The Greenscore an environmentally friendly development tool

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ORIL Industrie

Servier group

Located in Nomandie

ORIL Industrie

- 2 sites
- 33 Ha gathering both R&D and manufacturing activities
- 800 collaborators
- 85% of Servier Active Pharmaceutical Ingredients
- 2000 tones of API pear year
- Industrial portfolio:
  - 20 APIs + 35 APIs in development
  - 150 Intermediates

Bolbec

Baclair

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ORIL Industrie: Industrial Research center

- **Produce** API candidates for pre-clinicals and clinicals studies
- **Develop** efficient & sustainable synthesis for intermediates and new drug candidates
- **Ensure** our Industrialization of processes
- **Share** with the scientific community
- **Innove** and anticipate chemistry of the future

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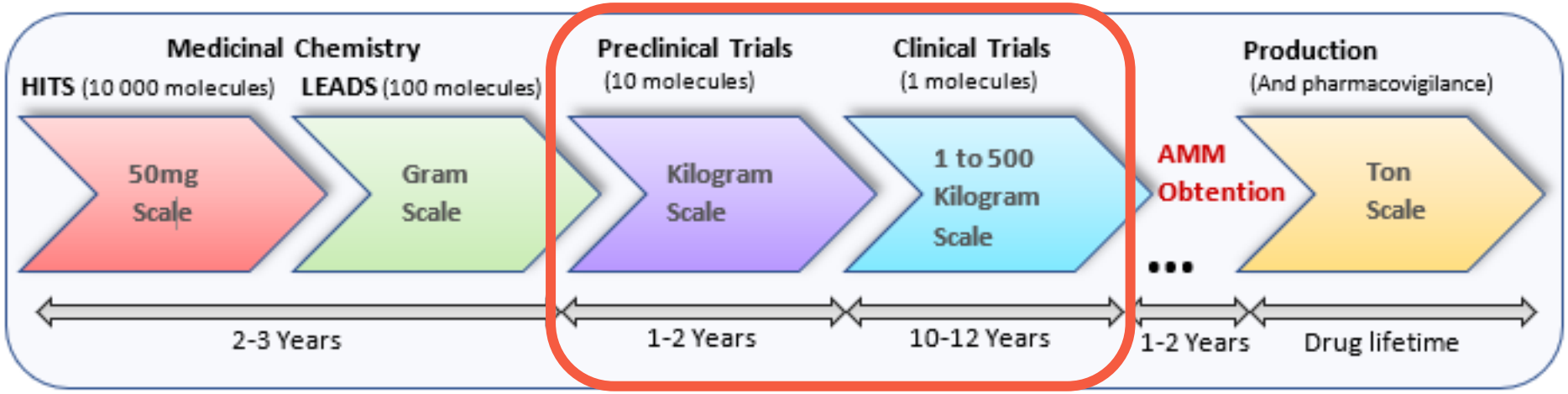
Remind Drug Development …

Chemical development



Saclay

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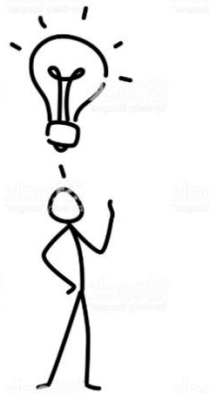
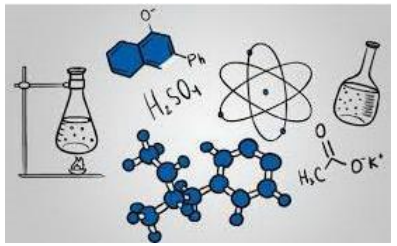
Sustainable Chemistry Group



2010



CHEMISTRY

HSE

PILOT PLANT

PRODUCTION

2018 solvents issue

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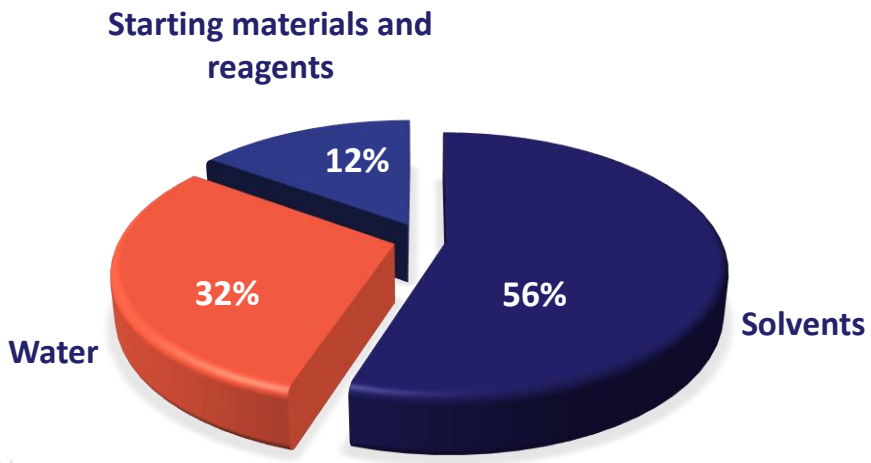
Twelve principles of Green chemistry

Pharmaceutical Industry



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Solvent selection Guide

Evaluation on 7 criteria

=> help the chemist in early development to select sustainable solvents in the news syntheses of new API.

Acetonitrile
Methylene chloride
DMI DMPU MMB
MEK Acetone
Toluene MCH
Propylene carbonate
Ethyl acetate
Dimethylcarbonate
AcO*i*-Pr
RPDE*
Cyclohexanone
AcO*n*-Pr
MMB-Ac
Anisole
t-Butanol
Butyronitrile
Butanol
Heptane
Ethyl lactate
Dioxolane
AcOMe
Isopropyl ether
NBP Cyrene
Chlorobenzene
Ethylene carbonate
CPME NMP
p-Cymene γ-Valerolactone
Cyclohexane
Pyridine NEP
3-methyl-pentanol Sulfolane
D-Valerolactone *p*-Xylene
Pentane Polarclean Equamide
Glycerol Carbonate
MTHP
L-limonene Ethyl lactate (D)
DMF Me.THF Dowclene TM-THF
Ethyl lactate (L) INFINITI*
D-Limonene Methoxypentane
Propionitrile MeOH
Dioxane THF
12 ETBE DME DEM
TFE
MIBK
MTBE
m-Xylene
DMSO
Isobutanol
Glycerol
o-xylene
Acetic acid
Ethanol
Isopropanol
Isobutyl acetate
IRIS*
Propylene glycol
Butyl acetate
Water

❑ Lack of toxicological data

❑ Subject to prefectural decree

* Cleaning solvent

Twelve principles of Green chemistry

GREEN SCORE

SOLVENTS

Use the greenest solvent it is not enough to have a green process

Other metrics are necessary

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What is greenscore ?

Who inspire us ?

GREEN MOTION by MANE

MANE

CHEM21

- Tool : evaluate the environmental impact of a chemical process step
- For the form, simple and friendly to use
- For the content, very complete and more relevant for pharmaceutical industry.

Green Chem., 2015, **17**, 2846-2852 (https://www.mane.com/innovation/green-motion)

Green Chem., 2015, **17**, 3111–3121

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How does it work?

One step

5 themes

15 questions

- ✓ Wastes
- ✓ Sustainability
- ✓ Solvent
- ✓ Energy
- ✓ HSE

Yield

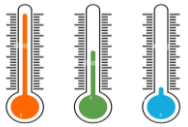
Economy of material
Cible < 25 Kg/Kg de PA

PMI
RME

< 50 ans

remaining years of stock

Nature of solvents



T°C, reflux

Toxicity and safety

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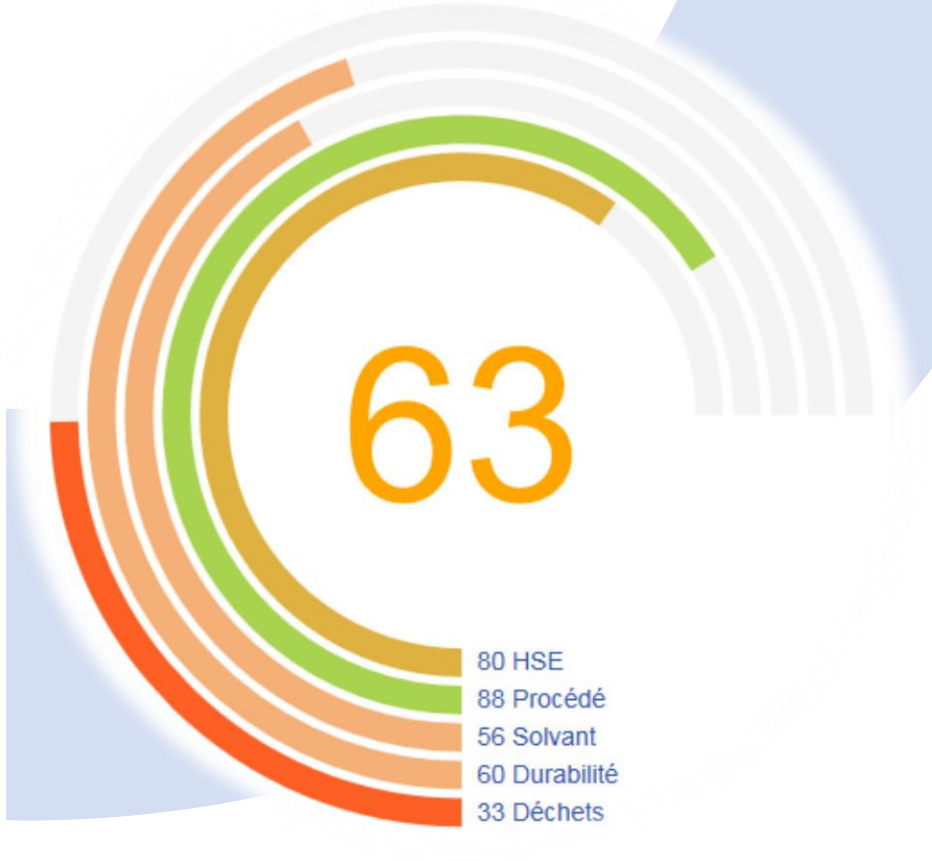
What does it look like?



Highlight potential issues
(environnemental performance)

2 aims:

- Make a MAP of actual industrial processes *(current commercial API)*
- Follow evolution, measure improvement during development phases

⇒ Help chemists in ecoconception of new processes
⇒ Make progress

⇒ Used since 2019 for new transposition to the pilote plant

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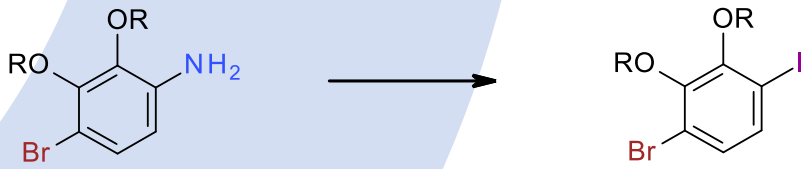
Example: Project in development (Phase 1)

Sandmeyer reaction



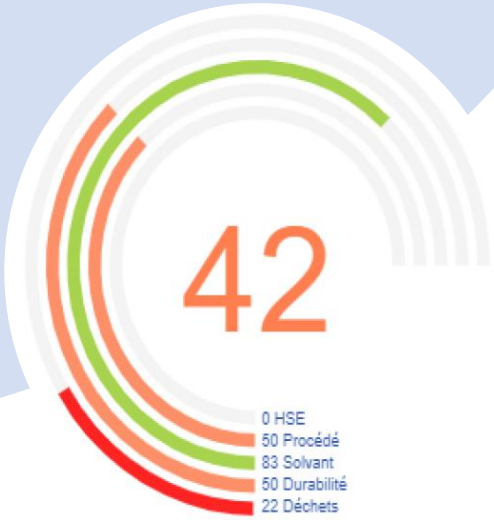
Optimization of process

Reaction: $NaNO_2$, KI, HCl, H_2O; between 0 and 52°c

Work-up: Ethyl acetate, multi-decantations, clarification, concentration until dryness.

Isolation: DCM, solvent switch to heptane (75°C), Charcoal, concentration until dryness.

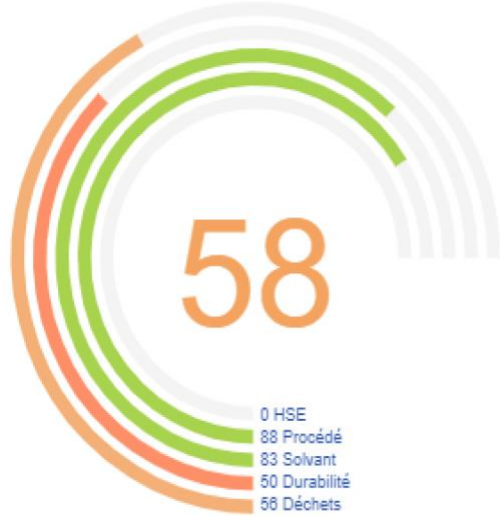
80%



Reaction: $NaNO_2$, KI, HCl, **H_2O/Acetone,** between -5 and 20°C

Isolation: Filtration, multi-washings

80%



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What could be improved? What was missing ?

- Improve the accuracy of the tool (scoring by range imprecise)

- Integrating environmental impact into Greenscore
  - The carbon footprint
  - The impact on the biodiversity

Quantis

Consulting company, Specialist of life cycle and environmental approach, witch guides organizations to define, shape and implement intelligent environmental sustainability solutions.

=> In 2022 Greenscore V2

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New version, what is changing?

One step

5 themes

24 questions

✓ **Wastes**

Yield

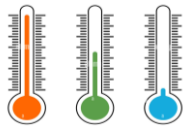
Economy of material
Cible < 25 Kg/Kg de PA

PMI
RME

✓ **Solvent**

➢ Nature **and quantities**

✓ **Energy**



T°C, reflux

Need to calculate more precisely the energy of our process:

- ➢ More details about the temperatures of process
- ➢ Quantity of solvent engaged

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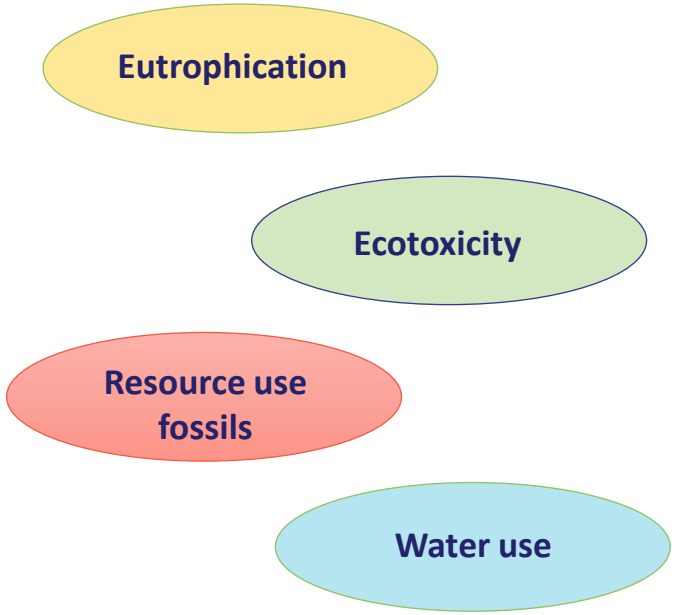
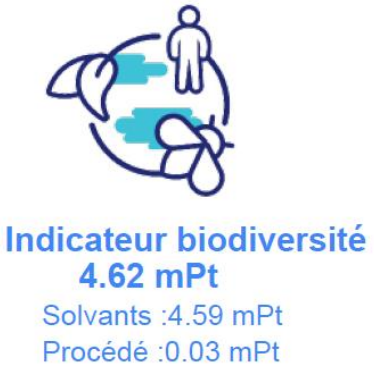
Greenscore V2





- Single common unit to have an overall score
- 1 Pt corresponds to the annual environmental impact of an European inhabitant.

Example: Project in development (Phase 2)

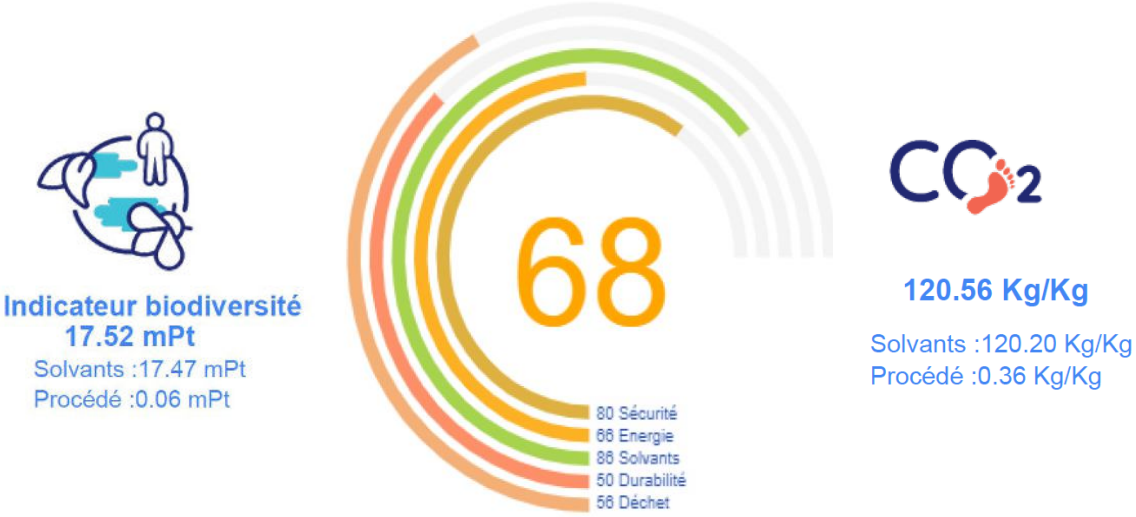
Heck coupling

Initial operating procedure

$(Ph_3P)_2Cl_2Pd$, AcOK
DMF (15L/kg),130°C
Multi-decantations, conc until dryness
Chromatography
Yield: **40%**

Operating procedure Phase 2

$Pd(OAc)4$, K_2CO_3, CTAB
Water/NMP (80:20, 10L/kg), 65°C
Filtration, Recrystallisation
Yield: **60%**



Example: Project in development (Phase 1)

Boc deprotection

Operating procedure (preclinical phase)

16 eq HCl, Water (8 L/Kg)
80°C, **54h**, Filtration
Yield : 82%

Indicateur biodiversité
2.06 mPt
Solvants :1.98 mPt
Procédé :0.08 mPt

25.30 Kg/Kg
Solvants :24.93 Kg/Kg
Procédé :0.36 Kg/Kg

Operating procedure (Phase I)

8 eq HCl, **IPA**/water (**13 L/Kg**)
80°C reflux, **5 h**, Filtration
Yield : 82%

Indicateur biodiversité
10.75 mPt
Solvants :10.15 mPt
Procédé :0.60 mPt

90.95 Kg/Kg
Solvants :86.56 Kg/Kg
Procédé :4.39 Kg/Kg

Gains : Productivity and quality of API

=> Greenscore is a good support decision tool but is not the only one

Green Card – Project A commercial

DRAFT

What is it?

Greeness indicator of Project A process

A score between 0 à 100

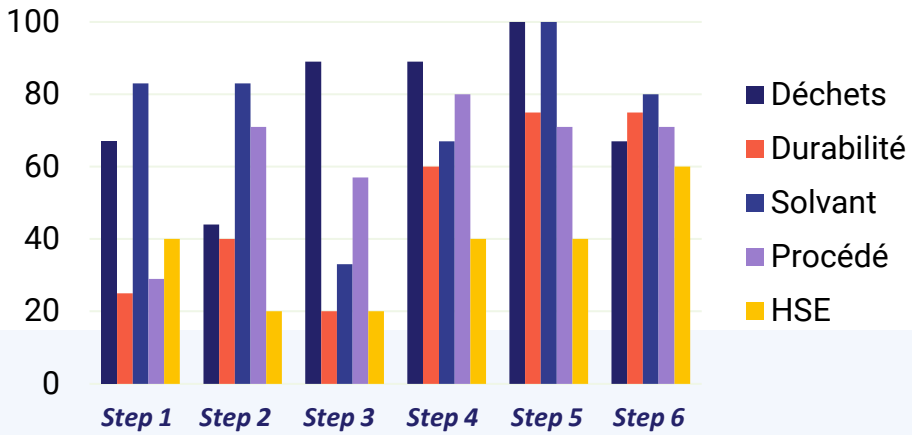
Five criteria

Waste Sustainability Solvent Process HSE

GreenScore by step

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
49	52	44	67	77	71

In details…



Keys forward sustainable process

Step 1 Step 2 Step 3

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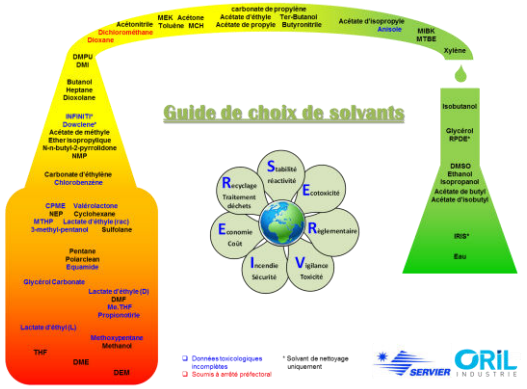
Conclusion

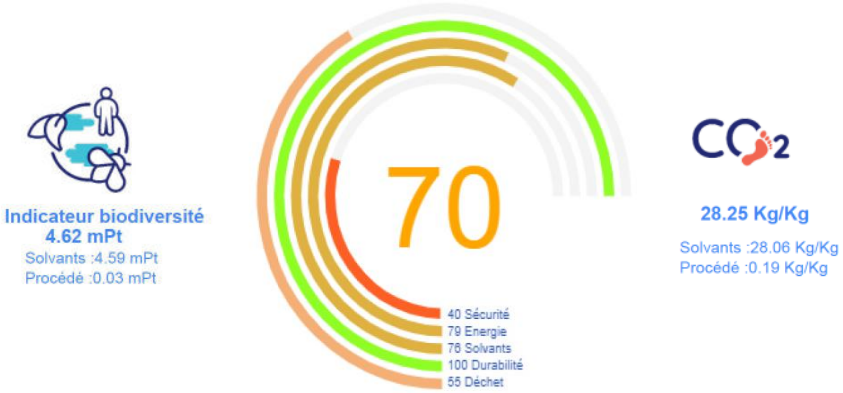
Measuring the “greenness” of different chemical processes

Make real progress and reduce the environmental impact

Ensure the sustainability of the pharmaceutical industry

Decision making





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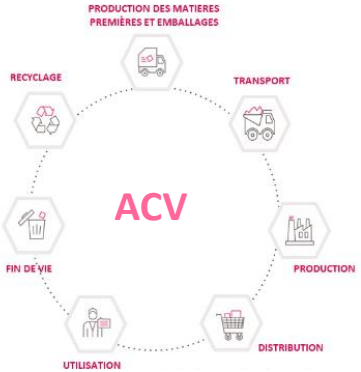
Thanks



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