# Manufacturing of Paclitaxel Bulk

**EXTRACTION**

- From *Taxus brevifolia,* Pacific Yew Tree
- 0.02% yield of the dry weight of bark
  (1kg of paclitaxel = 3,000 trees /500 patients)
- Complex extraction & purification, Expensive

**SEMI-SYNTHESIS**

- From *Taxus baccata,* European Yew Tree
- 10-DAB (10-Deacetylbaccatin III)
- High cost, Complex impurity profiles, Low yield

**PLANT CELL CULTURE**

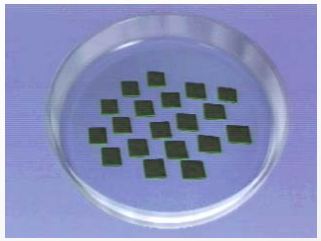
- From *Taxus chinensis,* Genexol®
- High purity (>99.0%), Low cost,
  Environmentally friendly, Reproducibility

*Genexol®*

# Plant Cell Culture Technology

**Genexol®** bulk is manufactured from the callus of *Taxus chinensis* by plant cell culture technology.

Yew Tree



Callus Induction

Callus

Suspension Culture

Scale-up

Purification


Genexol

# Plant Cell Culture Technology Advantages

| | | |
|---|---|---|
| ▪ **High paclitaxel content in Biomass**<br>**- Extraction: 0.005 ~ 0.01%**<br>**- Plant cell culture: 0.05% ~ 0.1%** | → | **Easier to purify** |
| ▪ **Less Impurities in Biomass**<br>**- Extraction: Many phenolic compounds (Tannine, chlorophyl)**<br>**- Plant cell culture: few phenolic compounds** | → | **Less purification steps** |
| ▪ **Low Analogue Concentration**<br>-Content in initial extraction: 70~80% of paclitaxel<br>* Low content of cephalomannine: structurally very similar to paclitaxel → Difficult to remove | → | **Efficient Purification process** |
| ▪ **Easy way to control the production parameters** | | |
| ▪ **No need to cut down fully grown yew trees to obtain biomass from bark or needles** | | |

→ **Competitive Method To produce Paclitaxel**

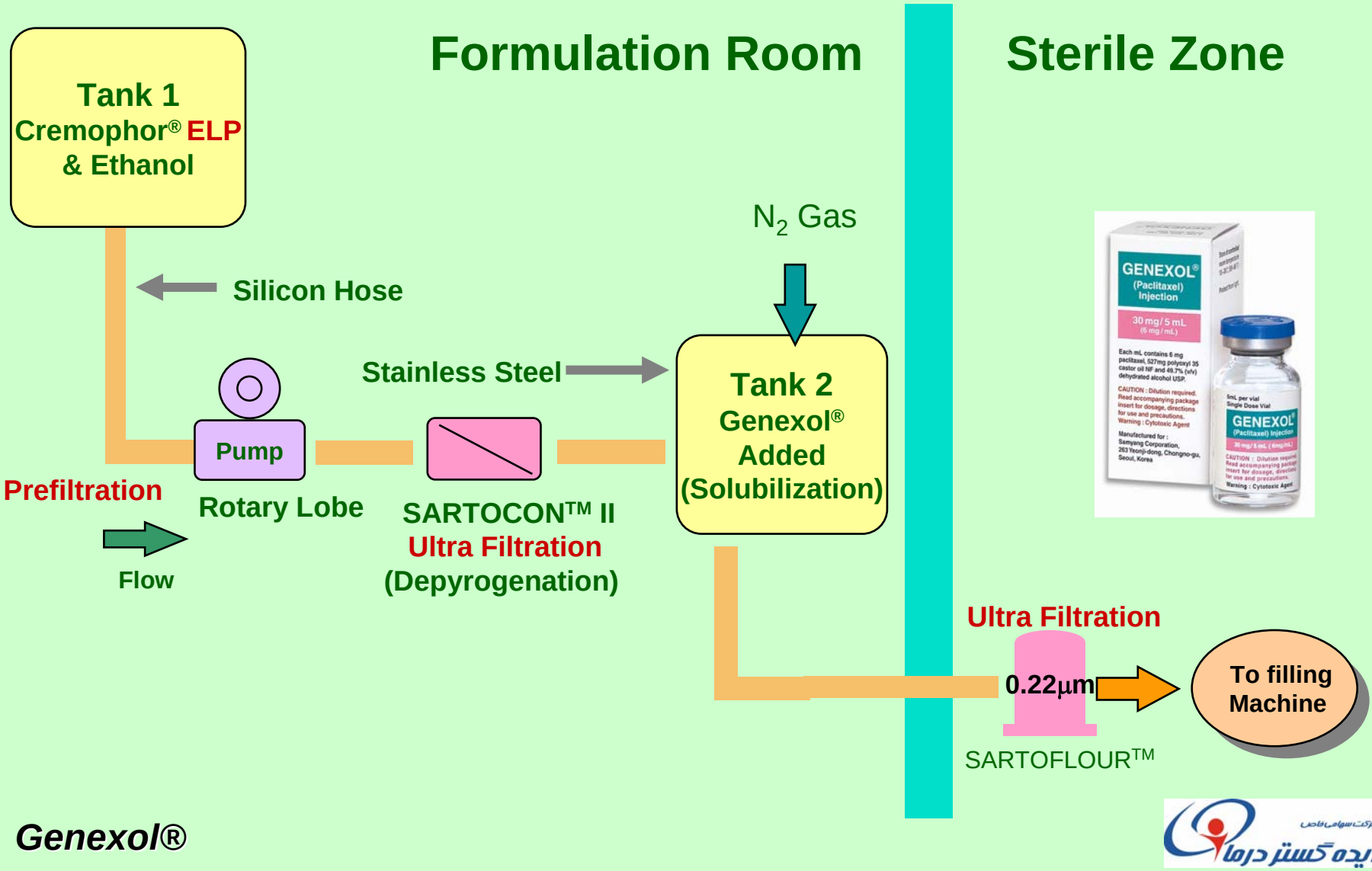
→ **Easy to Maintain High Purity (>99.0%)**

→ **Constant Quality**

→ **Environment Friendly**

***Genexol®***

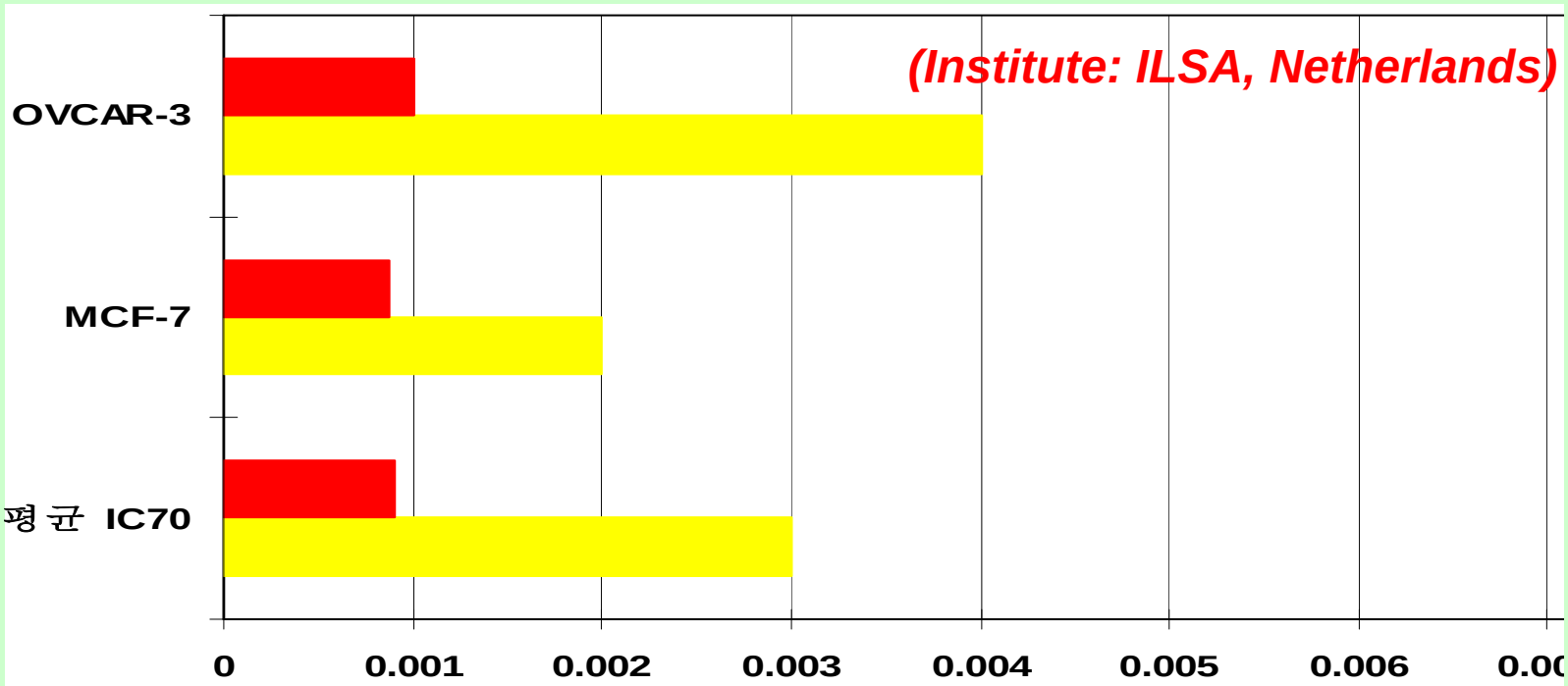
# Genexol Injection - Manufacturing Procedure




Genexol®

# Pharmacology - in-vitro Cytotoxicity

**Human**
**Tumor cell line**




**$IC_{70}$(μg/mL)**

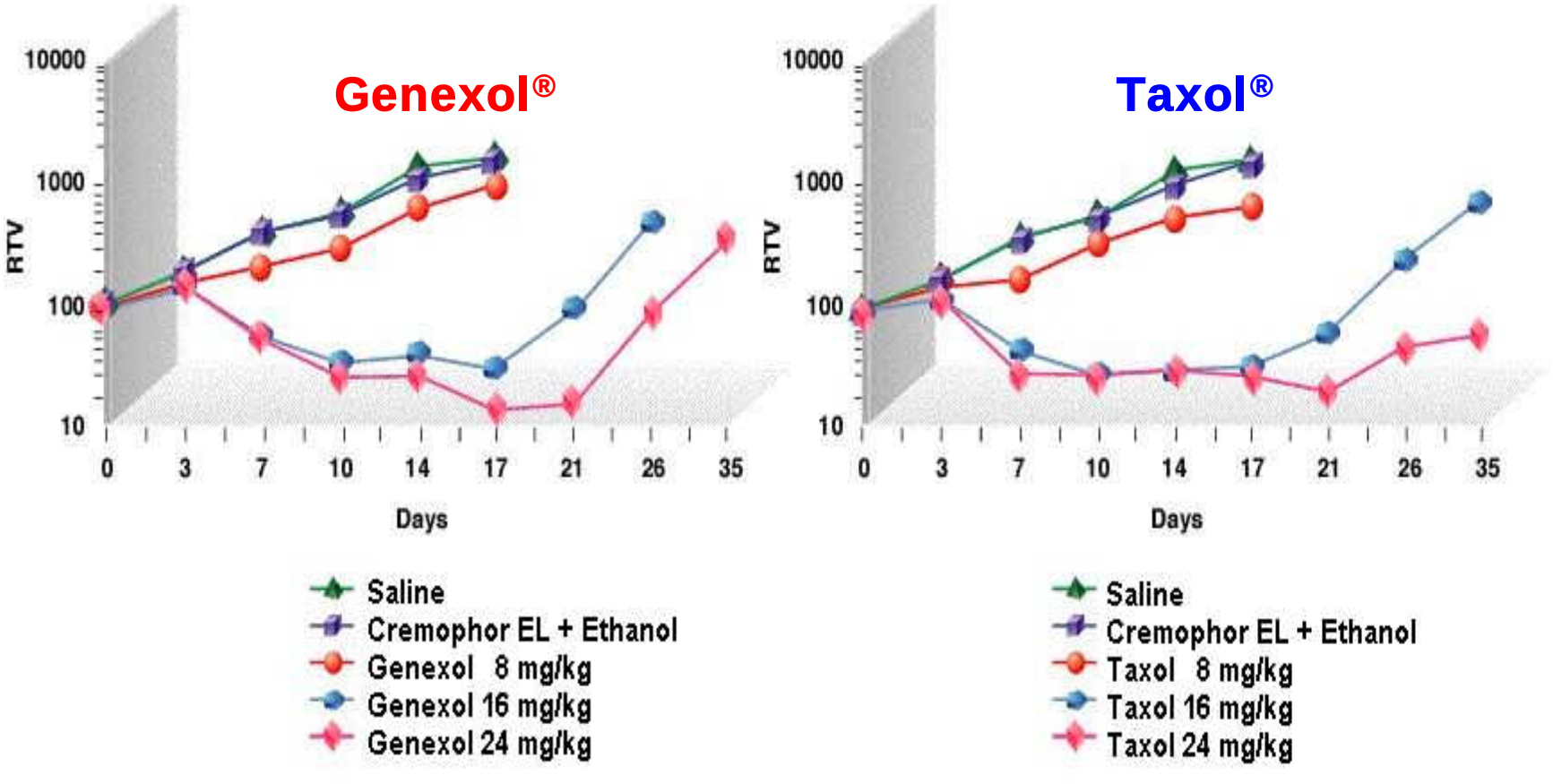
**$IC_{70}$ = inhibitory concentration of paclitaxel producing 70% cell inhibition or death**

## Conclusions

- The Cremophor® EL-vehicle shows no cytotoxicity at all concentration tested (0.0001 - 1 μg/㎖).
- The *in vitro* cytotoxicity of Genexol® and Taxol® is similar.

# Pharmacology - in-vivo Antitumor Efficacy

**Tumor size in group with Genexol or Taxol Decreased Significantly compared with Vehicle(Cremophor) or Control(saline).**



# Comparison Table Taxol vs Genexol

| Adverse Events (%) | | Taxol[1] | Genexol | | |
|---|---|---|---|---|---|
| | | | Breast[2] | Lung[3] | Gastric[4] |
| **Gastrointestinal** | Nausea and vomiting | 52 | 46.6 | 76 | 54 |
| | Diarrhea | 38 | 16.3 | 12 | 28 |
| **Myalgia/ Arthralgia** | Severe symptoms | 8 | 4.7 | 0 | 6 |
| **Peripheral Neuropathy** | Any symptoms | 60 | 44.2 | 68 | 46 |
| | Severe symptoms | 3 | 4.7 | 0 | 9 |
| **Alopecia** | | 87 | 53.5 | 76 | 97 |

**1 - Pooled Analysis of Adverse Event Experiences from Single Agent Studies**

Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single27 agent TAXOL. Two hundred and seventy-five patients were treated in 8, Phase 2 studies with TAXOL doses ranging from 135 to 300 mg/m2 administered over 24 hours (in 4 of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared 2 doses (135 or 175 mg/m2) and 2 schedules (3 or 24 hours) of TAXOL. Two hundred and thirty-six patients with breast carcinoma received TAXOL (135 or 175 mg/m2) administered over 3 hours in a controlled study. (BMS)

**2 - A phase II study of Genexol(paclitaxel) in Metastatic Breast Cancer,Cancer Research and Treatment 2001;33(6):511-517.**

**3 - A multi-center, Phase II clinical trial of Genexol(paclitaxel) and cisplatin for patients with Non-small Cell Lung Cancer,Cancer Research and Treatment 2003;35(1):30-34.**

**4 – A multi-center, Phase II clinical trial of Genexol(paclitaxel) and cisplatin for patients with advanced Gastric Cancer, oncology reports 12;1059-1064,2004**