



# New Rabies Vaccines Regimens

The manufacturer's perspective

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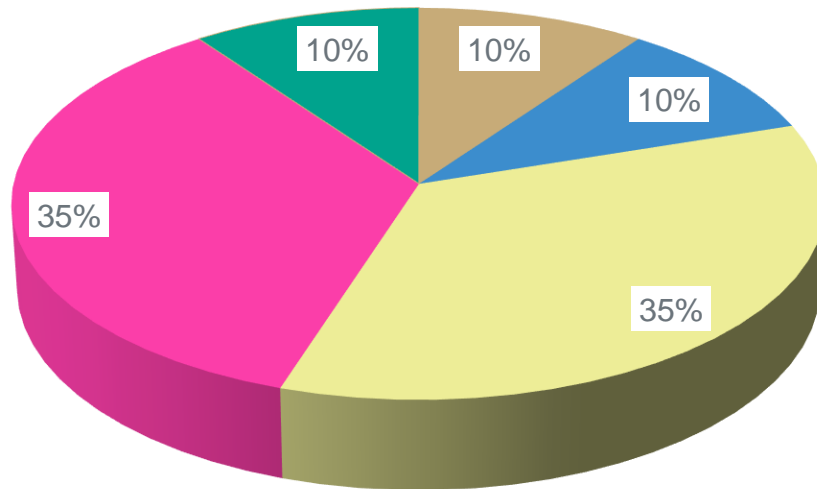
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# Sanofi Pasteur: a historical leader in rabies vaccines

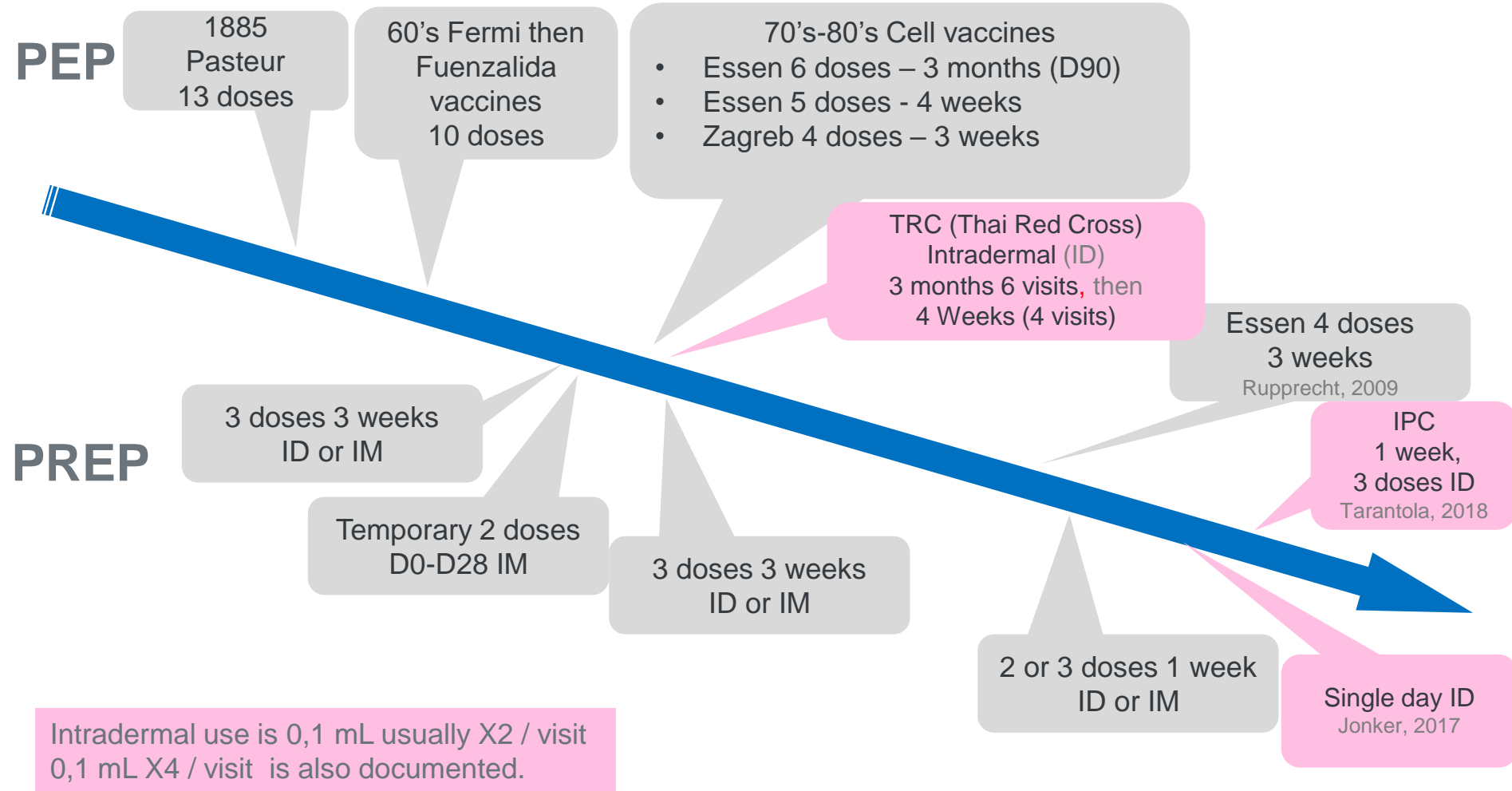
Total rabies vaccine market in volume  
Estimation 80-85 million doses(2017)



- SP mainly produces PVRV, of which around 20% is used ID.
- HDCV is mainly used in non endemic areas and represents less than 10% of total SP production.

- Main Indian production
- GSK
- Main Chinese production
- Other local production
- Sanofi Pasteur

# Evolution of rabies vaccine regimens, an overview



# Rabies vaccine regimens, often confusing

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- **Pre- and post-exposure**
  - Short or Long
  - IM or ID
  - With or Without RIGs

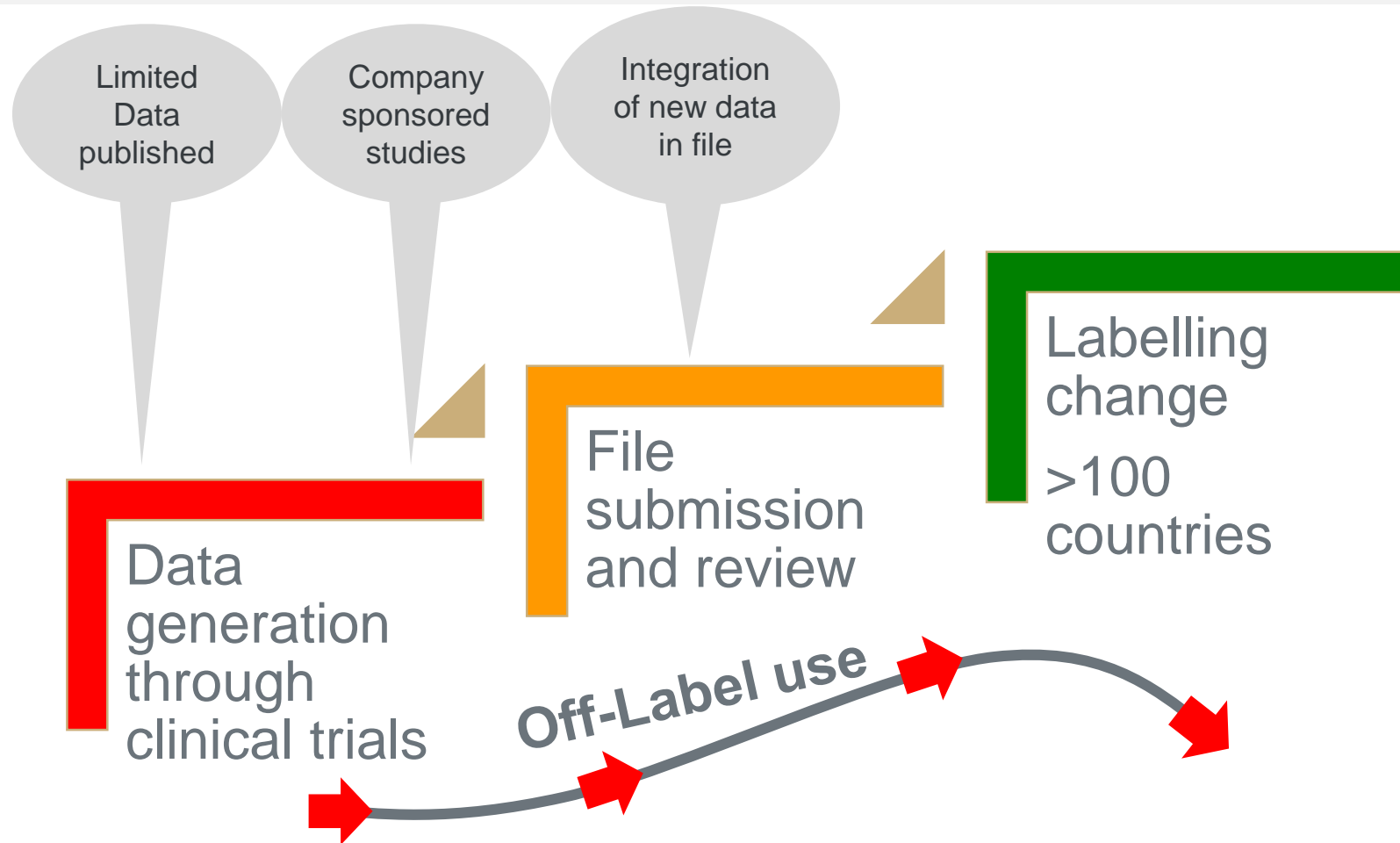
A PVRV literature review has identified more than 10 different PREP regimens and 13 PEP

The new WHO recommendation contributes to the simplification and reduction of doses for a better control of rabies disease.

Rabies vaccines: WHO position paper – April 2018

# From recommendation to field adoption

Full clinical demonstration may be available only at a later stage



# Field evolution of PEP and PrEP regimens

Internal survey among Sanofi Pasteur affiliates

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## • PEP

### • IM use

- ESSEN 5 is often replaced by ESSEN 4
- ZAGREB regimen is progressing; i.e has replaced ESSEN in Iran in 2018

### • ID use

- **TRC (2-2-2-0-2)** regimen remains the preferred one
- **IPC (2-2-2-0-0)** is currently being implemented, not yet present in all vaccine labels and sometimes challenged.

## • PreP

- One week three doses IM (PCECV) regularly used in Europe
- One week two doses is sometimes used « off-label » mainly IM in Europe or ID either for PVRV or HDCV (Canada, Australia)

# Sanofi Pasteur position on ID use and short regimens

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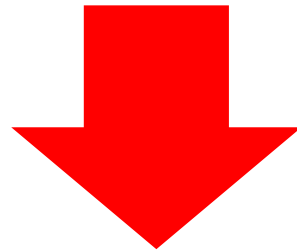
- **PVRV**: large amount of internal data
  - **PEP**
    - TRC part of labelling since 1996 in several Asian countries
    - IPC regimen is now documented (short term), will be submitted Q1 2020 in Europe and worldwide
    - 4-4-4-0-0 and TRC (2-2-2-0-2) documented with booster (single visit 4 sites) at 5 years (to be published Q1 2019)
  - **PrEP**
    - Ongoing study for PrEP D0-D7, ID, and IM with simulated PEP (D0-D3) at 1 year, primary phase completed, not yet analyzed
- **HDCV**: Very limited internal ID data as mainly distributed in USA, Europe, Australia: Countries are not using ID in PEP
  - Off label use in PrEP in Canada, Australia, Belgium
  - Ongoing study for PrEP D0-D7, ID and IM with simulated PEP at 1 year



# Constraints for labeling changes

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- Regulatory Authorities require sponsored data in priority
- External published studies are useful but only supportive\*
- The label legally engages the company



It takes time to generate data, change label when registered in >100 countries

\* RFFIT testing can be highly variable, not always used; methodology is variable

OVERVIEW OF 2 ONGOING STUDIES  
AIMING TO DOCUMENT NEW VACCINES REGIMENS

# PVRV one week 4-4-4-0-0 study versus TRC 2-2-2-0-2 for PEP + boost at 5 years (2012-2019)

N= 600 subjects; real exposure; The Philippines, Part 1 up to 1 year published, Vaccine 2019

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 (Group 3)	Visit 6 (Groups 1 & 2)	Visit 7 (Group 3)	Visit 8	Visit 9 to Visit 12	Visit 13	Visit 14	Visit 15
Trial Timelines (days)	D0	D03	D07	D14	D28	D35	D56	D90	Y1 to Y4	Y5		
Trial intervals (days)	Day 0	3 days post-V01	7 days post-V01	7 days post-V03	28 days post-V01	28 days post-V03	28 days post-V05	90 days post-V01	1 to 4 years post-primo vaccination	5 years post-primo vaccination	11 days post-V13	28 days post-V13
Time windows (days)						±3 days	±3 days	±3 days	±15 days	±15 days	±3 days	±3 days

## \*VACCINATION REGIMENS

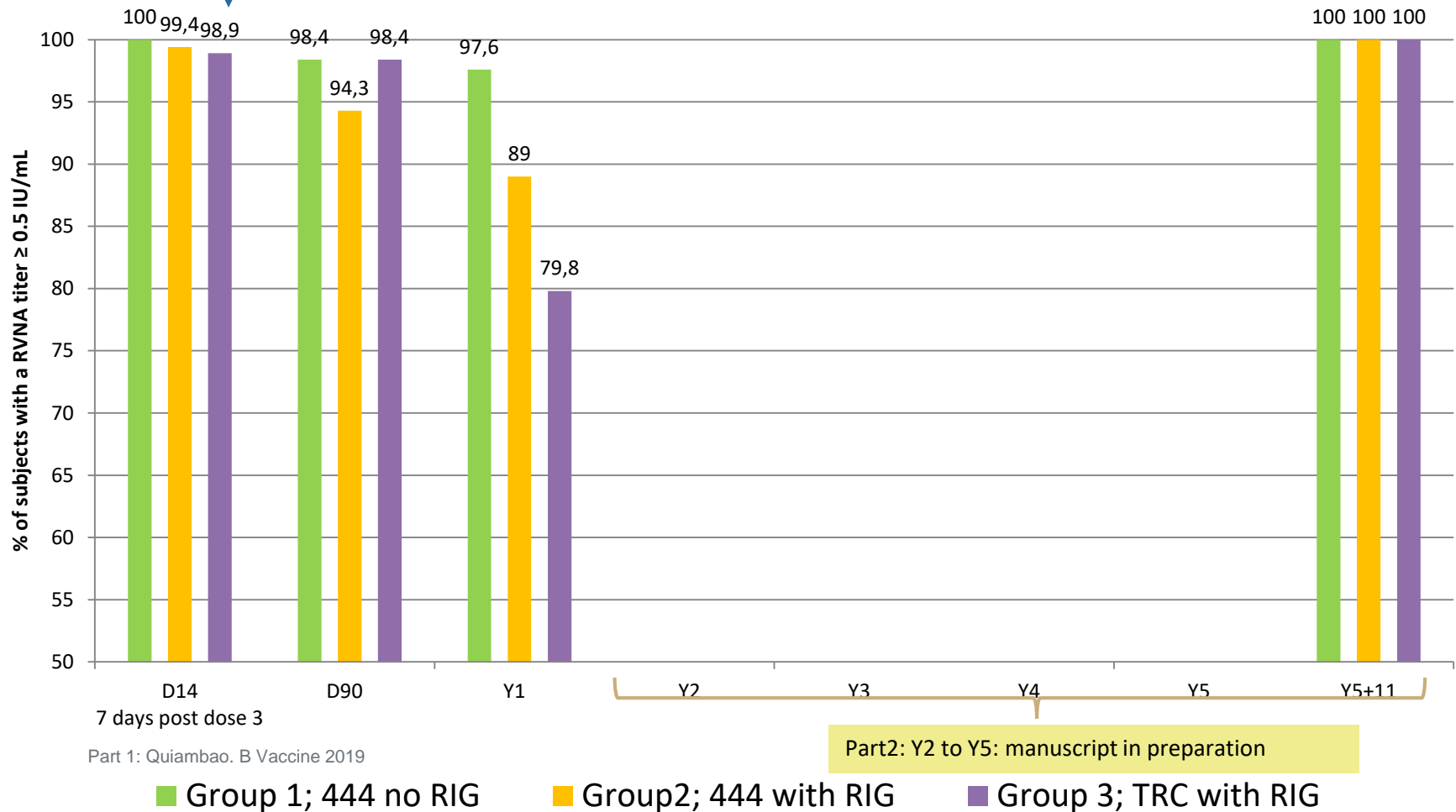
Timepoints	D0	D03	D07		D28					Y5		
<b>Group 1</b> (Cat II/4-site “one week” ID vaccination regimen)												
<b>Group 2</b> (Cat III/4-site “one week” ID vaccination regimen + pERIG)	 + pERIG											
<b>Group 3</b> (Cat III/2-site updated TRC ID vaccination regimen + pERIG)	 + pERIG											

To support IPC regimen

# Seroconversion rate (RVNA titer $\geq 0.5$ IU/mL)

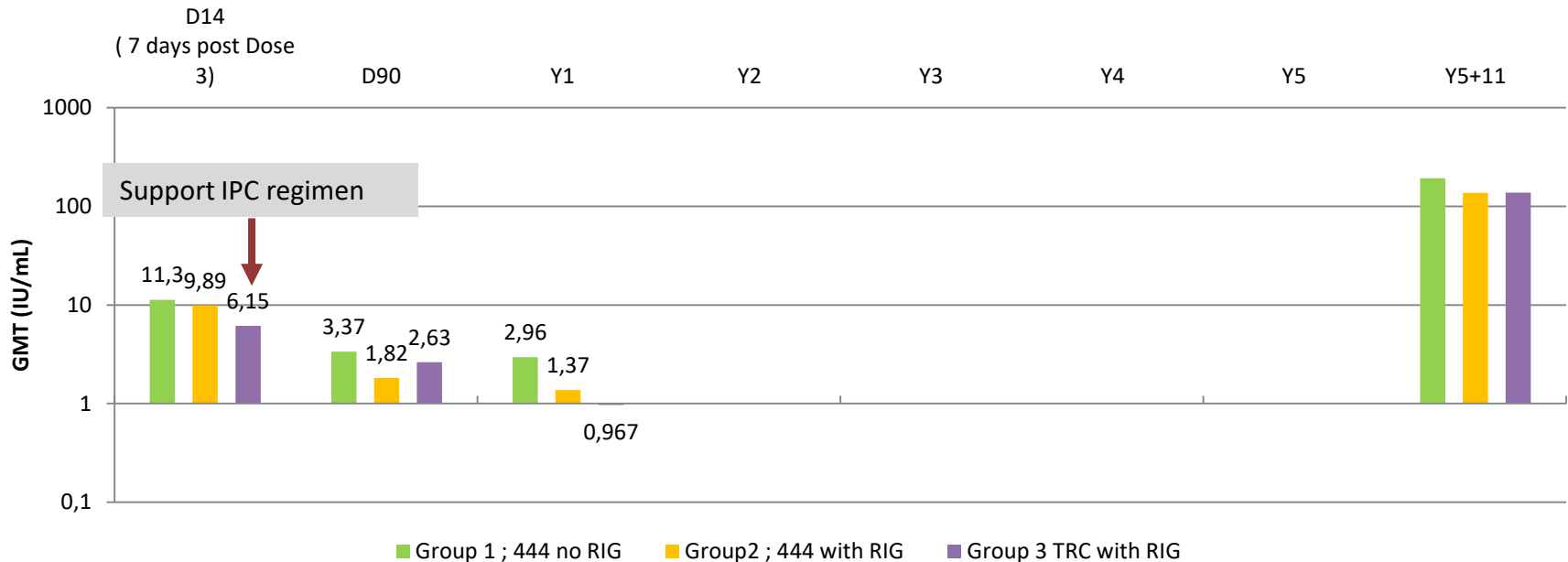
Support IPC regimen (as part of TRC)

## Full Analysis Sets



# Immunogenicity results: GMTs

## Full Analysis Sets

















Note: 17,8 % of subjects were re-exposed to potentially rabid animals during the 5 years of follow-up

Timiryasova. T, Moore S, [Journal of Immunological Methods](#) June 2019

Rapid fluorescent focus inhibition test optimization and validation: Improved detection of neutralizing antibodies to rabies virus

# Ongoing non inf.study for PrEP short regimens IM and ID for PVRV and HDCV rabies vaccines (n=570)

Group #	D0	D7	D21	D35	Month 6	Year 1	Year 1 + 3 days	Year 1 + 10 days	Year 1 + 17 days
Group 1 HDCV - IM									
Group 2 HDCV - IM (Ref)									
Group 3 HDCV - ID	 	 							
Group 4 PVRV - IM									
Group 5 PVRV - ID	 	 							



# Constraints for production: example of PVRV process

Drug substance stage 

Drug product stage 

## Vaccine production



1. Vero cell culture



2. Virus Cultivation



3. Inactivation



4. Purification



5. Filling and storage

6. Formulation & stabilization → 7. Filling & Lyophilization → 8. Visual inspection

## Diluent production- Sodium Chloride (NaCl)

1. Formulation → 2. Filling → 3. Visual inspection

8. Packaging

13 to 15 months



~9 to 10 months



# Conclusion

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- Time constraints are important
  - To generate clinical data including some follow-up.
  - Lab testing (RFFIT) is complex and requires skilled personal.
  - Reconstructing regulatory files (often based on early or historical data) requires more time than modern files.
  - Some manufacturing activities may be in competition with other vaccines...and rabies vaccines have difficulties to be prioritized.
- ID route will be added to PVRV label worldwide (PEP early 2020)
- Sanofi Pasteur continues to support the WHO initiative « Zero by 2030 » through GARC & IP training and education programs.



THANK YOU