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Restrictions in the use of biocides for disinfection procedures

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Research and Development

the plus of pure performance

Conclusion of previous presentation

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- **Effective biocides are still available. But how long?**
- **Usually, multi-resistant Gram-negative bacteria are not more resistant to disinfectants than sensitive strains**
- **Disinfectants that do not smell and are skin and material friendly such as QACs are sometimes not sufficient to fight pathogens**
- **Stronger active ingredients with a broad spectrum are also needed**

→ **Disinfectants (biocides) play an important role in infection prevention**

→ **There is a need for a variety of biocides now and also in future !**

Key Selection Criteria for Disinfectants

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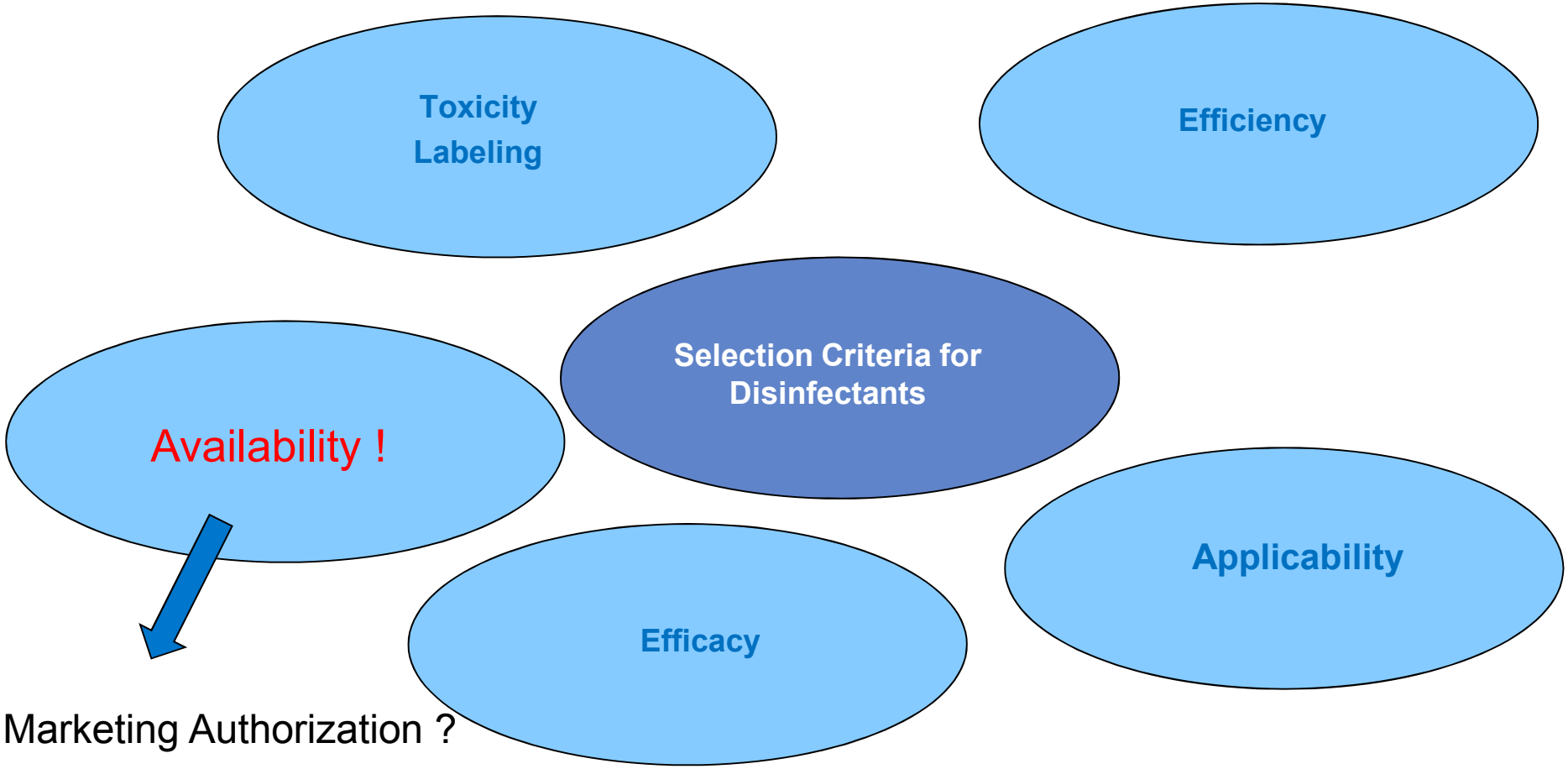

Marketing Authorization ?

Legal challenges with the development and marketing of antimicrobial products in EU (hygiene)

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REACH
Registration, Evaluation, Authorization of Chemicals
1907/2006

all w/o medicinal products

CLP
Classification, Labeling, Packaging
1272/2008

all w/o medicinal products w/o medical devices in direct contact with human body

MDD
Medical Device Directive
93/42/EC
→ MDR in planning

instrument disinfectants

surface disinfectants

MPD
Medicinal Products Directive
2001/83/EC

antiseptics

hand disinfectants (medicinal,DE)

BPR
Biocidal Products Regulation
528/2012
Incl. implementing regulations

hand disinfectants

surface disinfectants

Scope of BPR and CLP

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BPR

- improve the functioning of the internal market through the harmonisation of the rules on the making available on the market and the use of biocidal products,
- ensuring a high level of protection of both human and animal health and the environment.

CLP

- ensure a high level of protection of human health and the environment.
- free movement of chemical substances, mixtures and certain specific articles, while enhancing competitiveness and innovation

BPR – 2 step procedure

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1. Active Substances

a) the build up of a positive list of actives, which are allowed to be used in BP

- List of Approved Substances
- List of approved manufacturers of active substance (Art. 95 list)

- **Harmonized classification during evaluation procedure**

listing in positive list

EU
Positive list

Phase 1
for defined product types

2. formulated Biocidal Products

b) the authorization and the marketing of BP in the member states

c) the mutual recognition of the authorizations in the European Union

d) Union-Authorisation (= central authorization) in all Member States via ECHA, granted by Commission

Product authorisation
MR / UA

MS1 MS2 MS3 Union

Phase 2
for defined PTs and uses

Active Substances and Biocidal Products – Costs

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- Listing of an active substance
  - Data: 100-3000 T€ Dossier: 50-200 T€ fee ECHA: >120 T€ fee eCA: 50-400 T€

Total 320 - 3,800 T€

- Authorization of a Biocidal Product
  - UA data/dossier: 100-200 T€ fee ECHA: 80-150 T€ fee eCA: 10-100 T€
  - MR data/dossier: 100-200 T€ fee ECHA: 700 € per MS fee eCA: 10-100T€ + fee MR: 1-6 T€ per MS

Total 200 - 500 T€

(Calculation based on 30 countries)

- Annual Fees

BPR: active substance approval

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Identification:	759 active substances
Notification:	363 active substances
after dossier submission	~180 active substances

start ~ 1000 actives

after evaluation in positive list: ?

PT	notified actives	submitted dossiers	%	Review-Programm	positive list
1	87	44	50	28	5
2	163	91	56	78	7
3	108	59	55	43	5
4	105	60	57	48	10
6	143	56	39	44	4
7	89	45	50	26	3
8	80	40	50	7	38
9	138	69	50	37	2
10	94	47	50	26	2
11	127	64	50	49	1
12	118	59	50	36	2
13	104	37	35	25	2
14	17	14	82	1	14
15	2	1	50	0	1
16	13	4	31	0	0
17	3	2	66	1	0
18	104	59	57	28	33
19	41	16	36	7	8
20	25	13	52	0	1
21	46	11	24	6	6

BPR: active substances PT 1 / 2 / 4

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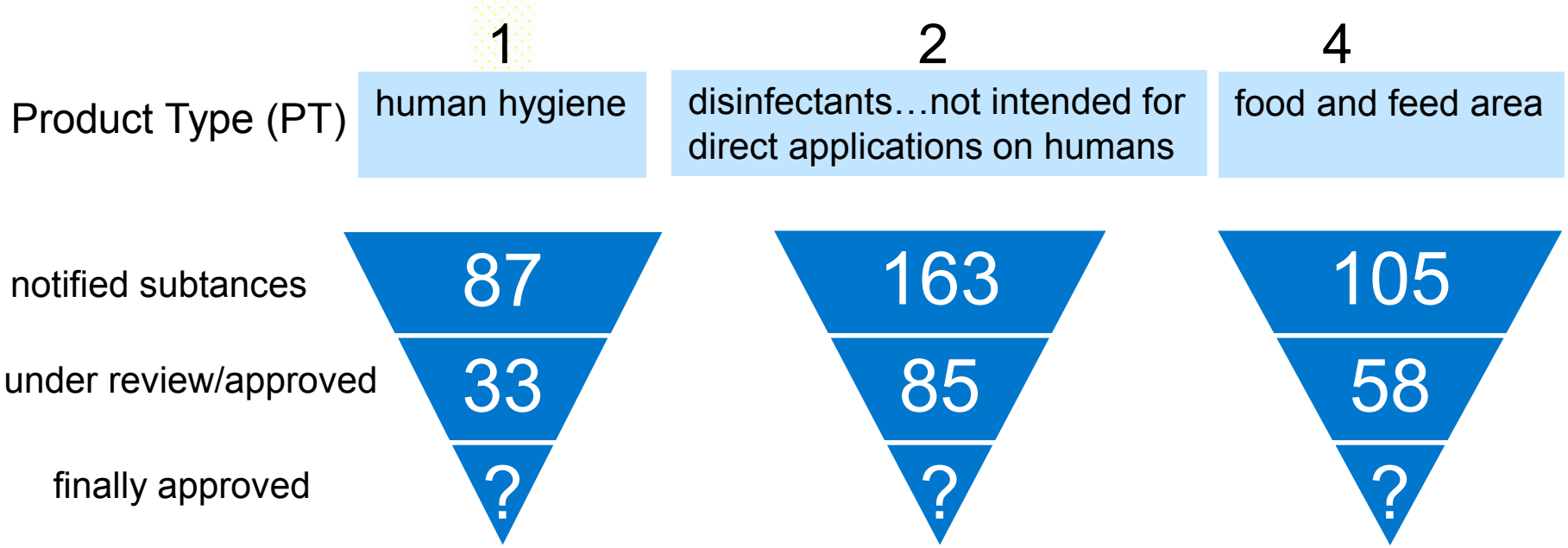

use in e.g. hand disinfectants surface disinfectants

BPR step 2: Union Authorisation Biocidal Products

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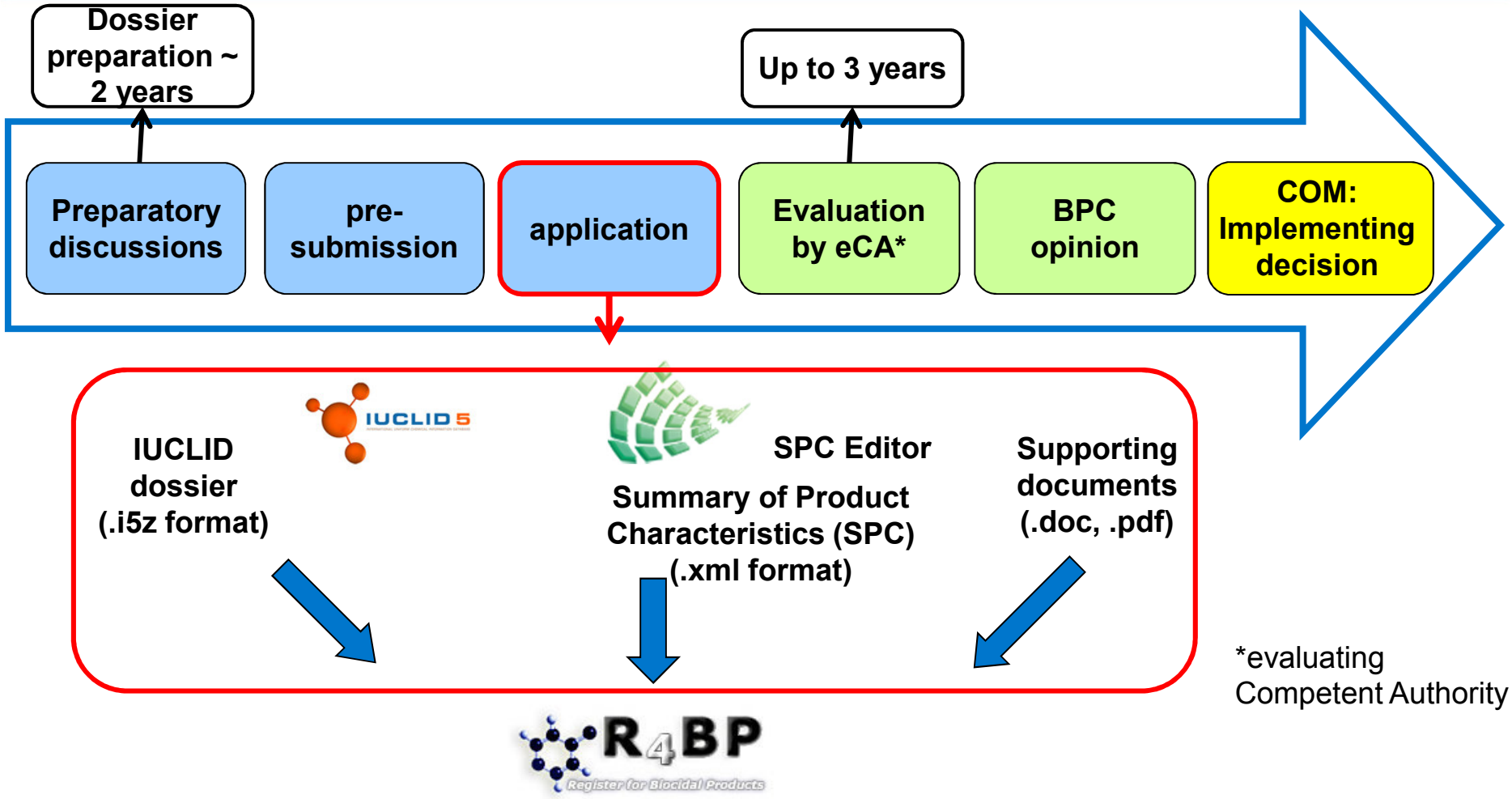

*evaluating Competent Authority

timeline PT 1,2,4 substances until 2019 products 2015-2022 (?)

Candidate for substitution / comparative assessment

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Substance evaluation

Candidate for substitution

Art.4: approval for max. 5 y
Art.10: renewal for max. 7 y

~~approval for max. 10 y~~
~~Art.12: renewal for max. 15 y~~

Art. 10: Substances
- fulfilling the exclusion criteria (Art. 5) → CMR Cat 1
- Respiratory sensitizers
- Fulfilling two of three PBT-criteria
- Significantly higher toxicity vs. other a.s.
- Reason for concern
- High amount of impurities or non active isomers

Consequence for Product Formulation

Biocidal Product evaluation

Comperatative assessment for BP

Art.23: approval for max. 5 y
Art.23: renewal for max. 5 y

~~Art. 17 approval for max. 10 y~~

Art. 23: Criteria
- No other authorized product for the same use with significantly lower risk
- Chemical diversity

Challenges (1)

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The problem of Approval of Active Biocidal Substances

- High investment for industry → only high volume substances survive
- Risk of non-approval
- Risk of candidate for substitution status → critical for product authorisation
- Basic research on new molecules less attractive

Availability ?

The problem of Biocidal Product Authorization

- High investment for industry → only high volume products survive
- Long-term process, complicated also for product modifications
- Risk of non-approval , risk of losing product applications

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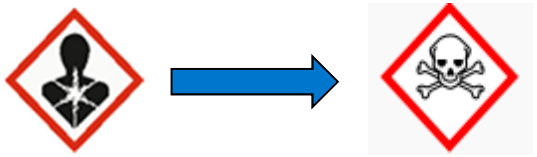
The problem of Reclassification of Active Biocidal Substances

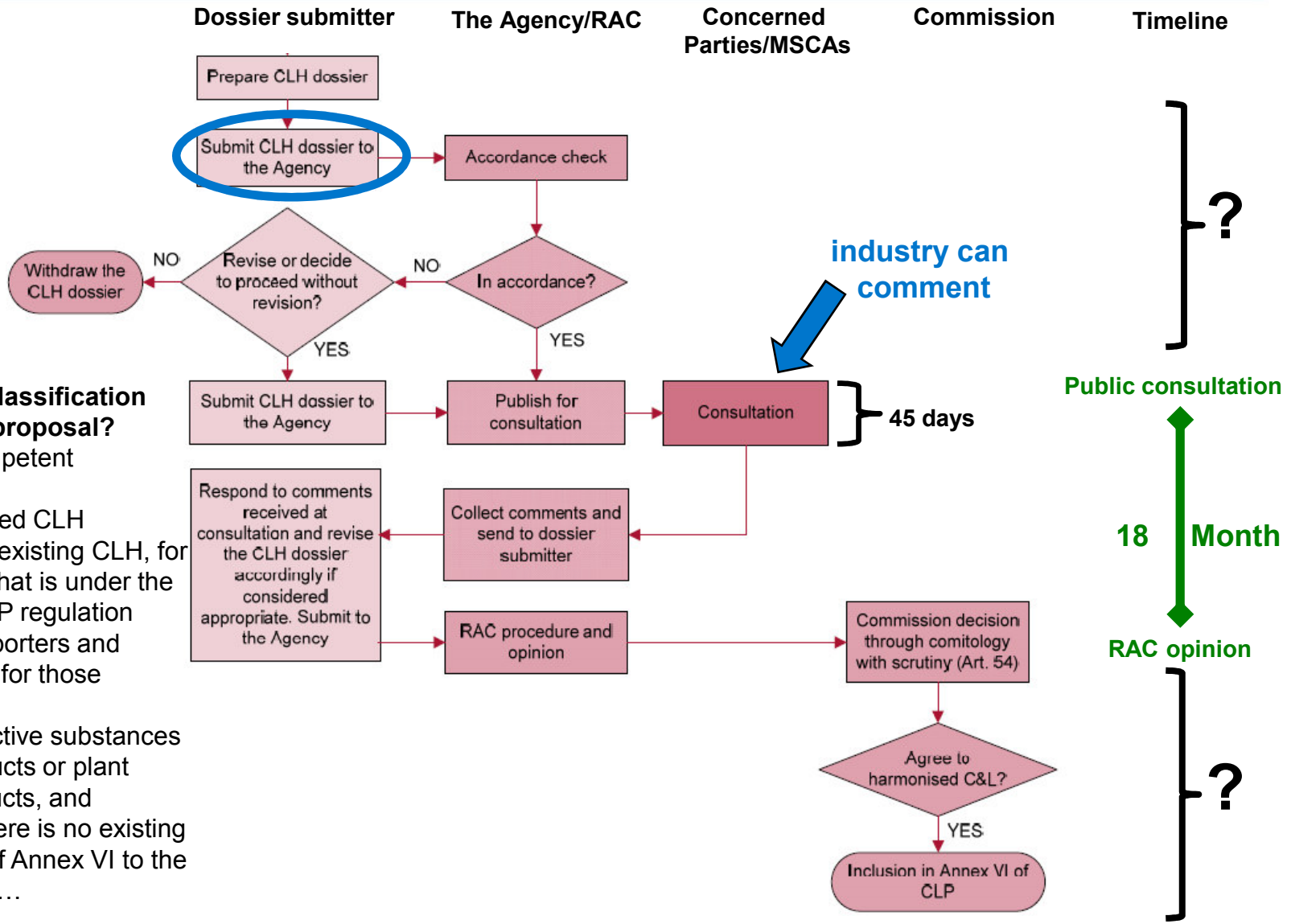
- EU harmonised classification is part of the BPR approval process (ECHA/RAC)
- Although safe use is corfirmed it may result in an „unfavorable „ classification
- It normally effects „unfavorable „ classification and labeling of **biocidal products**



User Acceptance ???

- The classification only represents the „hazard“ of a substance independend from its exposure route and is NOT a result of any risk assesment
- Classification often has an impact on handling and storage regulations
- The classification is valid for the substance also in all REACH applications

CLH-dossier - process



Who can submit a classification and labeling (CLH) proposal?

- Member State competent authorities
  - a new harmonised CLH
  - a revision of an existing CLH, for any substance that is under the scope of the CLP regulation
- Manufacturers, importers and downstream users for those substances
  - which are not active substances in biocidal products or plant protection products, and
  - provided that there is no existing entry in Part 3 of Annex VI to the CLP Regulation…

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It already real life !

Examples

polyhexamethylene biguanide hydrochloride (PHMB)

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- BPR: Support as biocidal active → required to maintain the use as biocidal active substance
  - BPC opinion: PT 1 use refused, PT 2: approved (no official inclusion decision)
  - Candidate for substitution
- harmonized classification by Risk Assessment Committee RAC/COM (944/2013)

valid since 01.01.2015 !

Pictogram, signal word		Hazard class	Hazard statement
GHS05	Danger	Eye Dam. 1	H 318
GHS07	Warning	Acute Tox 4, oral	H 302
GHS08	Danger	Skin Sens 1B STOT RE 1	H 317 H 372, inhal.
		Carc cat 2	H 351
GHS09	Warning	Aquatic Acute 1	H 400
		Aquatic Chronic 1	H 410

- Impact
  - No use within biocidal products accepted by users, even if safe use could be shown
    → Active substance will vanish from the biocidal market
  - No longer allowed in cosmetics, impact on medical devices

surface disinfectant label
1,2% PMBH + 18 % QAV

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past

H314: Causes severe skin burns and eye damage.
H317: May cause an allergic skin reaction.
H373: May cause damage to organs through prolonged or repeated exposure.
H410: Very toxic to aquatic life with long lasting effects.

today since 01.01.2015

H314: Causes severe skin burns and eye damage.
H317: May cause an allergic skin reaction.
H351: Suspected of causing cancer.
H373: May cause damage to organs through prolonged or repeated exposure.
H410: Very toxic to aquatic life with long lasting effects.

User Acceptance ???

Glutardialdehyde (GDA)

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- BPR: Support as biocidal active
  - BPC opinion and inclusion decision published (deadline for product authorization: 30.9.2016)
  - candidate for substitution
- harmonized classification by Risk Assessment Committee RAC
  - RAC opinion published, ATP is open

Pictogram, signal word		Hazard class	Hazard statement
GHS06	Danger	Acute Tox. 2, inh.	H330
		Acute Tox. 3, oral	H301
GHS05	Danger	Skin Corr. 1B	H314
		STOT SE 3	H335
GHS08	Danger	**Skin Sens. 1A**	**H334**
		Resp. Sens. 1	**H317**
GHS09	Warning	Aquatic Acute 1	H400
		Aquatic Chronic 2	H411

expected in 2017/18

- The occupational exposure limit of glutardialdeyhde is defined in Germany as 0.05 ppm

surface disinfectant label
9,8 % GDA + 18 % Quaternary ammonium compounds, benzyl-C12-16-alkyldimethyl, chlorides

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today

H302+332: Harmful if swallowed or if inhaled.
H314: Causes severe skin burns and eye damage.
H317: May cause an allergic skin reaction.
H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H335: May cause respiratory irritation.
H410: Very toxic to aquatic life with long lasting effects.

future 2017/18

H302: Harmful if swallowed
H331: Toxic if inhaled.
H314: Causes severe skin burns and eye damage.
H317: May cause an allergic skin reaction.
H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H335: May cause respiratory irritation.
H410: Very toxic to aquatic life with long lasting effects.
EUH071: Corrosive to the respiratory tract.

User Acceptance ???

The Ethanol Story…

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Enjoy !

Ethanol

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- BPR: Support as biocidal active by formulator task-force
  → required to maintain the use of ethanol as biocidal active substance

- harmonized classification by Risk Assessment Committee RAC likely
  - Up to now no CLH dossiers was submitted
  - Classification as CMR is proposed within BPR procedure due to cancer studies on humans (misuse of alcoholic beverages - chronic oral consumption in amounts beyond levels normally tested)
    - Carc. 1A or 1B H350 May cause cancer
    - Muta. 1B H340 May cause genetic defects
    - Repr. 1A H360FD May damage fertility or the unborn child
    - Lact. H362 May cause harm to breast-fed children

  - Classification valid for all uses
    → Even if no oral use is given → classification is independent from the exposure route
    → Even if all ethanol products were denatured and oral exposure is not possible
    → exclusion criteria BPR → restriction of biocidal uses / no consumer use
    → **Alcoholic beverages are exempted (food)**

Scenario :hand disinfectant label with 80 % Ethanol

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today

signal word: DANGER

H225: Highly flammable liquid and vapour.

H319: Causes serious eye irritation.

future ???

signal word: DANGER

H225: Highly flammable liquid and vapour.

H319: Causes serious eye irritation.

H340: May cause genetic defects.

H350: May cause cancer.

H360: May damage fertility or the unborn child.

H362: May cause harm to breast-fed children

User Acceptance = zero

Scenario :
surface disinfectant label with 30 % Ethanol

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today

signal word: WARNING

H226: Flammable liquid and vapour.

H319: Causes serious eye irritation.

future ???

signal word: DANGER

H226: Flammable liquid and vapour.

H319: Causes serious eye irritation.

H340: May cause genetic defects.

H350: May cause cancer.

H360FD: May damage fertility or the unborn child.

H362: May cause harm to breast-fed children

User Acceptance = zero

Impact – BPR/REACH/CLP

amount of actives decreases

- No support for political reasons
- No support due to high risk potential
  → more severe labeling
- No support due to economic reasons
- Support but exclusion due to risk potential
- Candidates for Substitution

application

- limitation to certain applications
- less new developments
- less variation in products
- no solutions for niche applications

costs

- increasing prices due to
  - fees
  - study costs
  - dossier costs

Discussion

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- A variety of Biocidal Products (disinfectants) are more than ever essential for infection prevention ⟹ protection of human health
- But : applying biocidal products means a potential risk for the environment
- Ethical scope of regulations (REACH/BPR/CLP/others)
  high level of protection of both human and animal health and the environment
- Risk / Benefit evaluation is missing
- No (clear) differentiation between consumer and professional use
- Risk assessments are performed on the basis of worst case scenarios
- Hazard labeling and classification leads to minor user acceptance
- A risky investment for industry in not the biggest markets
- How to assure the availability of biocides in future ?