National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Socio-Economic analysis for REACH Authorization

Use of the solvent 1,2-dichloroethane (EDC) in manufacture of an Active Pharmaceutical Ingredient

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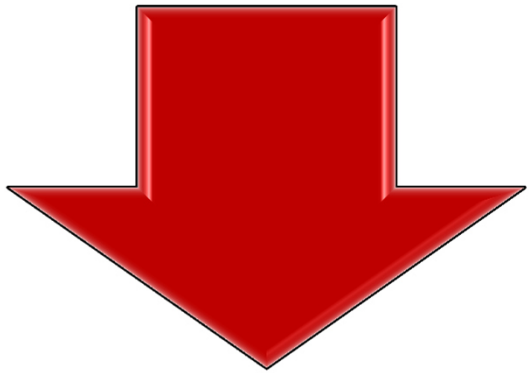
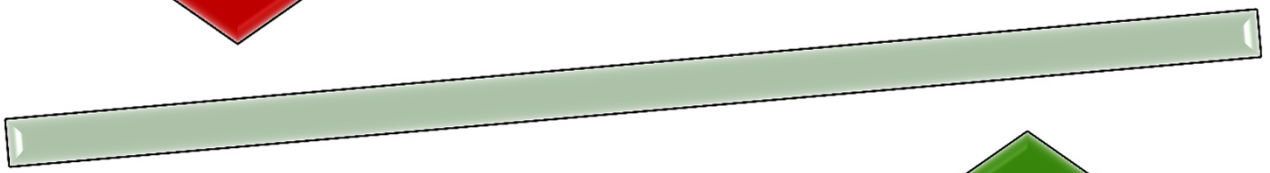
Authorization SEA route: benefits vs risks



Benefits of continued use

IMPACT: Costs incurred in the non-use scenario



Risks of continued use

IMPACT: E.g. human health impacts of applied for use scenario

Use applied for

- Requested review period: 13 years
- Major investment made in 2011
- Full use of the capacity expected in 2030.
- Around that time: intended decision on investment about whether or not to continue production and possible expansion.
- 13 year review period requested: decision on re-applying as close as possible to their business decision on prolongation and expansion of Iopromide production

Analysis of Alternatives

Efforts made in analysis of alternatives:

- Solvents
  - R&D since 1990
  - Drop-in: 11 families tested
  - Claim and detailed justification on non-technical feasibility

- Synthesis routes
  - 4 routes analysed (desk study)
  - Literature and patents
  - Not technically feasible

Analysis of Alternatives (contd.)

- Other API
  - Alternative LOCM X-ray contrast medium
  - Competing LOCM medicinal products listed
    - API name grouping
    - Manufacturers ID’s
    - Market shares
    - Not likely EDC is used in their (EU) manufacture. Conclusion: Technically feasible, not economically feasible

- Managerial options (shut-down, relocation)

Alternatives, how did SEAC approach this

- Applicant provided well-justified claim that currently no technically feasible alternatives to EDC are available, and there will be no such alternatives by the sunset date

- Economic Feasibility: None of the alternatives economically feasible
  - Use likely magnitude of costs of
    - Theoretical transition to other solvent (R&D, price difference, requalify API)
    - Other synthesis route (much more expensive due to technical demands and need to requalify API)
    - Relocation (costs of knowledge transfer, investment, requalification)
    - Shut-down (complete loss of market)

Human health impacts: approach

- Change in physical health impacts (disease burden) due to changes in exposures to chemical
- Linking quantitative relationships between exposure and the health impact of interest (cancer).
- Dose response relationship + Exposure > risk > disease burden > monetized impact

Risks of continued use

- Non-treshold substance: exposure workers (40 years) and man via environment (70 years): define the level of risk at one site of use (Germany)

- From risk to impact: Estimate statistical cancer cases (inhalation) based on dose-response relationship

- Workers: 1.13 x 10^{-2} additional statistical cancer cases (fatal and non-fatal), based on 217 workers exposed, calculated for requested review period of 13 years

- Man via environment: oral and inhalation: 1.17 x 10^{-3} cases

Human health impacts of continued use

- Starting points:
  - willingness to pay (WTP) value of €5 million to avoid a fatal cancer case
  - €396,000 for a non-fatal cancer case
  - nonfatal-fatal ratio of 55.92/44.08
  - 4% discount rate

- economic welfare losses associated with this number of excess cancer cases: €28,344, 13 years
  - Includes increased production estimates
  - Could be counteracted by planned exposure reduction efforts at the site

Costs of non-use scenario calculated

Other factors regarding profit losses:

- No compensation of losses possible: dedicated equipment cannot be used for manufacturing of other API
- No compensation possible by selling dismantled equipment

- EU suppliers of raw materials will loose market as Asian producer will source from Asian suppliers (less than 100 million Euro losses for upstream suppliers)
  - SEAC: some suppliers would find new customers

Costs of non-use scenario: social impacts

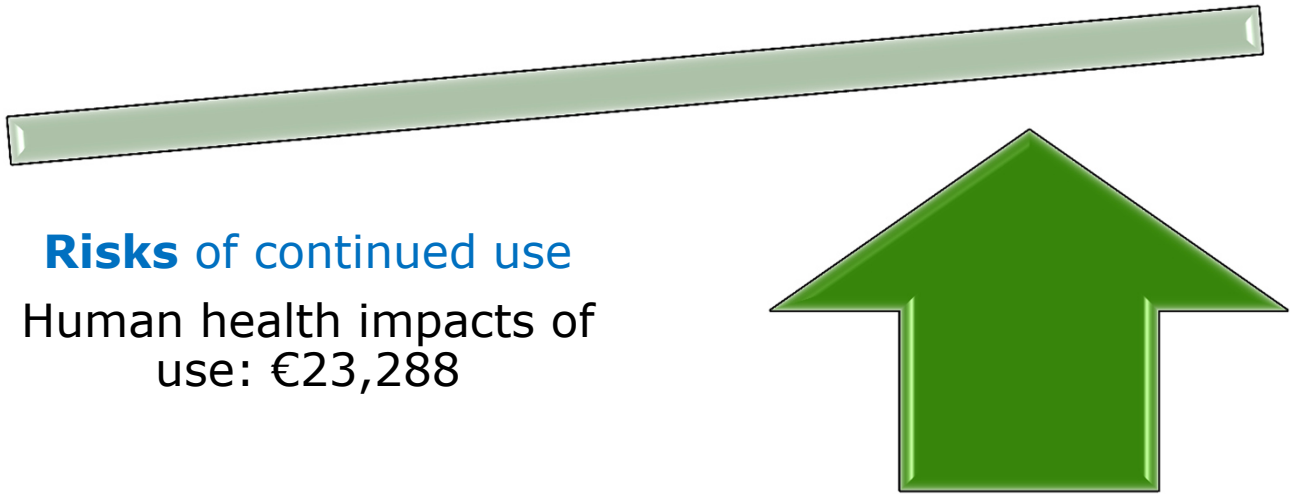
- unemployment associated with redundancies resulting from the cessation of production of Iopromide
  - redundancy payments (63% of salary costs) for one year times the number of unemployed workers.

Authorization EDC use for manufacture of Iopromide

Benefits of continued use

Sum of profits €100-500 million

Cost of unemployment €10-100 million



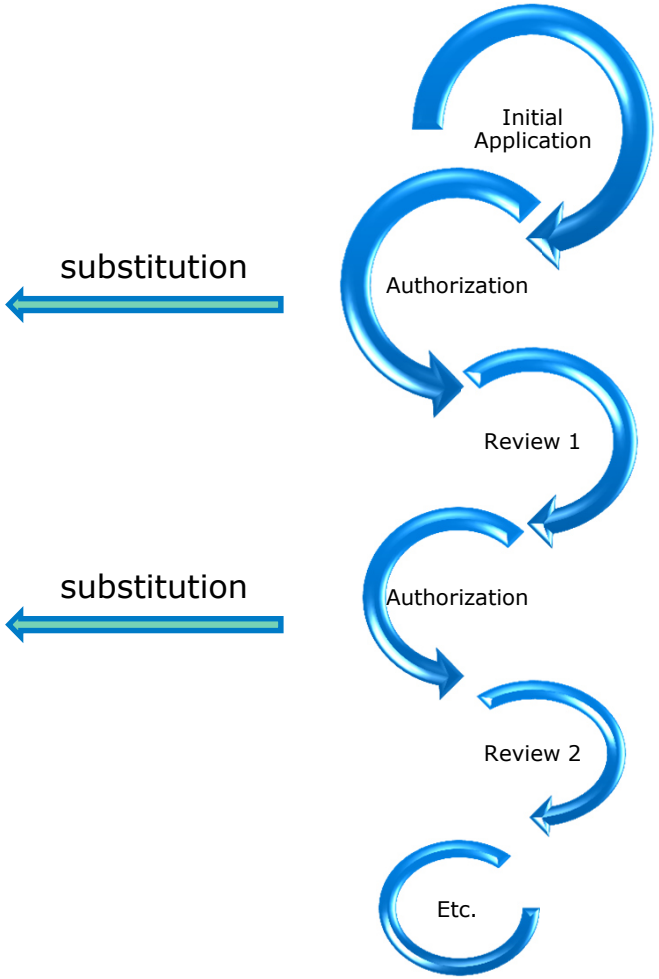
Risks of continued use

Human health impacts of use: €23,288

Benefits vs risk: how did SEAC approach this

- Benefits of continued use of EDC considerably exceed the risks of continued use

- Uncertainties considered minor such that they would not affect the overall conclusion



Downstream notifications (art. 66) and supply chain communication

More information on specific uses and users

Review of REACH Authorization, general principle

Review period

- A long review period (12 years) was recommended based on:
  - No suitable alternatives (also not expected within a normal review period)
  - Estimated costs much less than benefits
  - Benefit/risk ratio is not likely to change in the near future
  - API qualification and changes in marketing authorizations worldwide would incur high costs
  - Costs of theoretical change of manufacturing process would be high

Exceptional case discussion

- Applicant applied for 13 year: exceptional case. Decision on investment planned for 2030 at maximum capacity
- SEAC considers this an uncertain future scenario and no argument for an exceptional case
- Decision on re-applying needs to be made by every applicant
- Note: Exceptional case argumentation by SEAC is still pending discussions at policy level

Time for Discussion and Questions

Additional Slide with Question for attendants

- Which of the statements below is best describing the difference between applying for authorization following the SEA route and the Adequate Control route?
  - A: If the applicant argues there is Adequate Control, an analysis of alternatives is not needed
  - B: If the applicant argues there is Adequate Control, an SEA is not needed, decision to grant authorization is than based on conclusion on risk control
  - C: The applicant can build an Adequate Control case but has to account for the possibility that RAC disagrees with it and hence, the dossier should in principle be the same, applicant cannot assume a “route”
  - D: for substances with a threshold effect authorization can only be granted based on Adequate Control