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Context

State of play



- Production of 21,000 bags of anti-cancer drugs/year
- Maximum storage time of the bags : 7 days
- Préparation on D-1 of the administration, in case of deprogramming, reallocation of the preparation if physico-chemical stability:
 - 2,9 % ddeprogramming of which 15% of preparation are reallocated

Recommendations

- USP 797:** Conservation outside of any sterility testing for preparation:
- European Guidelines 2011** on Stability Studies for Cancer Drugs¹ : recommends sterility assessment in case of long-term conservation and for bacterial growth-promotion preparations (proteins)

Ambient temperature	+2°C à 8°C
48 hours	14 days

Rationale

- Rituximab
- Good physico-chemical stability (28 days²) in 0,9% NaCl
 - Protein**

No inhibitory effect of Rituximab according to the literature^{3,4}

Objective

↑ of the maximum shelf life to 28 days

↑ in the reallocation rate

Reduction in the number of bags destroyed + Economic gain

Material and method



Material

TG broth, TS broth, Bioball® with 6 Pharmacopoeia strains, Drug Rituximab, Solvents NaCl 0,9%, Mac Farland Densitometer® Except for *A.brasiliensis*

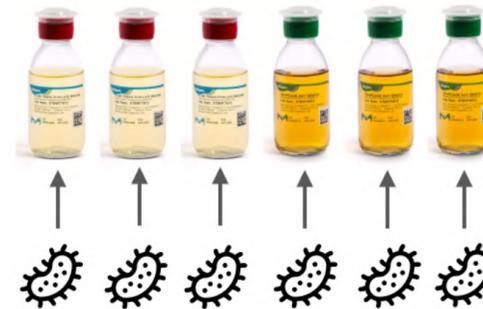
Method

Direct inoculation

Culture characteristics of European Pharmacopoeia strains for microbiological stability study

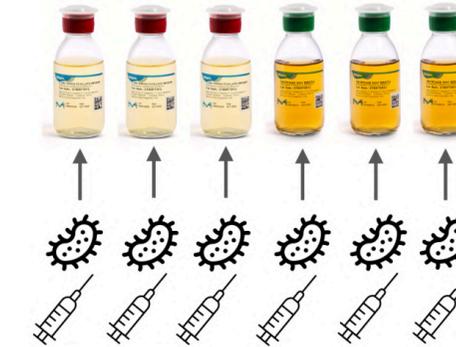
Pharmacopoeia 9.0 strains	Solid growth medium	Liquid growth medium	Incubation time (D)	Incubation temperature (°C)
<i>S.aureus</i> ATCC 6538	Blood agar	Thioglycolate (TG)	3	35
<i>P.aeruginosa</i> ATCC 9027	Blood agar	Thioglycolate (TG)	3	35
<i>C.Sporogenes</i> ATCC 19404	Blood agar	Thioglycolate (TG)	3	35
<i>B.subtilis</i> ATCC 6633	Blood agar	Triptycase soya (TS)	3	35
<i>C.albicans</i> ATCC 10231	Chromagar plate	Triptycase soya (TS)	5	35
<i>A.niger</i> ATCC 16404	Chromagar plate	Triptycase soya (TS)	5	31

Fertility testing



Method: 100µL of a 10³ UFC/mL suspension of each strain added to the broths
Objective: to test the fertility of the broths = **positive control (TP)**

Testing the applicability of the method



Method: similar to sterility test + 10 mL of Rituximab (4mg/mL): performed in triplicate
Objective: to test the absence of inhibitory character of the drug



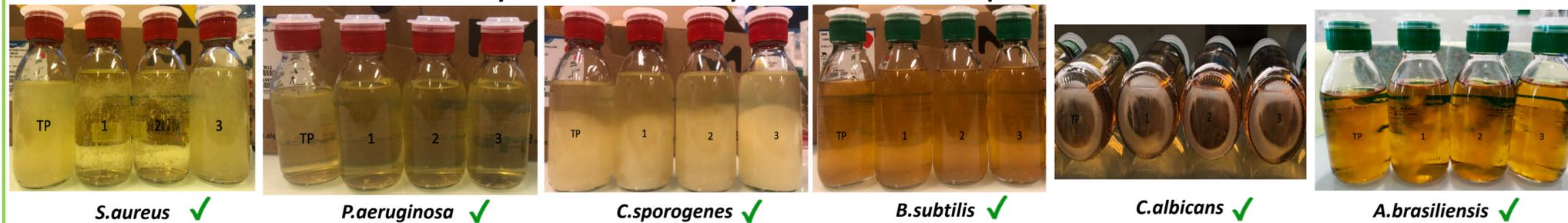
Stérility test

D0: 3 bags: 10 mL of drug in 2 TS and 2 TG
D 14 and D 28 : same with different bags

Method: 9 bags of Rituximab (1mg/mL) At D0: addition of 10 mL in 2 TG and 2 TS of each of 3 bags → **incubation 14 days. Operation repeated at D14 and D28, testing 3 new bags each time**
Objective: to test for the absence of bacterial growth

Results

Test of applicability of the method: comparable growth between TP and broths containing Rituximab
 → no inhibitory character → sterility test can therefore be performed



Results of the reading at Mac Farland

Day	MO	TP (McF)	N°1 (McF)	N°2 (McF)	N°3 (McF)
D3	<i>P. aeruginosa</i>	0,9	0,9	0,8	0,8
	<i>S. aureus</i>	4,4	3,6	3,6	4,4
	<i>C.sporogenes</i>	5,5	6,5	6,1	6,0
	<i>B.subtilis</i>	0,9	0,9	1,0	0,9
D5	<i>C. albicans</i>	3,9	3,7	3,7	3,7

Result of the sterility test

Absence of turbidity in all pockets tested

Conclusion

Lack of inhibitory character

Conducting the sterility test

No bacterial growth

Extension of the shelf of Rituximab bags

Prospects

Study only representative of one day of production → **implementation of a routine control**

Extrapolation of results to other monoclonal antibodies ? → monoclonal antibodies with similar profiles and formulations can be extrapolated