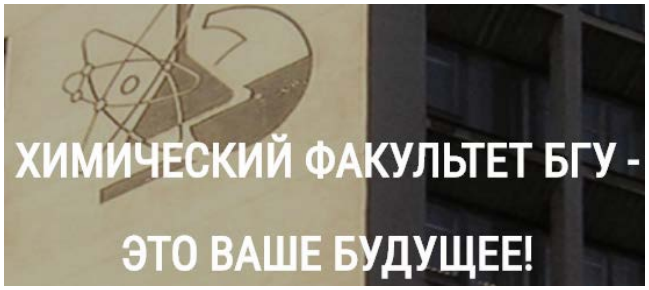

MODULE
Drug Chemistry and Technology Basics, Cleaner Production and Mega-Trends in Pharmaceutical Industry (Chemistry of Drug Substances)

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Lectures 3,4

Outline:
Management of Chemicals

- Responsible Care (RC) Initiative;
- RC: *DSM Sinochem Pharmaceuticals*;
- REACH Regulation;
- REACH's Impact on the Pharmaceutical Industry;
- REACH: *Pfizer*
- Globally Harmonized System of Classification and Labeling of Chemicals.

Global Trends

- More stringent requirements driven by the need to manage risks related to public health and the environment.
- Pressure from retailers and consumer product companies to substitute certain substances.
- General perception that existing regulations are not adequate.
- Increasing number of new regulatory schemes.

Chapter 19: Programme Areas

In 1992 the UN Conference on the Environment and Development established 6 programme areas to strengthen national and international efforts related to the management of chemicals:

- Expanding and accelerating international assessment of chemical risks;
- Harmonization of classification and labelling of chemicals;
- Information exchange on toxic chemicals and chemical risks;
- Establishment of risk reduction programmes;
- Strengthening of capabilities and capacities for management of chemicals;
- Prevention of illegal international traffic in toxic and dangerous products.

International Initiatives

Mandatory

- **REACH – in Europe,**
- Chemical Assessment and Management Program (ChAMP) – in USA,
- Domestic Substances List (DSL) – in Canada,
- National Industrial Chemicals Notification and Assessment Scheme (NICNAS) – in Australia,
- Toxic Chemicals Control Act (TCCA) – in Korea.

Voluntary

- **Responsible Care**
- High Production Volume Chemicals Initiative etc.

Responsible Care

- **A voluntary commitment by the global chemical industry to drive continuous improvement in performance of the pharmaceutical and chemical sector in all aspects, which directly and indirectly impact on the environment, employees or the general public.**

- Launched by the Chemistry Industry Association of Canada in 1985.

Responsible Care

- RC companies contribute to the vision that:

“By the year 2020 all chemicals will be produced and used in ways that minimize risks for human health and the environment”.

- From 1988 to 2014 RC companies have reduced hazardous releases to the air, land and water by more than 74 percent.

Responsible Care:

Key Elements

=

Responsible Care

=

- **Industry safety,**
- **Environment,**
- **Health,**
- **Labor Protection**

Responsible Care

60 countries, 75% of total chemical industry

Responsible Care

8 GUIDING PRINCIPLES

RC companies are committed to:

1. Legal requirements

Conform with all legal regulations and requirements and should operate in accordance with both government and industry codes of practice and guidance associated with their chemical activities.

2. Management of risk

Ensure that their activities do not present an unacceptable level of risk to employees, contractors, customers, the public or the environment.

Responsible Care

8 GUIDING PRINCIPLES

RC companies are committed to:

3. Policies and documentation

Have written documentation which covers their activities and ensure that their health, safety and environmental policies reflect their commitment to RC Programme as an integral part of their business strategy.

4. Provision of information

Provide relevant health safety and environmental information on company products and activities to employees, contractors, customers, statutory bodies and the public.

Responsible Care

8 GUIDING PRINCIPLES

RC companies are committed to:

5. Training

Ensure that all employees are aware of their commitment and provide the training necessary to enable them to be involved in the achievement of health, safety and environmental objectives.

6. Emergency response

Establish and maintain an appropriate emergency response system.

Responsible Care

8 GUIDING PRINCIPLES

RC companies are committed to:

7. Ongoing improvements

Support and participate in those activities which will improve the quality of their own operations and strengthen health, safety and environmental consciousness and awareness.

8. Community interaction

Maintain an awareness of and respond to community concerns which relate to their activities.

Responsible Care

The implementation of RC within the company:

- Assists to comply with environmental, health and safety legislation.
- Diminishes the risks of environmental, health and safety failures.
- Optimizes operational conditions and company performance.
- Improves the image and reputation of company towards the employees, authorities, customers and general public.
- Demonstrates an ongoing commitment to corporate social responsibility.

Responsible Care

On 7 October 2016 in Florence (Italy) **DSM Sinochem Pharmaceuticals (DSP) won the prestigious CEFIC European Responsible Care Award for Work in Sustainable Antibiotics.**

DSP develops, produces and sells raw materials, intermediates, active pharmaceutical ingredients and drug products.

Headquartered in Singapore, the group has operations in China, India, Egypt, the Netherlands, Spain, the USA and Mexico.

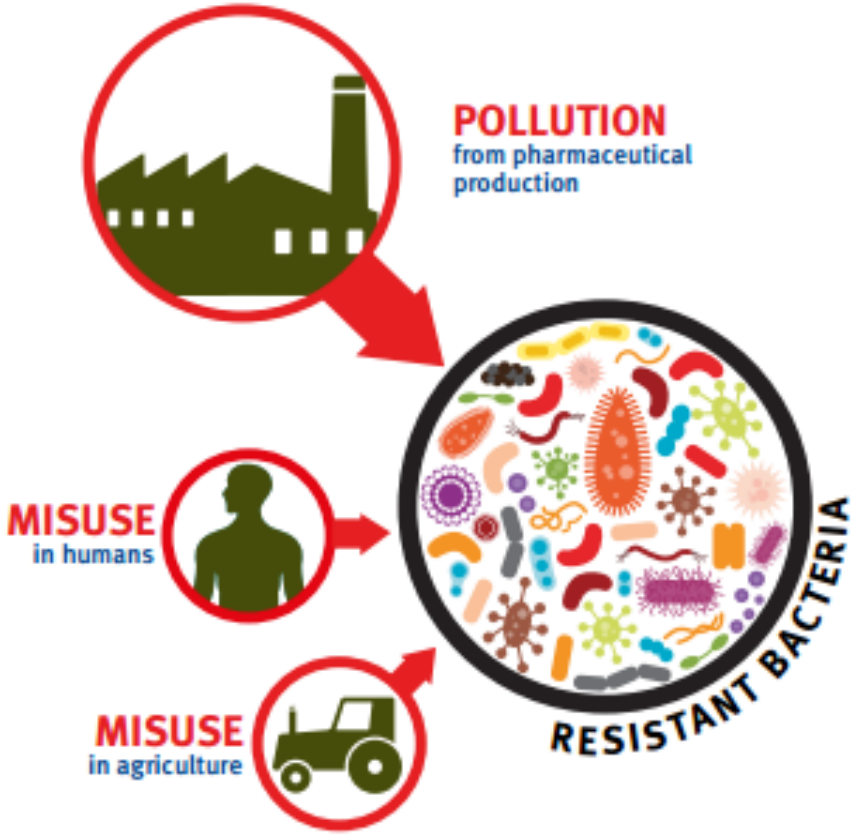
SINOCHEM | DSM

DSM Sinochem Pharmaceuticals

Responsible Care

Antimicrobial resistance (AMR) is a major global problem caused by the misuse and irresponsible manufacturing of antibiotics.

Antibiotic pollution is a significant cause of AMR.



~200 antibiotic production facilities - mainly India & China

>95% of antibiotic manufacturing waste is in liquid form

Environments polluted with this waste can create reservoirs of antibiotic resistance

The industry releases an estimated 30,000 - 70,000 tons of waste in the environment

Costs of no action:
ca. USD 100 trillion per year by 2050
ca. 10 million deaths by 2050

Source: AMR Review, May 2016

Responsible Care

DSP launched the Sustainable Antibiotics program in October 2014 and put in place the basic measures to manufacture antibiotics responsibly:

- Use the best technology available with the lowest environmental impact throughout the supply chain;
- Operate dedicated wastewater treatment plants 24/7/365 at every antibiotic manufacturing site;
- Apply antibiotics water tests to ensure disposed water is truly clean:
- Drive higher standards and transparency through the supply chain by initiating mechanisms such as a “quality mark” or “industry label” for the responsible taking, using and making of antibiotics.

SINOCHEM | DSM
DSM Sinochem Pharmaceuticals

Responsible Care:

Short conclusion

Voluntary initiative;

60 countries;

8 guiding principles;

Improvement in performance of the pharmaceutical and chemical industry to minimize risks for human health and the environment.

REACh:
Historical Background

- **1981** – 2 types of chemicals:
  "old, phase-in" and **"new, non phase-in"**

New chemicals are required to be estimated

BUT: "old, phase-in" – 99%!

~8% "old, phase-in" chemicals were well-investigated.

REACh:
Historical Background

- **1994** Act on chemicals introduced on the market before 1981.

  140 high-volume chemicals have to be tested for toxicity

- **2001** “White Paper on a Future Chemicals Policy”

  Protection humans and the environment from unknown risks through chemicals. The "promotion of non-animal testing" is one of the key elements of the proposed strategy.

- **2003 REACH**

REACh:
Background Introduction

- Many Regulations (~40).

- Lack of information on the effects of the majority of existing substances on human health and the environment.

- Reduced competitiveness of the chemical industry as a key sector of the European economy.

What is REACh?

Registration

Evaluation

Authorization (and Restriction)

Chemicals

December 13, 2006 in Brussels (Belgium) 529 - "for", 98 - "against", 24 - "abstained" The European Parliament adopted the new REACH legislation.
It was signed by the President of the European Union and the President of the European Parliament.

Regulation (EC) № 1907/2006

REACh:
Goals

Prevention of chemical pollution and biodiversity conservation

(Planet)

Labor Protection and safety

(People)

Increase of the competitiveness of European industry

(Profit)

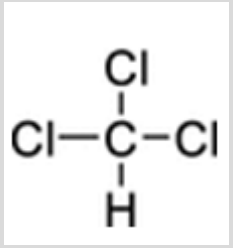
REACh

- Introduced in **01.07.2007**

- The REACH regulation requires **registration of the existing 30,000 substances** produced or imported within the European Union, which will result in a huge impact in the chemical industry.

- Any products found not to comply with the conditions established in REACH are removed from the market through the “rapid alert system for dangerous non-food products” (RAPEX) information scheme.

REACh

Chloroform 	**Shall not be placed on the market, or used, as substance, as constituent of other substances, or in mixtures in concentrations equal to or greater than 0.1 % by weight, where the substance or mixture is intended for supply to the general public and/or is intended for diffusive applications such as in surface cleaning and cleaning of fabric.**	**Suspected of causing cancer**

REACh

Substances causing serious global concern should be phased out from uses involving high risk.

Chromium oxide *Chromic anhydride* *Chromium oxide* *Chromium trioxide* *CrO3* *Kromoxid* *Krom(VI)oxid*	215-607-8 1333-82-0	Phase-out substance	CMR (category 1 and 2), Carcinogenic CMR (category 1 and 2), Mutagenic High chronic toxicity Environmentally hazardous, long-term effects Very high acute toxicity Allergenic

Chromium and its oxides are widely used because of their high conductivity and anticorrosive properties. While some forms of chromium are non toxic, chromium (VI) is easily absorbed in the human body and can produce various toxic effects within cells.

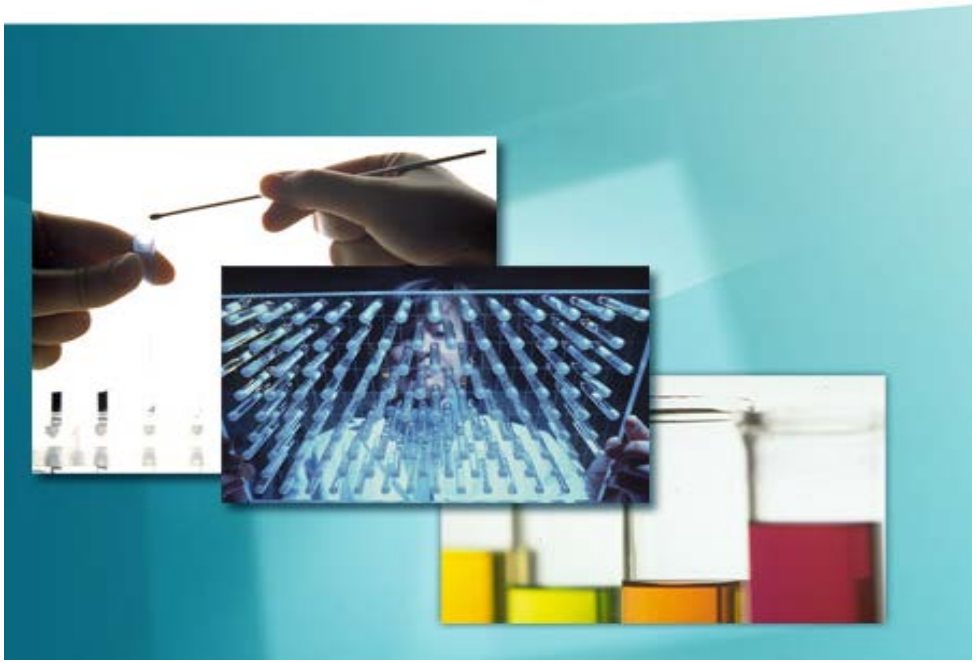
REACh:

Management System

Helsinki is the EU Chemical Capital

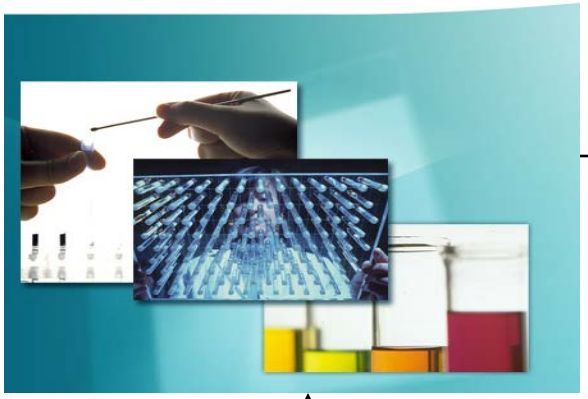
2007 - European Chemicals Agency

ECHA



REACh:
Management System

ECHA



HELPDESKS

(National Consulting Centers)

Consultation

ECHA provides IT tools and guidance

Coordination

Consultation

Registration

Evaluation of Technical Dossier etc.

REACh:
Principles

- Responsibility of manufacturers and importers of products.
- Transparency, availability of information.
- Replacing dangerous substances

The main principle:

No data – No market

REACh:
OSOR concept

One substance – one registration

Regulation (EU) 2016/9 of 5 January 2016 on joint submission of data and data-sharing came into force on 26 January 2016.

Companies are no longer able to submit a registration dossier separately if a registration for the same substance already exists.

If a separate registration dossier is submitted, it will be rejected at the “business rules” step of the submission.

REACh applies to:

Producing Company

Importing Company

substances imported or manufactured in quantities of more than 1 metric ton per year

Focus on priorities:
– high volumes
– greatest concern (Carcinogenic, mutagenic, reprotoxic (CMR) substances)

REACh

COVERS most chemical substances that are manufactured in or imported into the EU.
This can be:

- Substances on their own;
- Substances in a mixture (for example, ink or paint);
- Substances that make up an “article” (an object that is produced with a special shape, surface or design).

Some substances are exempt from all or certain aspects of REACh (“partial” exemptions).

REACh:

Total exemptions

- Radioactive substances within the scope of Council Directive 96/29/Euroatom;
- Substances which are subject to customs supervision, provided that they do not undergo any treatment or processing, and which are in temporary storage, or in a free zone with a view to re-exportation, or in transit;
- Non-isolated intermediates;
- The carriage of dangerous substances by rail, road, sea, air;
- Waste as defined in Directive 2006/12/EC.

REACh:

Registration

To make the regulation's implementation easier, the EU has initiated a phase-in period for existing substances that extend their registration timeframe over a 11-year time period to 2018.

Substance registration are prioritized according to the phase-in timeline based on volume and hazardous characteristics of the materials.

2007 2008 2010 2013 2016 2016 2018

>1 t/a	**11 Years** (May 31, 2018)
>100 t/a	6 Years (May 31, 2013)
>1000 t/a	3,5 Years (November 30, 2010)

REACh:

Documents

Safety Data Sheet

SECTION 1: Identification of the substance and of the company
SECTION 2: Hazards identification
SECTION 3: Composition/information on ingredients
SECTION 4: First aid measures
SECTION 5: Firefighting measures
SECTION 6: Accidental release measure
SECTION 7: Handling and storage
SECTION 8: Exposure controls/personal protection
SECTION 9: Physical and chemical properties
SECTION 10: Stability and reactivity
SECTION 11: Toxicological information
SECTION 12: Ecological information
SECTION 13: Disposal considerations
SECTION 14: Transport information
SECTION 15: Regulatory information
SECTION 16: Other information

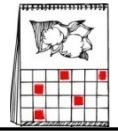
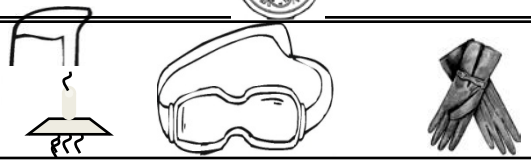
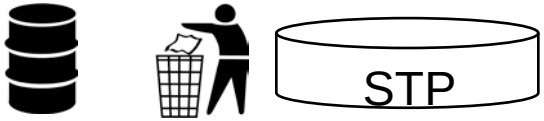
Amount of data is depending on volumes of substances

Costs of registration increase with volumes of substances

REACh:
Documents

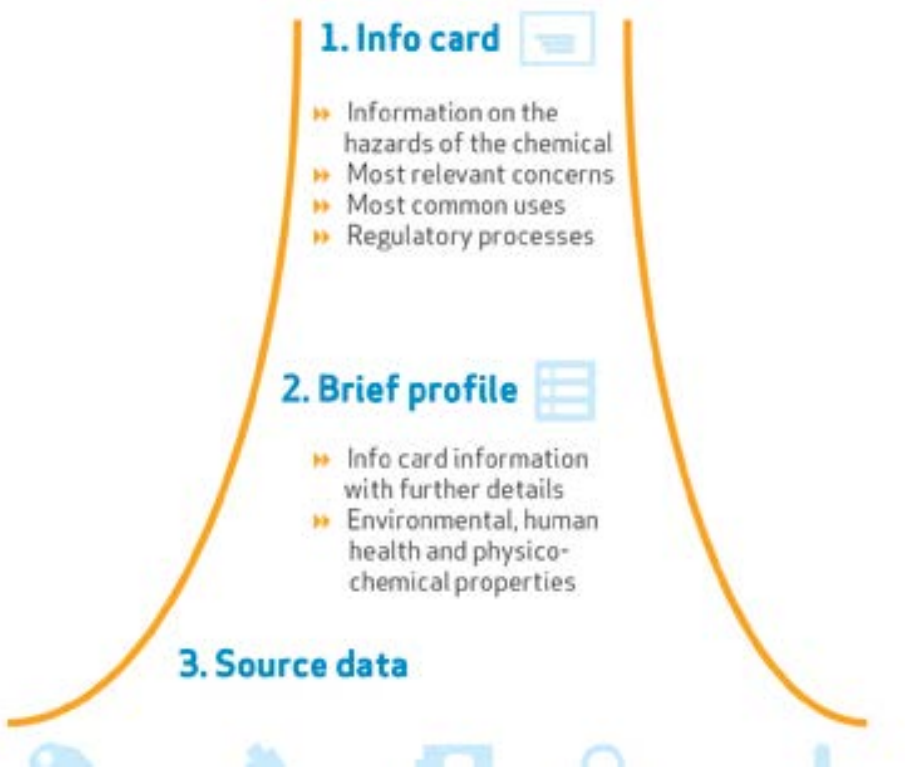
Chemicals Safety Report (CSR) if >10t/a

- Safety assessment
- Assessment of exposure on:
  - Workplace,
  - Environment,
  - Consumer.
- Description of safety in use.

Who	
Where	
How	
How many times	
Periodicity	
Duration	
Preventive Measures	
Waste Recovery	

REACh

As from 20 January 2016, information on up to 120 000 chemicals is enriched and structured in three layers: **infocard, brief profile** and detailed **source data**.



REACh:
Issue Price

- Administrative expenses associated with a 11-year time period of REACH implementation is ~ 2.3 billion Euro.

- Direct costs of the enterprise associated with the registration process and research chemicals is 2.8 - 3.6 billion Euro.

- The total cost of the reform is 13-30 billion Euro.

- **BUT:** the benefits in the labor protection field is 17-54 billion Euro.

REACh:
Problems

- High bureaucratization process;
- Increasing the product cost and reduction of cheap products (5 to 10% of the products will disappear from the market);
- Reduction of export opportunities of EU industry;
- Changing technology by replacing the ingredients.

REACh:
Republic of Belarus

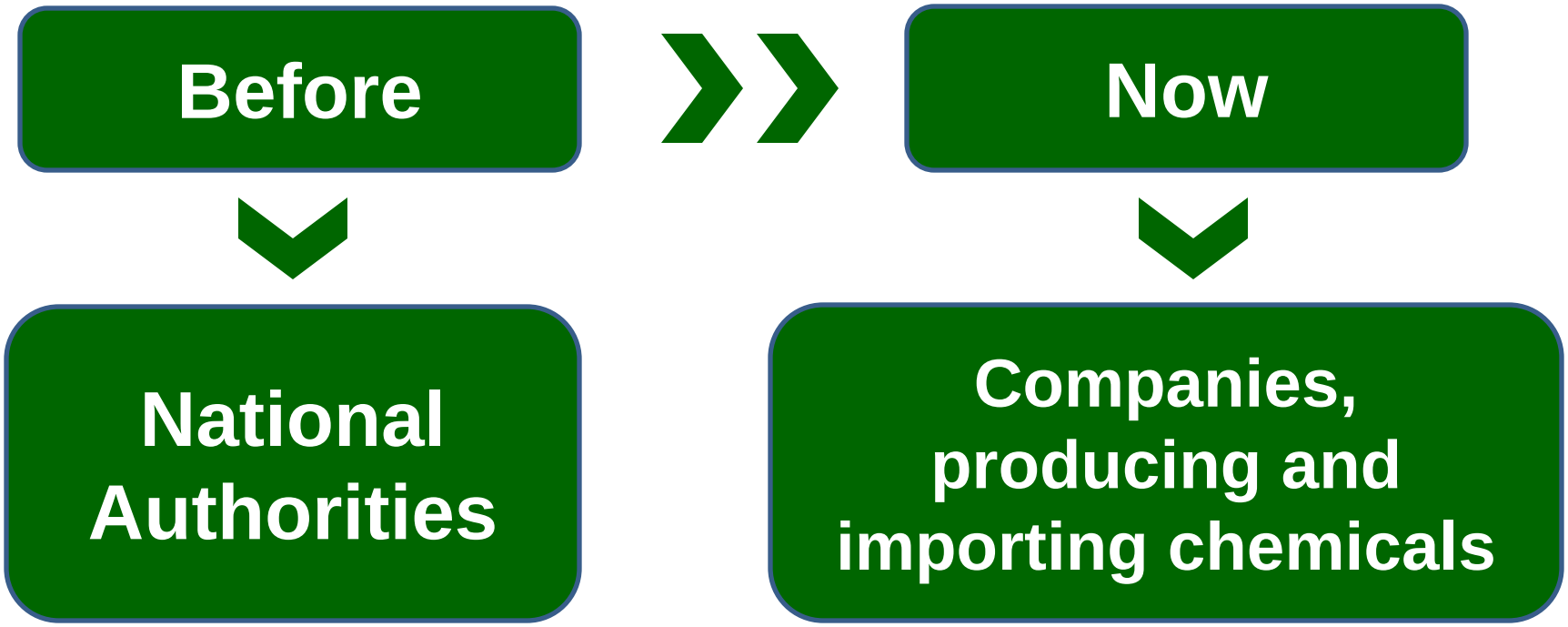
- Interdepartmental Working Group of Experts.
- Recommendations on Regulation for companies supplying products to the EU market.
- International Conferences and seminars.
- 17 companies have passed preliminary registration in conformity with the REACh.

REACH ≈40 rules applied before 2007 in Europe

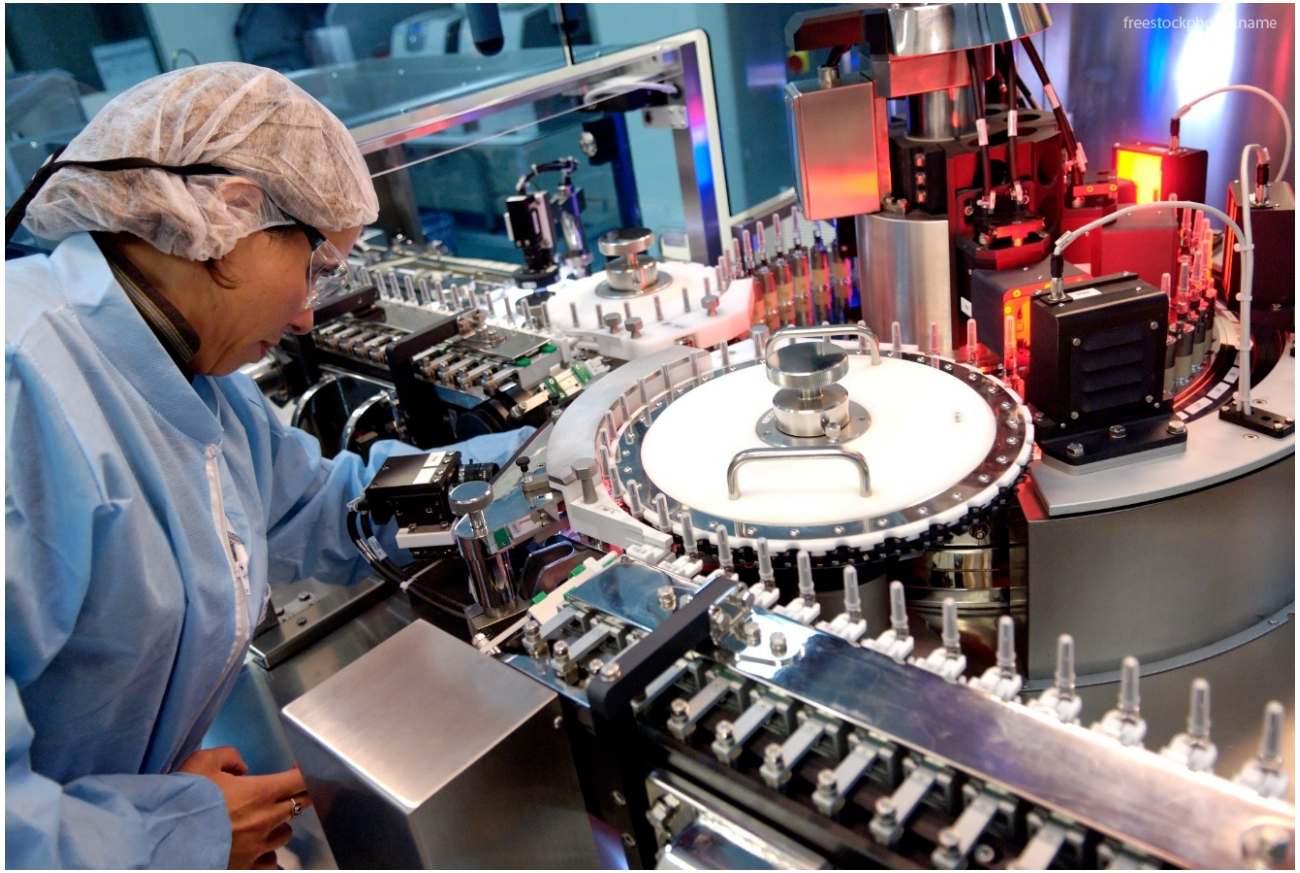
Under the “No Data—No Market” mantra, REACH requirements state that companies are required to register any substances imported or manufactured in quantities of more than 1 metric ton per year with the European Chemicals Agency (ECHA).

Substance toxicological data as well as risk assessment of the various uses is required information at registration.

New substances introduced on the EU market after 1981 require REACH registration within 18 months.


Before
Now
National Authorities
Companies, producing and importing chemicals

REACn in Pharmaceutical Industry



Terms and Abbreviations

- Active pharmaceutical ingredients (APIs).
- Excipient is an inactive substance that serves as the vehicle or medium for a drug or other active substance.
- Pharmaceutical intermediates - nonisolated intermediates, produced and kept within a reactor vessel to be transformed into a final molecule or any another intermediate.
- The European Medicines Agency (EMEA)
- The product- and process-oriented research and development (PPORD)

What Procedure for What Material

- **APIs and excipients are subject to REACh**

  but if they are already registered with EMEA as an ingredient of a medicinal product for human or veterinary use they are exempt from registration, evaluation, and authorization.

- Only quantities used as a registered API or excipient will be exempt; however, if the same substance is also produced for another use, such as food additives, it is still subject to REACH regulation.

What Procedure for What Material

- **Pharmaceutical intermediates are not subject to REACh.**

- Isolated intermediates have to be registered according to different rules, although they are not subject to authorization procedures. They are exempt from the evaluation process as well, provided they remain at the production site of origin. However, transported isolated intermediates are subject to REACH registration and evaluation.

What Procedure for What Material

- **Starting materials and reagents are subject to REACH** and are required to go through the registration process if they are produced or imported in quantities of more than 1 metric ton per year, per company (i.e., per legal entity). Moreover, compliance with authorization and restriction requirements is mandatory, even for volumes lower than 1 metric ton.

What Procedure for What Material

- **For APIs, excipients, intermediates, starting materials and reagents used during drug development and clinical trials, an exemption can be obtained via (PPORD) notification.**

- The exemption is valid for 5 years and can be extended for an additional 5 to 10 years upon proper application. **However, even with a PPORD exemption, users must document controlled use and apply health and environmental measures.**

REACh:

Pfizer

- The first company to publish their color-coded, hierarchical solvent selection guide for medicinal chemists.
- Solvents are listed as ‘preferred’, ‘usable’ or ‘undesirable’.
- 50 % reduction in chlorinated solvent use over 2 years.
- 97 % reduction in undesirable ethers.
- Increased use of heptane in place of the neurotoxic hexane and the more volatile and flammable pentane.

Globally Harmonized System of Classification and Labeling of Chemicals (GHS)

Requirements for labelling

- Chemicals Act (Finland).
- Act on dangerous products (Canada).
- EU Directive N 67/548.
- The standard system of identification of hazards of materials (USA).

GHS

- **1992 г.** - the UN Conference on the Environment and Development launched the system

- **2002 г.** – the World Summit on Sustainable Development encouraged countries to implement the new system ASAP with a view to having the system fully operational by 2008.

- Regulation № 1272/2008 („GHS“) is in the force since **20.01.2009**

Principal changes in GHS

1. New hazard classes and categories
2. New pictograms
3. New „Signal words“ (Hazard – Warning)
4. H-statements (Hazard Statement)
5. P-statements (Precaution Statement)

1. HAZARD CLASSES

Physical hazard

1. EXPLOSIVES
2. FLAMMABLE GASES
3. FLAMMABLE AEROSOLS
4. OXIDISING GASES
5. GASES UNDER PRESSURE
6. FLAMMABLE LIQUIDS
7. FLAMMABLE SOLIDS
8. SELF-REACTIVE SUBSTANCES AND MIXTURES
9. PYROPHORIC LIQUIDS
10. PYROPHORIC SOLIDS
11. SELF-HEATING SUBSTANCES AND MIXTURES
12. SUBSTANCES AND MIXTURES WHICH IN CONTACT WITH WATER EMIT FLAMMABLE GASES
13. OXIDISING LIQUIDS
14. OXIDISING SOLIDS
15. ORGANIC PEROXIDES
16. CORROSIVE TO METALS

Health hazard

1. ACUTE TOXICITY
2. SKIN CORROSION/IRRITATION
3. SERIOUS EYE DAMAGE /EYE IRRITATION
4. RESPIRATORY OR SKIN SENSITISATION
5. GERM CELL MUTAGENICITY
6. CARCINOGENICITY
7. REPRODUCTIVE TOXICITY
8. SPECIFIC TARGET ORGAN TOXICITY - SINGLE EXPOSURE
9. SPECIFIC TARGET ORGAN TOXICITY - REPEATED EXPOSURE
10. ASPIRATION HAZARD

Environment hazard

HAZARDOUS TO THE AQUATIC ENVIRONMENT

HAZARDOUS FOR THE OZONE LAYER

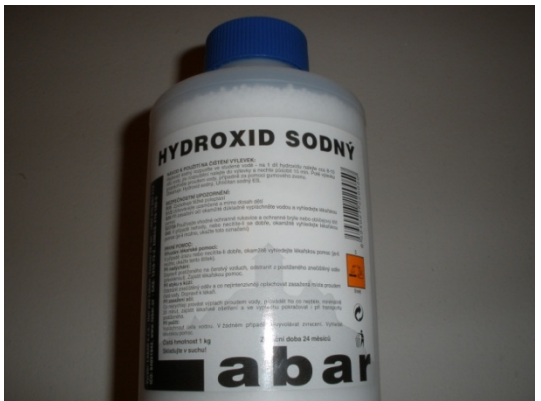
2. PICTOGRAMS

3. SIGNAL WORDS

Two signal words shall be used on the label:

1. “Danger”, indicating the more severe hazard categories;
2. “Warning”, indicating the less severe hazard categories.

Where the signal word “danger” is used on the label, the word “Warning” shall not appear on the label.



4. HAZARD STATEMENTS

Hazard	H-statement
Physical	H 201 – Explosive, mass explosion hazard
Health	H 300 - Fatal if swallowed
Environment	H 400 - Very toxic to aquatic life

5. PRECAUTIONARY STATEMENTS

Precaution measures	P-statement
General	P101 - If medical advice is needed, have product container or label at hand.
Prevention	P202 - Do not handle until all safety precautions have been read and understood.
Reaction	P310 Immediately call a Poison Center or doctor/physician.
Storage	P402 - Store in a dry place.
Disposal	P501 - Dispose of contents/container in accordance with local/regional/national/international regulation (to be specified).

Management of Chemicals

ZERO HARM, SAFETY FIRST