REACH 10 Year Anniversary Conference

June 15th 2017

Spencer Hotel, IFSC, Dublin 1

HEALTH AND SAFETY AUTHORITY

Registration and evaluation – what's done and what's ahead

REACH 2018 and beyond

15 June 2017
Dublin, Ireland

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ECHA

Registration

The 1st level of risk management under REACH

Registration: what is at stake?

- ✓ Better knowledge on hazards, uses and risks
- ✓ Improve communication in the supply-chain
- ✓ Better safety and control measures
- ✓ Reduce exposures and hence negative impacts
- ✓ Substitute (gradually) hazardous substances with less hazardous ones

➢ Registration & Classification: Main starting point for pro-active product stewardship

Registration dossiers are vital…

They demonstrate that:

- You know your portfolio
- All necessary information is available
- The chemical safety assessment is appropriate and convincing
- Your clients are informed adequately on how to safely use your substances

➢ Provide confidence to authorities, investors and your clients

What is the outcome so far?

	Dossiers	Substances
Registrations since 2008	50 171	10 831

Before REACH	Dossiers	Substances
New Chemicals (NONS) notifications	9 963	5 293
…which are still on the market (Registration number requested by a company)	5 208	3 796
…of which have been updated under REACH	1 866	1 589

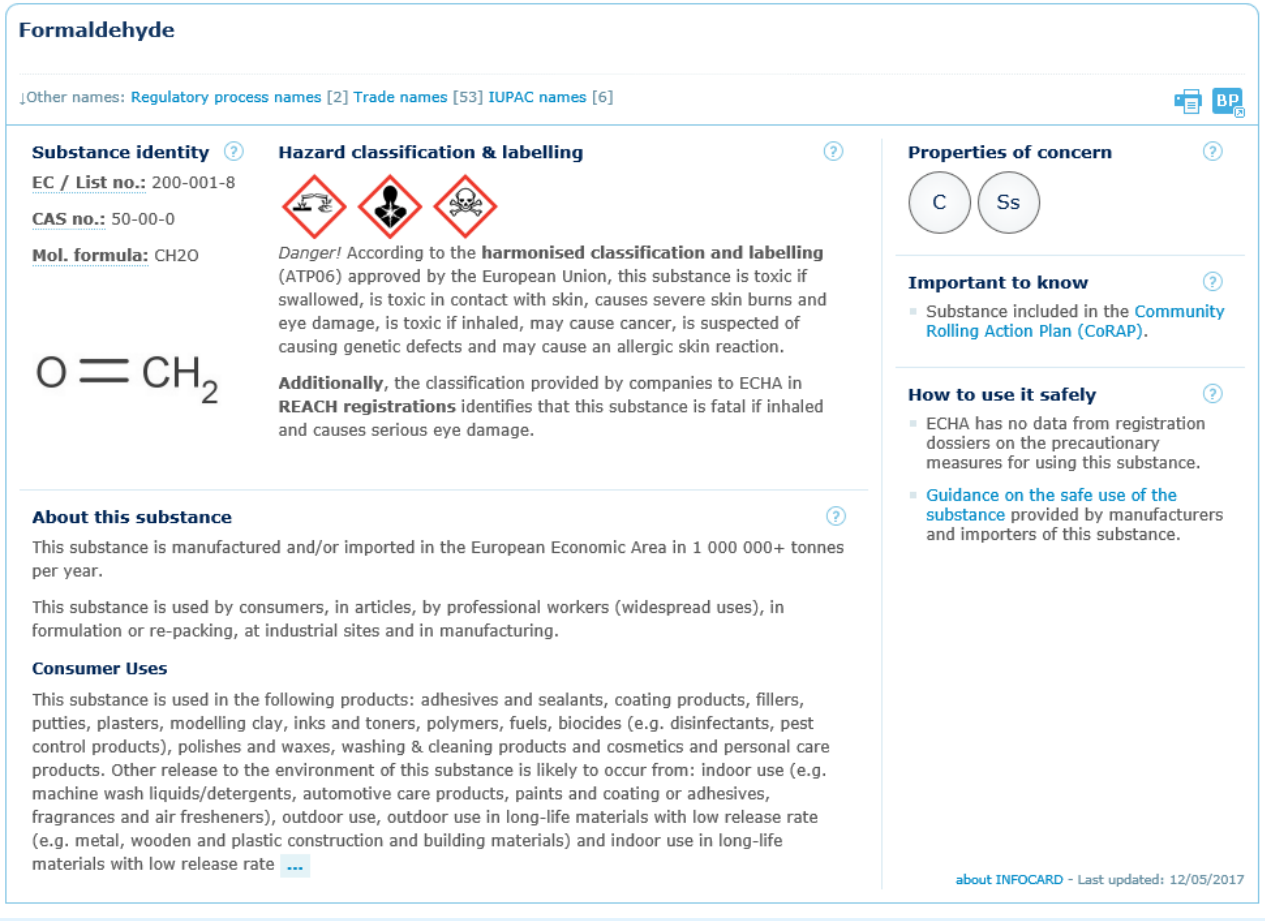
Ireland

	Companies	Substances
Pre-registrations	400	27 700
Registrations	130	851 (1050 with NONS)

	Registrations	% of all
2010 Registrations (>1000t, CMR & toxic to aquatic organisms)	712	1,1 %
2013 registrations (100-1000t)	567	3,3 %
Non phase-in	278	6,9 %
Total since 2008 for > 100 t/y	1 557	3,5 %

Data as of 6 June 2017; unique company names; NONS and 1-100t registrations are excluded.
Total since 2008 includes 1st time on the market registrations submitted after the deadlines.

Information is published on ECHA website



Formaldehyde

↓Other names: Regulatory process names [2] Trade names [53] IUPAC names [6]

Substance identity

EC / List no.: 200-001-8

CAS no.: 50-00-0

Mol. formula: CH_2O

$O=CH_2$

Hazard classification & labelling

Danger! According to the **harmonised classification and labelling** (ATP06) approved by the European Union, this substance is toxic if swallowed, is toxic in contact with skin, causes severe skin burns and eye damage, is toxic if inhaled, may cause cancer, is suspected of causing genetic defects and may cause an allergic skin reaction.

Additionally, the classification provided by companies to ECHA in **REACH registrations** identifies that this substance is fatal if inhaled and causes serious eye damage.

Properties of concern

C Ss

Important to know

- Substance included in the Community Rolling Action Plan (CoRAP).

How to use it safely

- ECHA has no data from registration dossiers on the precautionary measures for using this substance.
- Guidance on the safe use of the substance provided by manufacturers and importers of this substance.

About this substance

This substance is manufactured and/or imported in the European Economic Area in 1 000 000+ tonnes per year.

This substance is used by consumers, in articles, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

Consumer Uses

This substance is used in the following products: adhesives and sealants, coating products, fillers, putties, plasters, modelling clay, inks and toners, polymers, fuels, biocides (e.g. disinfectants, pest control products), polishes and waxes, washing & cleaning products and cosmetics and personal care products. Other release to the environment of this substance is likely to occur from: indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners), outdoor use, outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials) and indoor use in long-life materials with low release rate ...

about INFOCARD - Last updated: 12/05/2017

2018 Registration deadline
1 year to go …

What do we know

- Up to 60 000 dossiers for up to 25 000 substances
- Most registrations in 1-10 tonnage band
- Small SIEFs
- Higher % of SMEs
- More SMEs as lead registrants
- Many actors still in wait-and-see mode

➢ Our aim: Make registration possible for SMEs through recommendations, best practices, simplified tools and guidance

DL2018 Progress so far

Total:

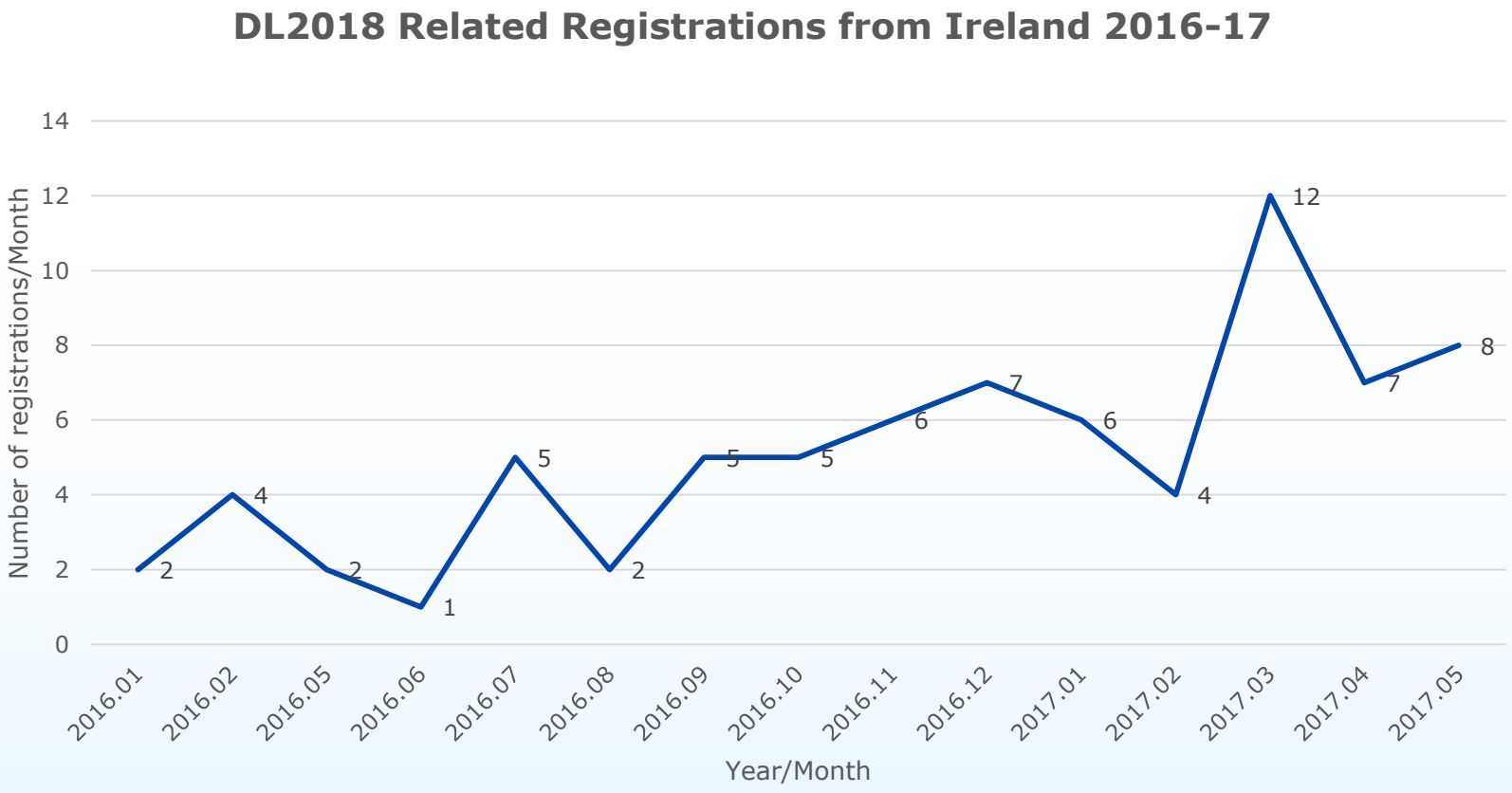
- 9 472 registrations received for 4 633 substances*
- 15% SME registrants

Ireland:

- 196 registrations received for 165 substances*
- 12% SME registrants

*Phase-in substances. Excluding NONS

Ireland: Increasing trend



What has changed over the years

Enhanced completeness check

- Manual verification introduced
- Prevents from bypassing the system
- Still in the scope of completeness check (no assessment of quality)
- Areas of attention:
  - Unclear substance identity
  - Information requirements waived by registrants
  - Dossiers include testing proposals
  - Chemical safety report missing

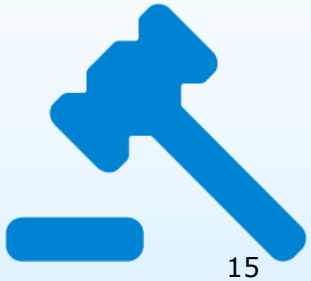
Manual verification: results so far

- **33%** of all incoming dossiers manually verified
- **20%** of verified dossiers failed first check
- **95%** of failed dossiers successfully updated
- If updates fail, no registration number issued

- Existing registrations are being verified retrospectively

OSOR principle reinforced

- Commission Regulation in force since 2016 → ECHA to ensure joint submissions
  - No submissions outside joint submission possible
  - Legacy cases currently being addressed
  - Leads acting without SIEF agreement can be demoted
  - Contact ECHA with a dispute in case of a difficult situation



New generation of IT tools for registration

- One-click installation
- Integrated help
- More structure for reporting SID, uses and hazard data and improving data quality

- For CSA and Exposure scenarios
- Step by step approach for CSA
- Keep data consistent with IUCLID for easier updates
- Generate exposure scenarios for the safety data sheet

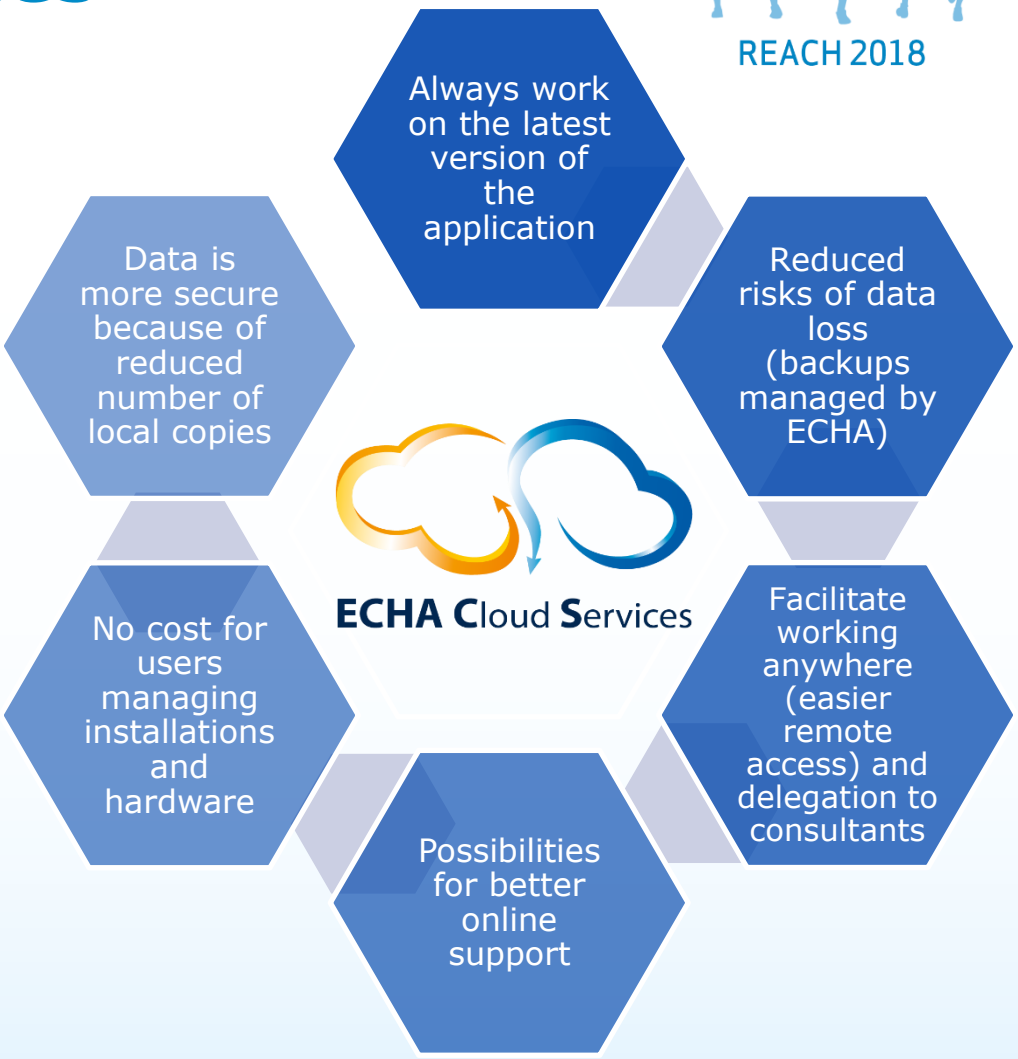
New generation of IT tools for registration

- More intuitive user interface
- Integrated help in all EU languages (early 2017)
- Easier to identify co-registrants and existing joint submission

- **If you are a Member of a joint submission**:
  You can prepare your dossier directly in REACH-IT without having to install and use IUCLID!

ECHA Cloud Services

- For SME users
- Online tool: No need to install IUCLID
- 24/7 availability from anywhere in a secure environment
- Backups and data migration done by ECHA
- Trial version available for testing out the application
- Full version in July 2017



Customer-oriented approach to company support

echa.europa.eu/reach-2018

What is there to come

- Last registration deadline on 31 May 2018
  - Closes the gap on information needed for proper risk management
- **But, obligations continue:**
  - You have the obligation to keep your dossiers updated
  - Your dossiers are watched by the authorities
    - Convinced by your assessment and conclusions?
    - Screened to identify substances of concern
    - Assessed for the need for further risk management measures, at company or EU level

Evaluation

Main instrument to verify dossier quality and clarify potential risk

Evaluation processes

Dossier evaluation		Substance evaluation (SEv)
Testing proposal examination	Compliance check (CCh)	Examine any information on a substance

- Accept/reject a testing proposal
- **Request information:** dossier is not compliant (CCh) or the potential risk needs clarification (SEv)

Achievements in numbers

Testing proposals: 1252 examinations concluded

- ✓… resulting so far in 701 final decisions

Compliance check: 2124 concluded

- ✓… resulting so far in 825 final decisions and 677 conclusions with no action

Follow-up evaluation: 1168 performed

- ✓…resulting in 783 Article 42(2) conclusions

Substance evaluation

- ✓ 243 evaluations started
- ✓ 80% leading to a decision
- ✓ Only relatively few conclusions yet finalised

What you can expect from ECHA

- We will screen your dossier
  - To select for compliance check or other measures
  - To (de-)prioritise substances for further regulatory action
- We give you prior warning (and a last chance to update):
  - Consult the list of substances that may potentially selected for compliance check: List of substances potentially subject to evaluation
  - Consult the Public Activities Coordination Tool (PACT) for ongoing or planned risk management or substance evaluation activities: PACT – RMOA and hazard assessment activities

… and from the Member States in 2017-2019

- Community Rolling Action Plan (CoRAP):
  - **115 substances** for evaluation by 22 Member States
  - ➢22 substances to be evaluated in 2017, 46 substances in 2018 and 47 in 2019
  - ➢22 new substances and 93 already included in the previous CoRAP

Compliance and quality

- More needs to be done to be compliant!
- REACH requires to update:
  - Annual and total volumes that change
  - New identified uses, uses advised against
  - New knowledge on hazard (including C&L) and risks leading to changes in your CSR

64 % of registration dossiers submitted since 2008 were <u>never</u> updated!

The consequence of poor data

- Insufficient basis for safe use in supply chain
- Slows down identification of risk management measures needs
- Your substance might be unnecessary prioritised
- Damage to your image? Your data are publicly available on ECHA's website associated with your name and your update rate
- Bad quality dossier: a business risk?

➢ Do we address substances of concern quick enough?

Integrated regulatory strategy

Coherently brings all the REACH and CLP processes together to better and quicker achieve the objectives

By 2020 we want to know

- For all substances over 100 tonnes
  - Are they of potential concern?
  - Do we need more (hazard) information?
  - Do they need to be addressed through (the most appropriate) regulatory risk management action?

  OR

  - Can we safely put them aside as being currently of low priority for further work?

Focus on substances that matter

- Higher-tonnage registration dossiers with
- Important data gaps and with
- High exposure potential for:
  - Workers or
  - Consumers or
  - Environment

How?

- Target compliance check on most important human health and environment endpoints for clarifying CMR and PBT concern
- Tackle groups of substances e.g. by structural similarities or specific functions (e.g. plasticisers)
- Increase cooperation with industry sectors to stimulate dossier updates and agree on possible strategies for testing the substance
- Increase cooperation with other bodies worldwide
- Deprioritise if we can conclude low risk

If you are preparing your registration

- Aim at good quality information – it will be reviewed by ECHA
  - Alternatives to be used – recommendations in ECHA's guide
  - Quality reduces future work and costs
  - Main aim is to use chemicals safely
- Plan carefully: It takes time and scientific input to fill in data gaps
- Read available support documents
  - Practical guide for SME managers and REACH coordinators on low tonnage information requirements
  - ECHA's Annual Evaluation Reports

If you have already registered

- Proactively improve your dossier!
  - Provide precise and relevant information on **uses** and **tonnage**
  - Improve adaptations from standard data requirements

    e.g. use of read across: Structural similarity **plus** consider toxicokinetics (hypothesis) and screening studies. Appropriate documentation is essential!
  - Ensure substance identity information is clear (ask ECHA if in doubt) and adequate information on physico/chemical properties used in the hazard/risk assessment (e.g. Log Kow used in environmental assessment)
  - Improve human health and environment data, in particular the higher tier endpoints

Conclusions

- Successful registration is not the goal but a milestone
- Demonstrating safe use is a dynamic task
- Your dossier is an investment and an asset – get it right from the start – and keep it right
- It pays off to be proactive
- Commitment to quality is an investment for a sustainable business model

Thank you!

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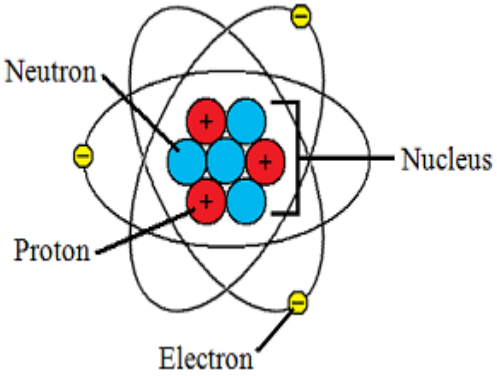
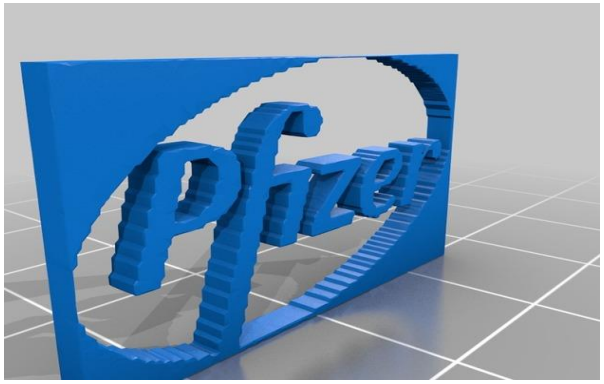
REACH 10 YEAR ANNIVERSARY CONFERENCE
INDUSTRY CASE STUDY - AUTHORISATION

Presented By: Timmy Carey



22 years
EHS



BIOMARIN

2017: BioMarin's 20 Year Anniversary

Two Decades of Innovation & Productivity

>1200% increase in revenues from 2006 to 2016

1.1 BILLION+ achieved product revenue for FY 2016

Forbes VOTED AMONG **TOP 10 MOST INNOVATIVE COMPANIES 3 YEARS IN A ROW**

2,200+ global employees

68 global markets served

118 abstracts accepted at global medical meetings in 2016

27 congress presentations around the globe in 2016

6 APPROVED PRODUCTS

14 MILLION units of product manufactured in 2016

4 PRODUCTS IN CLINICAL DEVELOPMENT

5 YEARS on average from IND to approval for all marketed products

Six Approved Products and a Robust Clinical Portfolio

Commercialized Products

Brineura™ (cerliponase alfa)

Naglazyme® (GALSULFASE)

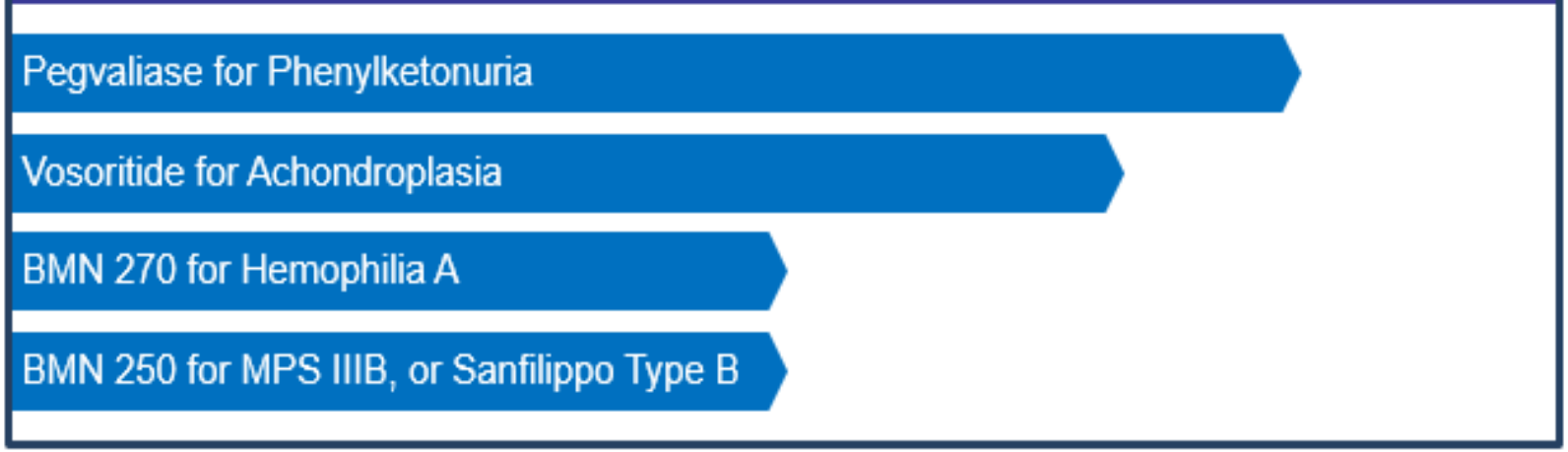
KUVAN® (sapropterin dihydrochloride) Tablets

ALDURAZYME® (LARONIDASE)

VIMIZIM® (elosulfase alfa)

FIRDAPSE™ amifampridine

Late-stage Development Pipeline

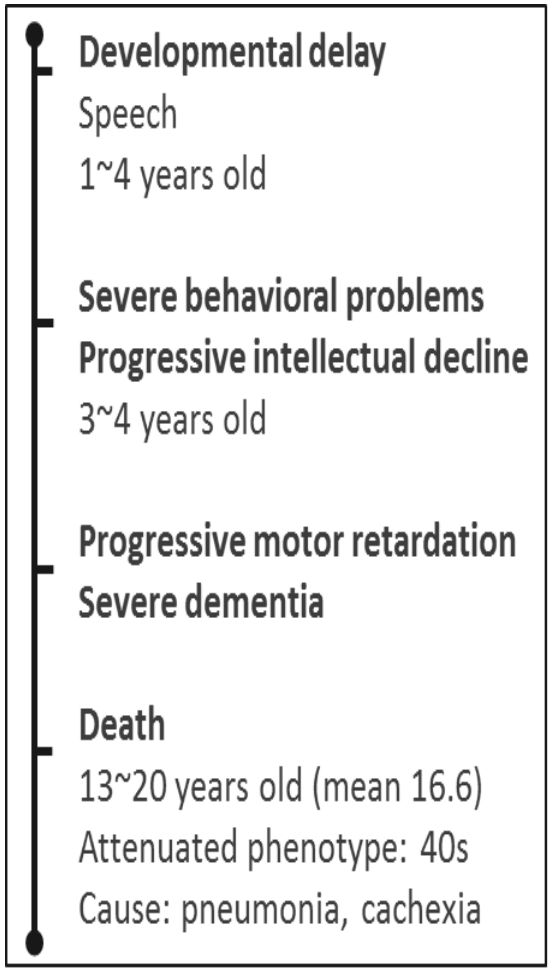


Rapid Product Development Track Record

Efficient drug development drives strong returns on R&D investment

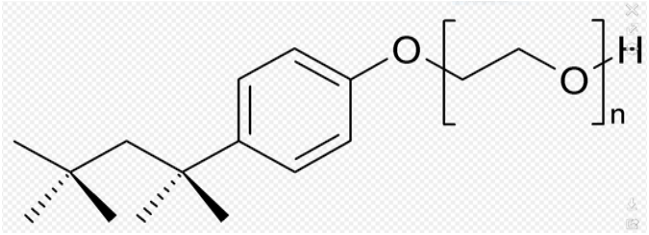
Time to Approval from IND/CTA filing

MPS IIIB



- There are an **estimated 1,000 – 2,000 patients** in the developed world with MPS IIIB (Sanfilippo Syndrome Type B).
- Mucopolysaccharidosis IIIB (MPS IIIB) or Sanfilippo Syndrome Type B is **caused by deficiency in the enzyme alpha-N-acetyglucosaminidase (NAGLU),** one of the four enzymes required for heparan sulfate (HS) degradation in people.
- MPS III is predominantly a **neurological disease**. The first symptoms typically appear between the ages of two and six years old, with behavioral disorders, intellectual deterioration, disturbed sleep.

Triton X - 100



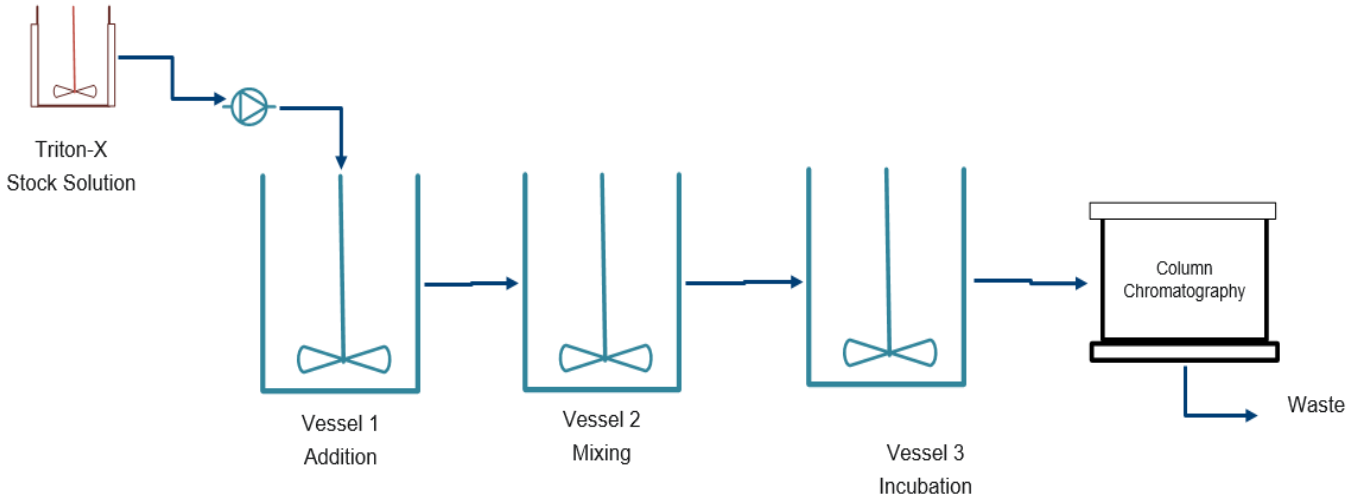
4-(1,1,3,3,-Tetramethylbutyl)phenyl-polyethylene glycol

Properties:

- Triton X-100 is a non-ionic surfactant / detergent that has hydrophilic, aromatic & hydrophobic groups.
- Mol. Wt. : 600 – 650
- Soluble in water and most organic solvents
- Boiling point: 270°C.
- CMC: approx. 0.02% w/v (0.2 – 0.9 mM).
- Vey Limited Biodegradability
- It is an Endocrine Disruptive compound - toxin.

Viral Inactivation (VI) Process step

- Triton-X is widely used in the Biologics Industry to inactivate enveloped virus
- Viral reduction/removal steps are a regulatory expectation for Biologics



- Post Viral Inactivation – material normally is processed by column chromatography
- Triton-X will largely be removed in the load and wash phases as a diluted solution

Authorisation Impacts – some considerations

Naglu cant tolerate any of the other standard anti viral clearance agents on the market – we have already tried

Validation requirements for drug periods are very onerous and take long time periods – many years

Standard authorisation periods are not long in the context of drug development and changes

Fiscal cost- we estimate – over 250 K plus resourcing on top of same of 2 person years

REACH is not that well understood outside the EU

THANK YOU

BIOMARIN

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