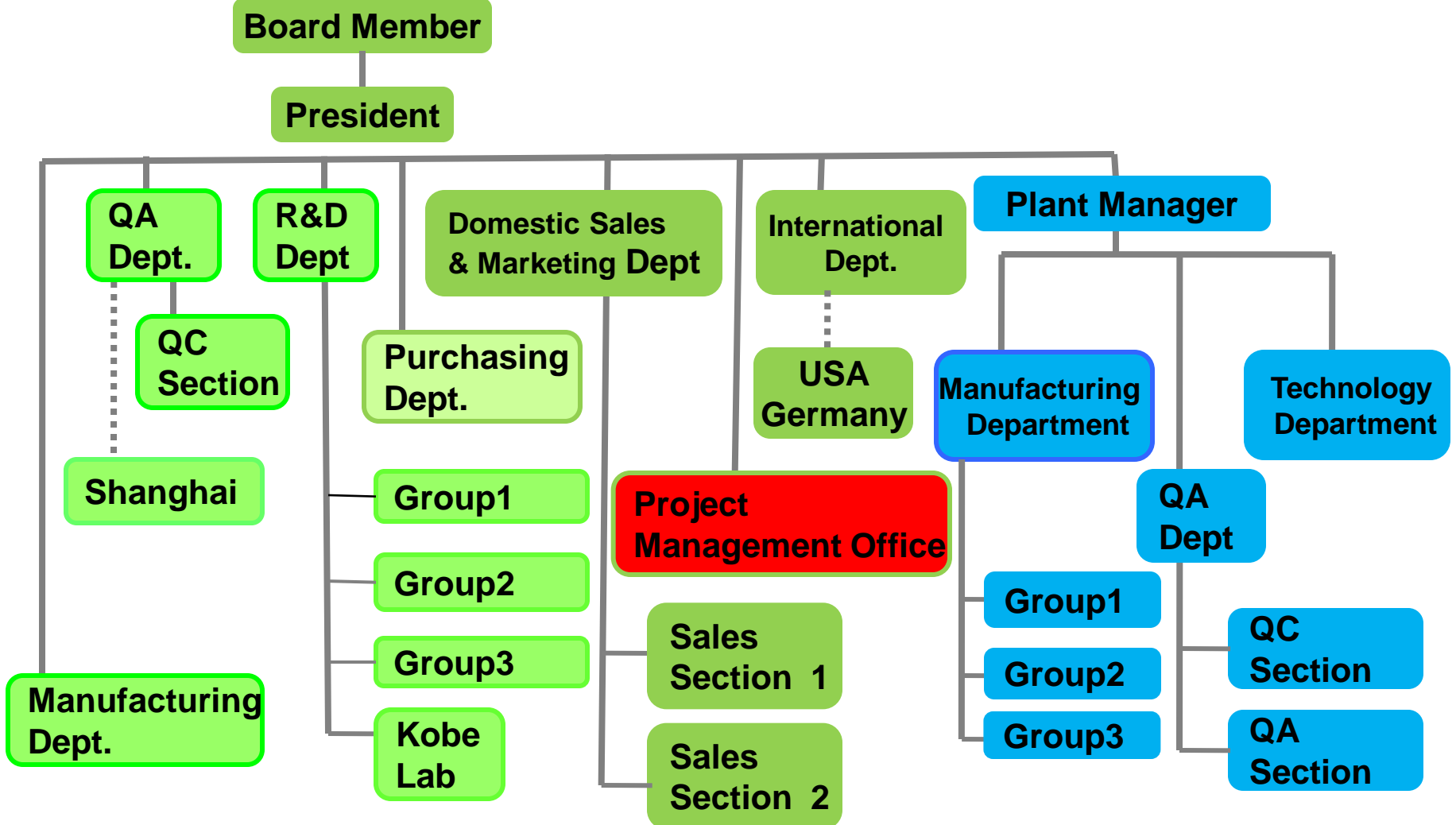
| <u>Chemical Name</u> | <u>Brand name</u> | <u>Trademark</u> |
|---|-------------------|---|
| ■ Zinc Carnosine (L-Carnosine Zinc complex) | Pepzin GI |  |
| ■ Benfotiamine (Vitamin B1 derivative) | BenfoPure |  |
| ■ L- Carnosine (β-alanyl-L-histidine) | CarnoLife |  |





Hamari (Osaka)

Yonezawa Hamari



Hamari Chemicals-Osaka

Sales &

Marketing Dept.(12)

International Dept.(4)

R&D Dept. (36)

Manufacturing Dept.(14)

- Process Development
- Scale up, Pilot production
- non-GMP Production
- GMP Production

QA Dept.(5)

QC Section (9)

- Analytical study
- Method Validation
- Stability Test

Manufacturing gram-100 kg

(Lab, Pilot, Pre-clinical, Ph I , Ph II a)

Yonezawa Hamari Chemicals

Technology Dept.(10)

- Process Optimization
- GMP Production
- Process Validation

QA Dept.(9)

- CMC Preparation
- Pre-approval Inspection

QC Section (21)

- Method Validation
- Stability Test

Manufacturing Dept.(87)

- GMP Production
- Validation Batch
- Commercial Production

Manufacturing 50-200kg

(Ph II b, Ph III, Validation, Commercial)



**Technical
Transfer**



Hamari Chemicals, Ltd.

Quality and R&D Employees

| Research & Development | Total | Osaka | Yonezawa |
|-----------------------------------|--------------|--------------|-----------------|
| New products | 3 | 3 | 0 |
| Process Chemistry | 43 | 33 | 10 |
| Quality | Total | Osaka | Yonezawa |
| QA | 14 | 5 | 9 |
| QC | 30 | 9 | 21 |



Osaka

- Size 1970 m²
- New low temperature cooling system
- Total reactor capacity > 21 m³ , from 50 – 2000 L
- 0.5 KPa – 0.96 MPa , -90 – 150 °C
- Two clean rooms
- Autoclaves, resin columns, centrifuges, dryers, mills...



Yonezawa

- Size 52.806 m²
- Production started in 1981
- Total reactor capacity >240 m³, from 200 – 5000 L
- 12 independent product lines
- Kilo laboratory
- 1.3 Kpa – 6.8 MPa, -50 – 150 °C
- Autoclaves, centrifuges, dryers, mills, resin columns...



Yonezawa API plant

- Glass-lined 5
- Stainless Steel 12
- Vertical Dryer 2
- Autoclave (1 Mpa) 2500 L



Chitose commercial plant

- Size 56.760 m²
- Foundation: Chemical Factory 1999 Food Factory 1990
- Total reactor capacity 21.4 m³, from 300 – 2000L



| Osaka plant | | 2000 | 1500 | 1200 | 1000 | 500 | 200 | 100 | 50 | 10 | Total | Total (m ³) |
|-------------|-----------|------|------|---------|------|----------|-----|----------|----|----------|-------|-------------------------|
| Reactor | GL | 1 | | 3 | 5 | 3 | 2 | 1 | 1 | | 16 | 12.65 |
| | SUS | 1 | 1 | | 4 | 2 | 2 | 1 | | | 11 | 9.00 |
| Autoclave | GL | | | 0.1 Mpa | | | | | | | 1 | |
| | SUS | | | | | 0.48 Mpa | | 0.19 Mpa | | 0.48 Mpa | 3 | |
| | Hastelloy | | | | | 0.96 Mpa | | | | | 1 | |

Clean room
 ·2 systems
 GL 1000L
 GL 200L

| Yonezawa plant | | 5000 | 4500 | 4000 | 3000 | 2500 | 2000 | 1800 | 1700 | 1600 | 1500 | 1200 | 1000 | 800 | 500 | 200 | Total | Total (m ³) |
|----------------|-----|------|------|------|------|----------|------|----------|----------|------|------|------|----------|-----|----------|-----|-------|-------------------------|
| Reactor | GL | 2 | - | 5 | 14 | 1 | 19 | - | 3 | - | 11 | 4 | 2 | 2 | 5 | 3 | 72 | 145.6 |
| | SUS | - | 1 | - | 6 | 5 | 20 | 3 | 1 | 1 | 12 | - | 14 | 5 | 6 | 1 | 75 | 122.9 |
| Autoclave | SUS | | | | | 0.96 Mpa | | 0.96 Mpa | 0.96 Mpa | | | | 0.19 Mpa | | 0.68 Mpa | | 5 | |

Clean room ·2 systems
 · GL 2000L, GL 800L, GL 200L
 · GL 3000L, SUS3000L

Clean room ·5 systems
 · GL 3000L ×2, GL 2000L, GL 1700L,
 · SUS3000L



Other Equipments

| Osaka | Centrifuge | | Filter | | Dryer | | | Mill | |
|--------------|------------|---------|--------|-------|---------|------------|-------------------|-------------|----------|
| | 24 inch | 36 inch | Vacuum | Press | DBL Con | Tray Dryer | Vacuum Tray Dryer | Cutter Mill | Pin Mill |
| Rubber-lined | | 1 | | | | | 2 | | |
| SUS | 2 | 4 | 4 | 3 | 1(200L) | 3 | 1 | 2 | 1 |
| GL | | | 1 | 1 | 1(800L) | | | | |
| Teflon-lined | | | | 1 | | | 1 | | |

| Yonezawa | Centrifuge | | | Filter | | Dryer | | | | Mill | | | |
|--------------|------------|---------|---------|--------|-------|---------|----------------|------------|-------------------|--------|-----|------|--------|
| | 36 inch | 42 inch | 48 inch | Vacuum | Press | DBL Con | Vertical Dryer | Tray Dryer | Vacuum Tray Dryer | Cutter | Pin | Ball | Hammer |
| Rubber-lined | 4 | | | | | | | | 1 | | | | |
| SUS | 19 | 3 | 1 | 8 | 19 | 3 | 8 | 5 | 5 | 6 | 3 | 1 | 3 |
| GL | | | | 1 | 2 | 4 | | | | | | | |
| Teflon-lined | 2 | | | | | | | | | | | | |

➤ Spray Dryer, Column, Centrifugal-flow Thin-film Vacuum Evaporator, purified water system, etc.



| Equipment | Model | Osaka | | Yonezawa | |
|---------------|--------------------|-------|-----|----------|-----|
| | | QC | R&D | QC | R&D |
| HPLC Gradient | PDA | 3 | 1 | 1 | |
| | UV | 4 | 29 | 13 | 6 |
| UPLC or UFLC | PDA | 1 | | 1 | |
| | UV | | 2 | | |
| HPLC Iso | UV | 1 | 4 | 8 | 4 |
| | Ion Chromatography | 1 | | | |
| | RI | 1 | 1 | 1 | |
| GC Capillary | FID | 3 | 1 | 7 | |
| | Head space sampler | 1 | | 2 | |
| GC Packed | FID/TCD | 1 | | 1 | |
| | FID/ECD | | | 1 | |
| LC/MS | | 1 | | | |
| GC/MS | | | | 1 | |
| NMR | Varian 200MHz | | 2 | | |



| Equipment | Maker | Osaka | Yonezawa |
|--|--------------------------------------|--------------|-----------------|
| Atomic Absorption Spectrophotometer | Shimadzu | | 1 |
| Laser Diffraction Particle Size Analyze | Malvern | | 1 |
| TOC | Hiranuma | | 1 |
| FT/IR | Shimadzu, Jasco | 1 | 2 |
| UV Spectrophotometer | Shimadzu, Jasco | 1 | 1 |
| Polarimeter | Jasco, Horiba | 1 | 1 |
| Karl Fischer | Kyoto Electronics, Mitsubishi | 2 | 2 |
| Electrometric Titrator | Kyoto Electronics, Hiranuma | 1 | 2 |
| DSC | Rigaku | | 1 |
| TG-DTA | Rigaku | | 1 |
| XRD | Rigaku | 1 | |
| Toxinometer | Charles River, Wako | 1 | 1 |

Audit Experience (2008-2010)

| Osaka | Yonezawa |
|-------|----------|
|-------|----------|

| | |
|---|----|
| 2 | 12 |
|---|----|

| | |
|----|----|
| 27 | 63 |
|----|----|

| | |
|---|----|
| 3 | 11 |
|---|----|

Number of Audits

Foreign clients

14

Domestic clients

90

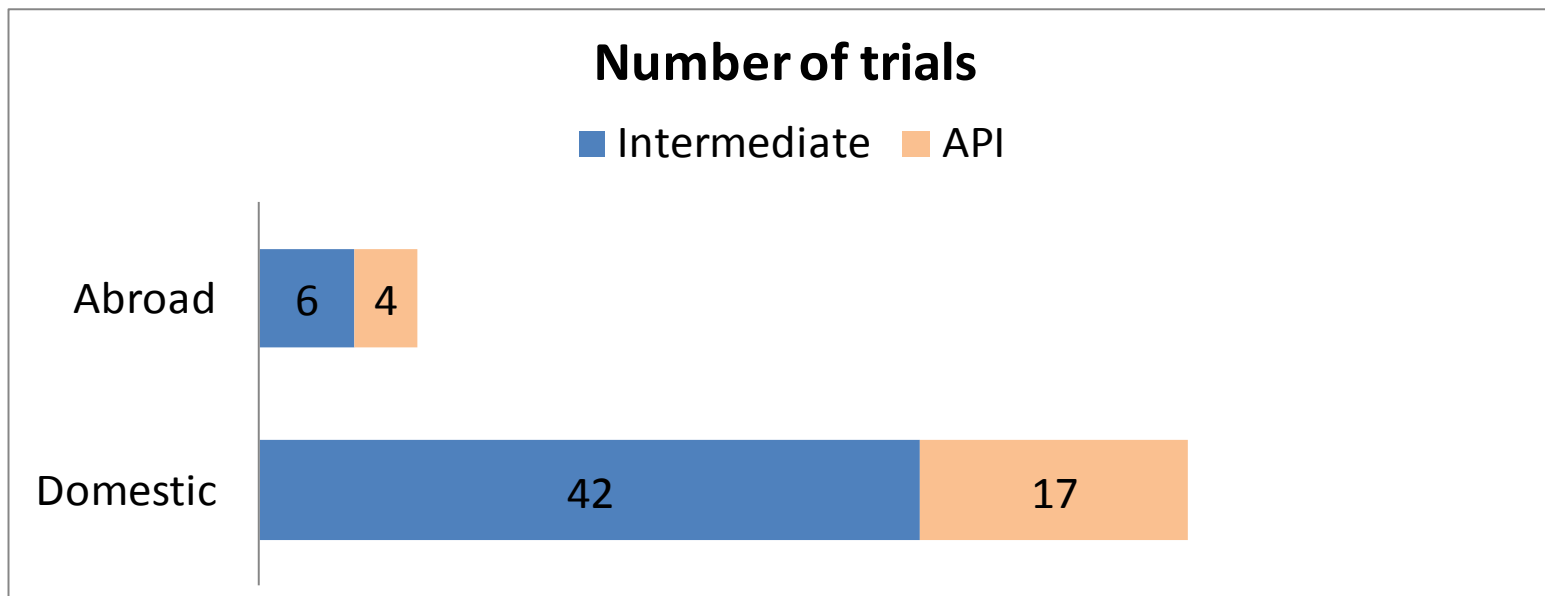
Authorities

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Clinical Trials

(IND manufacturing in 2008-2010)



DMF's Held by Hamari

| | |
|---------------------|----------|
| Type II | 2 |
| EDMF | 1 |
| Korea | 2 |
| Client's DMF | 2 |

| DMF Number | Status | Type | Submit Date | Holder | Subject |
|------------|--------|------|-------------|-------------------------------------|--|
| 21259 | A | II | 1/14/2008 | YONEZAWA HAMARI CHEMICALS CO LTD | POLAPREZINC AS MANUFACTURED IN YAMAGATA, JAPAN |

| DMF Number | Status | Type | Submit Date | Holder | Subject |
|------------|--------|------|-------------|-------------------------------------|---|
| 23196 | A | II | 10/18/2009 | YONEZAWA HAMARI CHEMICALS CO LTD | LULICONAZOLE AS MANUFACTURED IN YAMAGATA, JAPAN |

