IN VITRO ALTERNATIVES FOR THE IN VIVO RABIES VACCINE POTENCY

Wlamir Corrêa de Moura
INCQS/FIOCRUZ
BraCVAM
Brazil
Rabies Vaccine of Human Use
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Rabies vaccines of human use

- Produced in Cell Culture - GMP;
- HDCV, PVCV, PCECV;
- Beta-propiolactone inactivated;
- Purified;
- Highly potent;
- Efficacy and safety has been demonstrated in Clinical Trials.
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Current Good Manufacturing Practices

• Based upon principle that quality must be built in to a product, and not just tested in to a product;
• Requires the validation of all processes and assay methods;
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Guidelines for Production

Minimum quality requirements:

- WHO TRS 941, (2007);
- European Pharmacopoeia (Ph. Eur.) mon. 07/2014 :0216 ;
- Ph. Bras. (2010).
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Guidelines for Production

Minimum potency requirement:

NIH test - $\geq 2.5$ IU/dose

- WHO and Ph. Bras. – 16 mice
- Ph. Eur. a suitable n°
- USA/Canada - duplicated tests
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Drawbacks of NIH test

- Developed in the 1950s;
- Animal welfare and number;
- Inaccurate (low trueness and low precision) so, not validable;
- Takes 4 weeks to conclude;
- THERE ARE ALTERNATIVES!
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Alternative in vitro tests:
Final bulk
Ph. Eur. and WHO recommend Ag content assays using:
- SRD;
- ABT;
- ELISA.
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Alternative in vitro tests:
Final lot
- Ph. Eur. From 2014 recommends Using, alternatively, validated:
  - Serological test;
  - Immunochemical assay;
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Which Immunochemical assay?
• SRD;
• ABT;
• ELISA.
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Which Immunochemical assay?

X SRD;
X ABT;
✓ ELISA.
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Why an ELISA?

• Versatile;
• Simple;
• Sensitive;
• Quantitative;
• Accurate (good trueness and precision) so validable;
• Not indicative of efficacy!
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• 2011 - Paradigm shift – Report of ECVAM/EPAA workshop – Brussels – Belgium - 2010

Meeting report

The consistency approach for quality control of vaccines – A strategy to improve quality control and implement 3Rs

Fabrizio De Mattia a, Jean-Michel Chapsal b, Johan Descamps c, Marlies Halder d,1, Nicholas Jarrett e,2, Imke Kross a, Frederic Mortiaux c, Cecile Ponsar c, Keith Redhead f, Jo McKelvie g, Coenraad Hendriksen h
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Paradigm shift - Biologicals

Classical Approach
Each lot is unique – Test Safety and Efficacy lot-to-lot
In vivo tests

Consistency Approach
Each lot is similar to one of proved Safety and Efficacy
Replace
In vitro tests

Shift
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- 2011 - Workshop - Ames – USA
- Way forward for Rabies vaccine. Which of the Rs to apply?

Potency evaluation of rabies vaccine for human use: The impact of the reduction in the number of animals per dilution

Wlamir Corrêa de Moura\textsuperscript{a,b,*}, Humberto Pinheiro de Araujo\textsuperscript{a}, Pedro Hernan Cabello\textsuperscript{c}, Phyllis Catharina Romijn\textsuperscript{d}, José Paulo Gagliardi Leite\textsuperscript{e}
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• 2011 - Workshop rabies vaccine testing: — Ames – USA – Replacement by an ELISA!

Meeting report

Report on the international workshop on alternative methods for human and veterinary rabies vaccine testing: State of the science and planning the way forward

William Stokes a,*, Richard McFarland b, Jodie Kulpa-Eddy c, Donna Gatewood d, Robin Levis e, Marlies Halder f, Gayle Pulle g, Hajime Kojima h, Warren Casey a, Alexander Gaydamaka i, Timothy Miller j, Karen Brown k, Charles Lewis d, Jean-Michel Chapsal l, Lukas Bruckner m, Sunil Gairola n, Elisabeth Kamphuis o, Charles E. Rupprecht p, Peter Wunderli q, Lorraine McElhinney r, Fabrizio De Mattia s, Koichiro Gamoh t, Richard Hill d, David Reed u, Vivian Doelling v, Nelson Johnson v, David Allen v, Lori Rinckel v, Brett Jones v
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2012 – Workshop - ELISA for rabies vaccine testing: — EPAA Arcachon – France

• International Working Group;

• Two Phase Study Planed.
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2016 - Study ELISA for rabies vaccine testing: — Phase 1 concluded

Replacement of in vivo human rabies vaccine potency testing by in vitro glycoprotein quantification using ELISA – Results of an international collaborative study

Sylvie Morgeaux a, Bertrand Poirier b, C. Ian Ragan c,*, Dianna Wilkinson d, Ulrich Arabin e, Françoise Guinet-Morlot f, Robin Levis g, Heidi Meyer h, Patrice Riou f, Shahjahan Shaid c, Dmitriy Volokhov g, Noël Tordo i, Jean-Michel Chapsal k

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Phase 1 Details:
• 5 Labs (3 NCL and 2 Private);
• 3 ELISA formats;
• 7 vaccine samples (4 pot + 3 sub pot);
• 3 virus strains (PM, PV, Flury);
• Agreement, not correlation.
✓ EILISA – D1-25 + WI 1112
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2018 - Study ELISA for rabies vaccine testing: - Phase 2

• ELISA proposed to EDQM in 2017;
• Aproved BSP 148 project;
• Project started;
• International Collaborative study is being arranged for validation.
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Next step

• ELISA D1-25 + WI 1112 will be proposed to the Ph. Eur. for replacing NIH test;
• Producers will make the mab commercially available, as agreed.
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What else?

• **Serological tests** are in study for human use vaccines in PEI and in INCQS;

• **Veterinary vaccines** – Serological test already validated and described in Ph. Eur. And there are some ELISAs in study.
Thank you!