GLOBAL TESTING STRATEGY

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INDUSTRIAL CHEMICALS

Around the world

Well known regulatory frameworks in

- USA, Canada, EU, Switzerland, South-Korea, China, Japan, Philippines, Australia, etc.
- What to do with your industrial chemicals when you wish to enter different markets?

CONTENT

COUNTRY SPECIFIC INFORMATION

SOME EXAMPLES

COUNTRY SPECIFIC INFORMATION

USA

- Authority EPA, Inventory TSCA
- Low volume: exemption dossier ,<10t/y
- Polymer: exemption possible (self regulated)
- Only representative cannot be appointed - Authorized person, USA resident must submit via CDX system
- Remarks:
  - Information required: Chemical identity (CAS report), Byproduct information, Production/import volume, Description of uses, human exposure, disposal practices
  - No study requirements with submission, but all available test data must be submitted
  - Effect of TSCA reform

COUNTRY SPECIFIC INFORMATION

Canada

- Authority CEPA, Inventories DSL/NDSL
- Registration levels (Schedules) are tonnage based
- Low volume: ≤100 kg/y exempt, ≤1000 kg/y if NDSL listed
- Polymer: needs registration as such, limited data
  - RRR polymer Schedule 9, NDSL listed Schedule 10
- Only representative: can be appointed (Canadian Agent)
- Remarks:
  - Both NDSL and DSL have public and confidential sections.
  - Substances on USA TSCA inventory for one year are eligible for listing on the NDSL

COUNTRY SPECIFIC INFORMATION

Switzerland

- Authority FOEN/FOPH/SECO, Swiss Chemicals Ordinance ChemO
- Remarks:
  - New substances, > 1 t/y, on Swiss market are subject to notification requirements under ChemO
  - New substances, < 1 t/y but classified must be registered
  - New substances are those not listed on EINECS, i.e. those placed on the market for the first time after 18 September 1981.
  - Manufactured/imported amount in the EU must also be taken into account
  - Technical dossier info can be submitted in IUCLID format. REACH registered substance files can be used for notification under ChemO
- Only representative can be appointed (Sole representative)

COUNTRY SPECIFIC INFORMATION

China

- Authority CRC-MEP, Inventory IECSC
- Registration levels are tonnage level based
- Low volume: Simplified notification (<1 t/a)
- Polymer: Simplified notification special condition
- Only representative: can be appointed
- Remarks:
  - Some eco-tox testing needs performance in MEP approved labs in China
  - Read-Across is not accepted
  - When in doubt, discussion with Authorities is advised (eg whether a NOAEL from a 28-day study triggers further testing)
  - CSR is obligatory at level 2 and higher (polymers do not require CSR)

COUNTRY SPECIFIC INFORMATION

Philippines

- Authority EMB-DNER, Inventory PICCS
- All new substances imported >1 t/a must be notified (PMPIN)
- If substance is already registered under a Chemical legislation anywhere else in the world, an abbreviated PMPIN will suffice.
- Low volume: SQI (<1 t/a, needs yearly renewal)
- Polymer: needs registration as such
- CSR is not obligatory
- Only representative cannot be appointed – local importer or subsidiary must notify:
    - Every importer (Philippine-based) has to submit its own notification or request PICCS certification

COUNTRY SPECIFIC INFORMATION

Australia

- Authority NICNAS, Inventory AICS
- Registration levels are tonnage based *(Permits and Certificates)*
- Low volume: LVC permit ≤100 kg/y for 3 years
- Polymer: needs registration as such, limited data requirements for Polymer of Low Concern (PLC)
- Only representative cannot be appointed – local importer or subsidiary must notify
- Remarks:
  - AICS discloses the identity of the chemical but not the identity of the manufacturer/importer.
  - New chemicals are included on the public AICS section 5 years after the certificate date.

GLOBAL TESTING STRATEGIES

INITIAL CONSIDERATIONS

GLOBAL REGISTRATION STRATEGIES

To avoid unnecessary or duplicated testing

To make sure data can be used in several countries/regions

To be cost effective

Taking into account timelines

INITIAL CONSIDERATIONS

Where is your market, now, in 5 years time

Investigate whether the chemical is listed on a national inventory

What is the annual tonnage you want to import or manufacture? *This year and in the coming years?*

&

What is your role in the supply chain?

Producer, importer, formulator, distributor

INITIAL CONSIDERATIONS

Most jurisdictions lay obligations

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INITIAL CONSIDERATIONS

Data requirements

Understand country specific data requirements in key markets

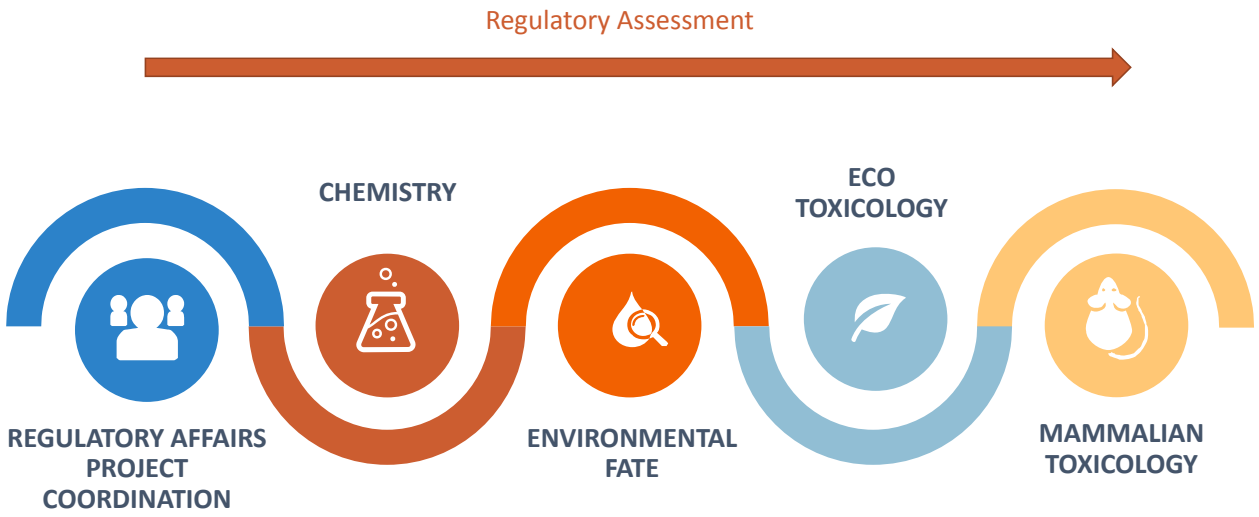
- What are the core data requirements?
- What additional studies might be triggered?
- Where should the studies be conducted?
- What is the best order in which to initiate registrations? (e.g. Philippines: less/no studies needed if registered in at least one other jurisdiction, USA: only submit data already available)

Try to avoid unnecessary, duplicated testing, plan ahead.

INITIAL CONSIDERATIONS

- ✓ **Project Coordination**
  - *To make sure all studies and dossier work run in the right order in time, avoid time loss*
- ✓ **Pre-registration consultancy meetings with Authorities**
  - *Have good relations with Authorities and to reach out to them in their native tongue proves to be invaluable. Work with trustworthy local subcontractors to ensure the correct approach.*
- ✓ **Study Monitoring**
  - *Outsource studies to other countries (e.g. China, Japan)*
- ✓ **Full regulatory package**
  - *Perform hazard assessment, classification and labeling (GHS), (Q)SAR, read across, grouping, risk assessment and risk refinement, Safety Data Sheet*
- ✓ **Consultancy**
  - *All questions arising have to be addressed*

WHERE TO START



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DATA REQUIREMENTS

GLOBAL DIFFERENCES

SUBSTANCE IDENTITY

Starting point

General identifiers, e.g. CAS number, etc.

► ***to determine whether substance is on e.g. inventory list***

Spectral data set to determine substance identity, purity, impurities

Type of substance?

- Mono- or Multi-constituent
- Unknown, of Variable Composition, or of Biological Origin (UVCB) – only known under REACH!
- Polymer:

In Europe: exempt! But obligation to register monomer(s)
In other countries: register as such (e.g. polymer of low concern)

GENERAL CONSIDERATIONS

On toxicological and ecotoxicological data

Are data scientifically valid?

Performed according to guidelines
Analytical data included
Test substance identity/ purity included
Sufficient number of animals
Concentration range sufficient

} Data sufficient for GHS/CLP purposes?

If no: consider to re-do test work

SKIN/EYE IRRITATION, SKIN SENSITIZATION

EU – in vitro

Skin irritation

- Completely *in vitro*

Eye irritation

- *In vitro*
- No conclusion possible then *in vivo*

Skin sensitization

- QSAR – DEREK
- DPRA, Keratinosens
- h-CLAT/MUSST
- WoE
- No conclusion, or no potency: LLNA

Other regions

Skin irritation

- Canada, Australia: *in vitro*
- China: *in vivo*

Eye irritation

- Canada: not required
- China: *in vivo*

Skin sensitization

- China: *In vivo*

OTHER DIFFERENCES

EU	Other regions
Repeated dose toxicity • 4-week + repro-screening	**Repeated dose toxicity** • China, South-Korea: similar • Japan: 4 week + recovery group • Australia, Canada: 4-week
Reproduction • Only EOGRTS	**Reproduction** • China: 2-generation reproduction
Toxicokinetics • Only a theoretical assessment	**Toxicokinetics** • China: Theoretical assessment – Full ADME study

OTHER DIFFERENCES

EU	Other regions
Ecotoxicity • New studies mandatory to be performed under GLP	**Ecotoxicity** • Japan: Determination of readily biodegradability, bioconcentration • China: Several studies (e.g. fish, biodegradation, earthworm)
Fast degradation in aqueous solution? • Adopt ecotoxicity testing	**Fast degradation in aqueous solution?** • China: Waive further testing if degradation products are already listed

GENERAL CONSIDERATIONS

Read Across

- EU: might be possible for data required from 10t/y onwards
- China: not accepted

Are available data scientifically valid and sufficient for GHS/CLP purposes

- If not, consider re-testing
- China GHS: include 5000 mg/kg bw in acute oral toxicity study?
- Studies performed in other countries, should be according to GLP for REACH

Evaluation by authorities after submission

- Japan, China, Australia, USA, Canada: evaluate all dossiers
- REACH: when passed completeness check one obtains a registration number

TSCA Reform

Environmental Protection Agency (EPA)

TSCA REFORM

Introduction

TSCA Update – Lautenberg Act

- Frank R. Lautenberg Chemical Safety for the 21st Century Act, H.R. 2576Section 5 (LSCA)
- LCSA passed by US Senate in December 2015
- Modifications were made
- TSCA Modernization Act passed by House in June 2016
- New TSCA law signed by US President Obama on June 22nd , 2016
- Known as TSCA reform, LCSA or New TSCA

Why reform?

- The 1976 law was never updated
- EPA had to demonstrate unreasonable risk to require testing from applicant
  - Testing was required on less than 300 existing substances in the last 40 years
  - Only 9 attempts to ban a substance was made (1 failed)
- Lacks transparency
- CBI claims limit access to information by the public
- Individual US states started their own diverse requirements for chemicals (e.g. California Proposition 65)

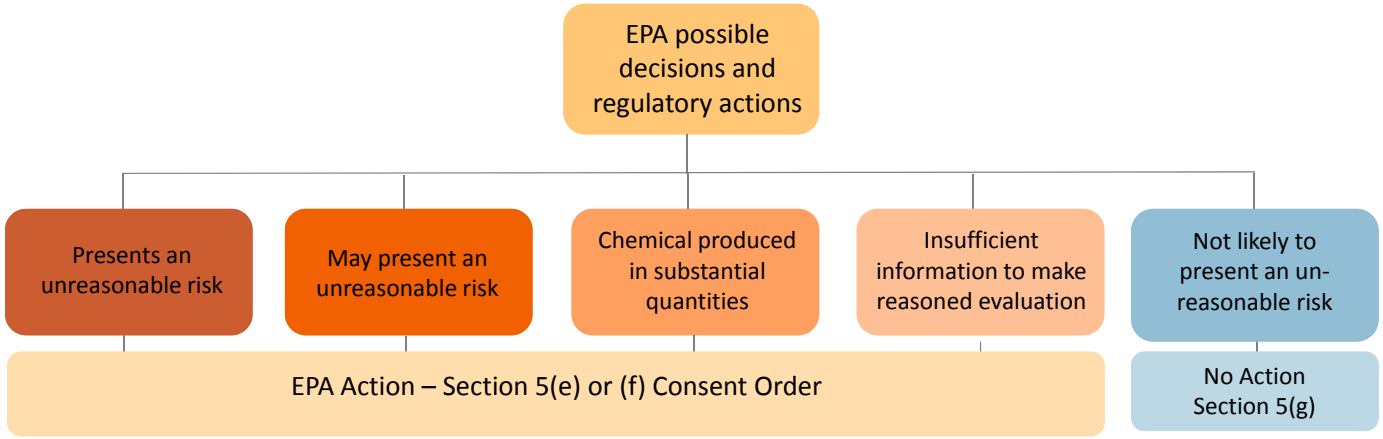
TSCA REFORM

Key Provisions – New Chemicals

- EPA must make an affirmative finding on the safety of a new chemical before it is allowed on the marketplace
- More attention towards “Potentially Exposed or Susceptible Subpopulations” (PESS)
- Still no upfront testing requirements, but increased attention to exposure, (anticipated) uses and human- or eco toxicity
  - Condition of Use: “… the circumstances, as determined by [EPA], under which a chemical is intended, known, or reasonably foreseen to be manufactured, processed…”
  - More information on downstream processes need to be provided by submitter
- EPA groups PMN chemicals with shared properties into categories.
- Exemptions still in place (e.g. LVE, polymer exemption, TME etc.)
- Fixed 90 day review period, but EPA and submitter can agree on voluntary suspension process
- Interim findings are communicated via an Action Letter describing the submitters options

TSCA REFORM

Key Provisions New Chemicals



- Testing request for toxicity or environmental fate (1) once a certain production volume or time period is reached, (2) insufficient information
- Use of worker personal protective equipment
- New Chemical Exposure Limits (NCELs) for worker protection

- Hazard communication language
- Distribution and use restrictions
- Restrictions on releases to water, air and/or land
- Recordkeeping

Submitter may commence manufacturing. EPA publishes findings on their website

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STRATEGY PMN / LVE UNDER NEW TSCA

New chemical registration

- Use QSAR to get a feeling on possible EPA concerns and include only information that may take away those concerns (e.g. ECOSAR, Epi Suite, category List, EFAST), but often not a predictor of EPA's new chemical ruling
- Check if the NCS falls under any EPA Category
- Pre-submission testing is not advised unless needed for other legislations. In case of a solid a particle size distribution test could be helpful
- Central Data Exchange (CDX): Web-based software, data and uploaded attachments are stored encrypted in the "cloud" (EPA server)
- No more paper submissions except certain exemption letters
- Include available test reports with at least a clear copy right protection designation on it
- Chemical ID in test reports cannot be kept confidential even when applying for confidential TSCA listing.
- Give a solid description how waste is handled; available data on expected release and exposure should be included.
- Include use information from (end)users / clients of submitter. If not willing to give information try a "joint" submission set-up.

TSCA REFORM

Key Provisions Existing Chemicals - Prioritization & Risk Evaluations

- EPA must prioritize chemicals as:
  - High-priority substance = "…may present an unreasonable risk of injury to health or the environment because of a potential hazard and a potential route of exposure under the conditions of use, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant by the Administrator"
  - Low priority = sufficient information is available to determine not-high priority
- EPA must conduct a full risk evaluation on high-priority substances
- Industry may nominate up to 50% of high-priority chemicals that EPA assesses
- Final Rule required June 2017

Risk Evaluation substances – first 10 Priority chemicals

- *1,4-Dioxane*
- *1-Bromopropane*
- *Asbestos*
- *Carbon Tetrachloride*
- *Cyclic aliphatic bromide cluster*
- *Methylene chloride*
- *N-methylpyrrolidone*
- *Pigment Violet 29*
- *Trichloroethylene*

TSCA REFORM

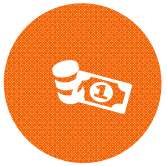
Key Provisions Overall

Testing (Section 4)

- Extension of EPA's ability to demand additional health and safety tests of chemicals
- EPA no longer needs to show risk or exposure to require testing
- EPA can issue a test order instead of a test rule
- EPA can require testing for existing and new chemicals
- Testing still not prerequisite for submitting a notification
- EPA must consider alternative testing methods where feasible

Fees may increase (Section 26)

- To perform its new responsibilities, a consistent funding source is provided, which means EPA can collect funds in the form of user fees from chemical processing and manufacturing facilities.



TSCA REFORM

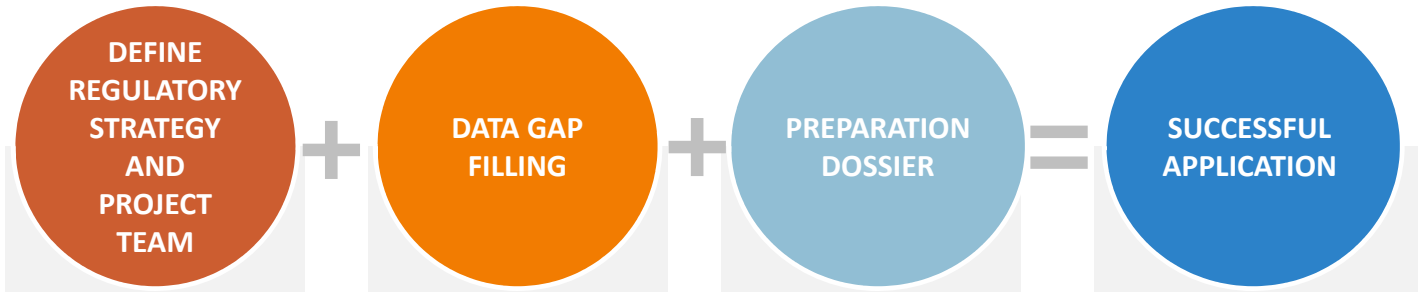
Key Provisions Overall – Confidential Business Information (CBI)

- New TSCA requires from EPA:
  - To review and make determinations on all new confidentiality claims for the identity of chemicals and a subset of other types of confidentiality claims
  - To review past confidentiality claims for chemical identity to determine if still warranted.
- Certain kinds of information are presumed to be CBI and require no substantiation (e.g., manufacturing process, product uses).
- Substantiation questions available in CDX

- When a chemical identity is claimed as CBI, a non-CBI structurally descriptive generic name must be provided according to EPA guidance
- EPA will review ≥25% of all claims, and 100% of chemical ID claims
- Health and safety data may not be claimed as CBI
- Not just new chemicals but also “active” existing chemicals will be reviewed so there is a chance that some current CBI protection could be lost
- Fees for claiming CBI, not decided yet

CONCLUSION

GLOBAL STRATEGY FOR YOUR PRODUCT



Define your markets, perform a data gap analysis for setting your testing strategy

Missing studies in your substance data portfolio to be performed

Prepare dossiers in respective formats, C&L, QSAR modelling, hazard, exposure and risk assessment

Get your registration number, be able to market, consider the post submission activities/support

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