Factors that influence industry investment in vaccine development

UK Veterinary Vaccinology Network

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C. Charreyre

Agenda

1. How the industry decide to launch a veterinary vaccine development programme
   What is “development” for private companies
2. Regulatory constraints
3. Promising areas of development

   “Gaps” in veterinary vaccines

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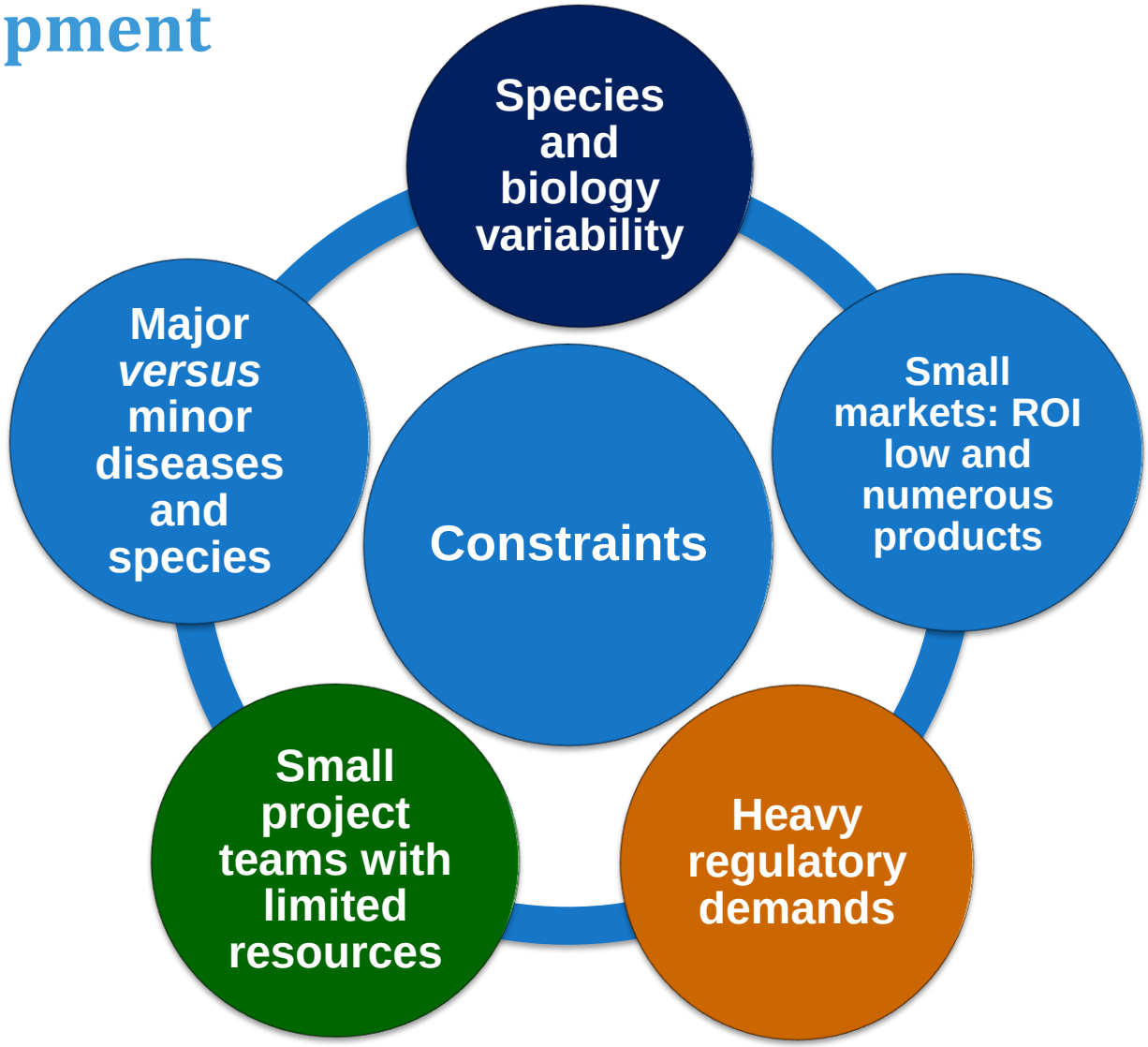
- Even within the “One Health” concept, **the market for animal medicines is different** of the human medicines market:
  - It caters to a wide variety of species with a wide range of different physiologies and pathologies
  - It is substantially smaller, only 2-3% the size of the human medicines sector, and highly fragmented
  - It is almost entirely a private market, with no state reimbursement of the cost of the medicine (The likelihood of animals being treated is critically influenced by the animal owners’ ability to afford the cost of the treatment)

Constraints in veterinary medicine development



What is development for a vet vaccine?

ROI

- Motivated and initiated by the **Return On Investment** . Financial assessment is essential and budget constraints are very stringent

TTM

- Projects must be as quick as possible, with **Time to Market** of only a few years if possible…

Polyvalent experts

- Project teams are small but must cover **a large diversity of expertises** and necessary functions

- A first driver to launch a vaccine development is **money**
- One example of how this financial aspect is assessed: the calculation of Net Present Value (NPV)

What is NPV (Net Present value)?

- The NPV is a standard financial method to appraise the interest of long-term projects
- It is a risk-adjusted financial calculation and an indicator of how much value an investment or project can bring, taking into account all outgoing and incoming cash flows over a given period of time

  - **NPV > 0:** the investment would add value to the firm and the project may be accepted
  - **NPV < 0:** the investment would subtract value from the firm and the project should be rejected
  - **NPV = 0:** the investment would neither gain nor lose value for the firm but may be interesting for other reasons

NPV evaluation

4 types of factors for NPV calculation

1. Market potential	Geographical areas and countries	Populations concerned	Persistence of the problem	Achievable Market Share
2. Return on investment	R&D costs	Capital expenditures	Revenues	Operating expenses
3. Environmental risks	Vaccine need	Control policies	Veterinary capacities	Budget
4. Technical feasibility	Technical proof of concept	Intellectual property	Available laboratories	Regulatory strategy

Market potential	Geographical areas and countries	Populations concerned	Persistence of the problem	Achievable Market Share

- Market analysis is a foundation of vaccine development:
  - In what geographical areas and countries is the problem located?
  - What populations of animals and humans are concerned?
  - Is the problem likely to be persistent over time?
  - Can the firm achieve some market share in that context?

This is linked to pathology and epidemiology but also to sociology, finance, history (of the firm), economy and politics

Return on investment	R&D costs	Capital expenditures	Revenues	Operating expenses

- The return on investment is another foundation for vaccine development:
  - How much is this going to cost in R&D?
  - Does the firm have to invest in manufacturing or other large facility/material?
  - How much is this going to cost the firm in marketing and sales?
  - Will this bring revenues (of various kinds)?

This is linked to finance, R&D, manufacturing, marketing, regulatory and legal matters but also to history (of the firm), economy and politics

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Development costs a lot of money!!!

- 8-12% of turnover of private compagnies is re-invested in R&D
  - New product for pets: 10 to 30 M€
  - New product for large animals: 20 to 40 M€
  - New product for "minor" species: 5 to 15 M€
  - Generic product: 2 to 6 M€
  - New claim: 1 to 5 M€

IFAH Benchmarking survey, 2011

Environmental risks	Vaccine need	Control policies	Veterinary capacities	Budget

- Environmental risks must be assessed before vaccine development:
  - **Is there a need for vaccine in the markets?** For the animals? For the humans?
  - What are the control policies associated with that pathology/disease?
  - If the vaccine exists, can it be used in the fields by the veterinary community? The farmers? Others?
  - What kind of budget can be engaged?

This is linked to biology, immunology, clinical assessment, regulatory but also to legal matters, finance, history (of the firm), economy and politics

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- How to address the « market needs »?
  - By writing a **product profile**
  - A picture of what the ideal product should be
  - A moving target…
  - A sacred covenant between R&D and Marketing (and others, like Manufacturing)

Technical feasibility	Technical proof of concept	Intellectual property	Available laboratories	Regulatory strategy

- Technical feasability is still important for vaccine development:
  - Do we have a Proof Of Concept/Principle? **What is a POC?**
  - What is the IP situation, can the firm increase IP portfolio and value?
  - Does the firm have the resources (and manpower) to pursue all associated technical issues? Can this be done with partners?
  - What is the regulatory environment?

This is linked to biology, immunology, clinical assessment, regulatory but also to legal matters, finance, history (of the firm), economy and politics

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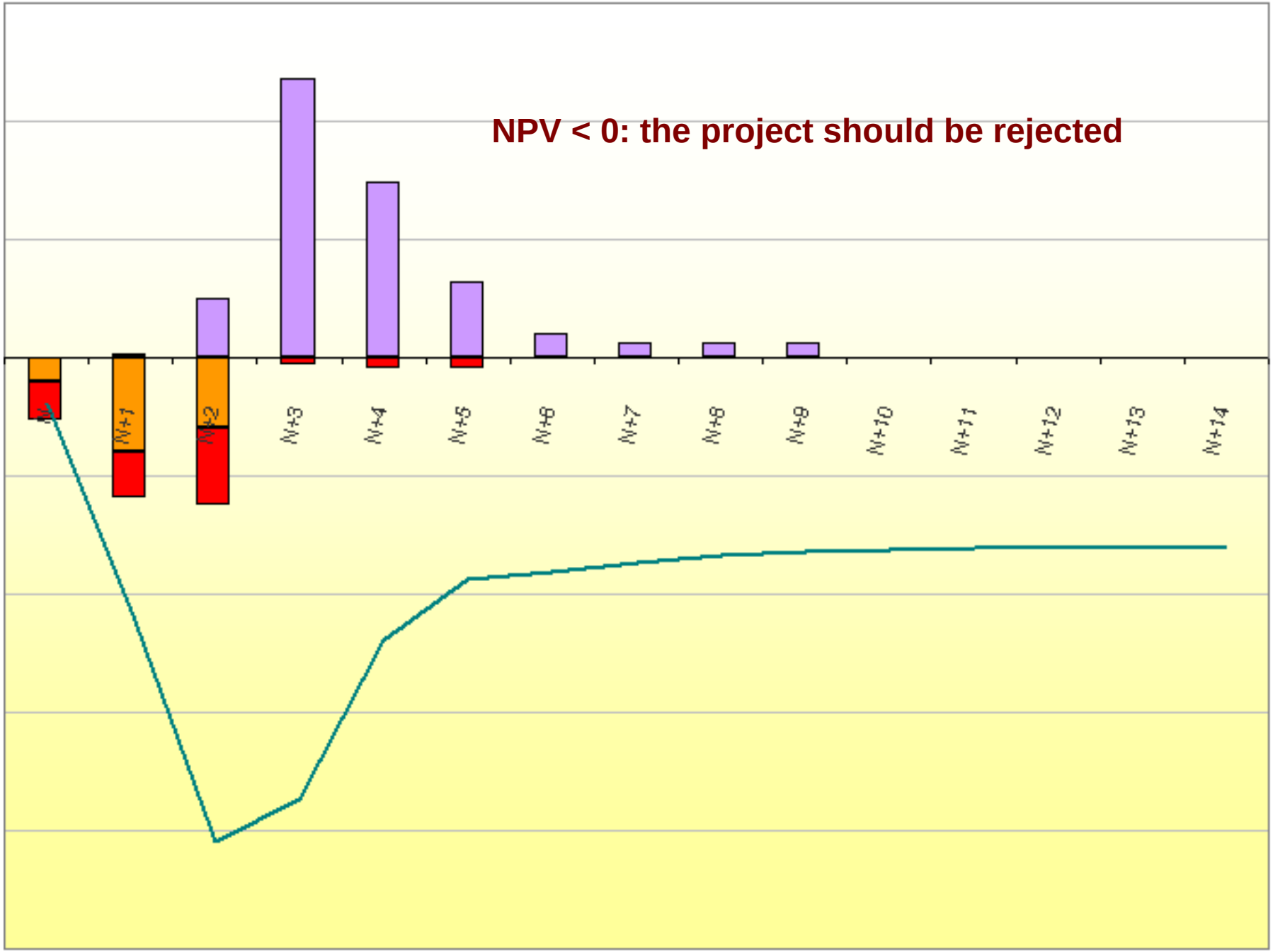
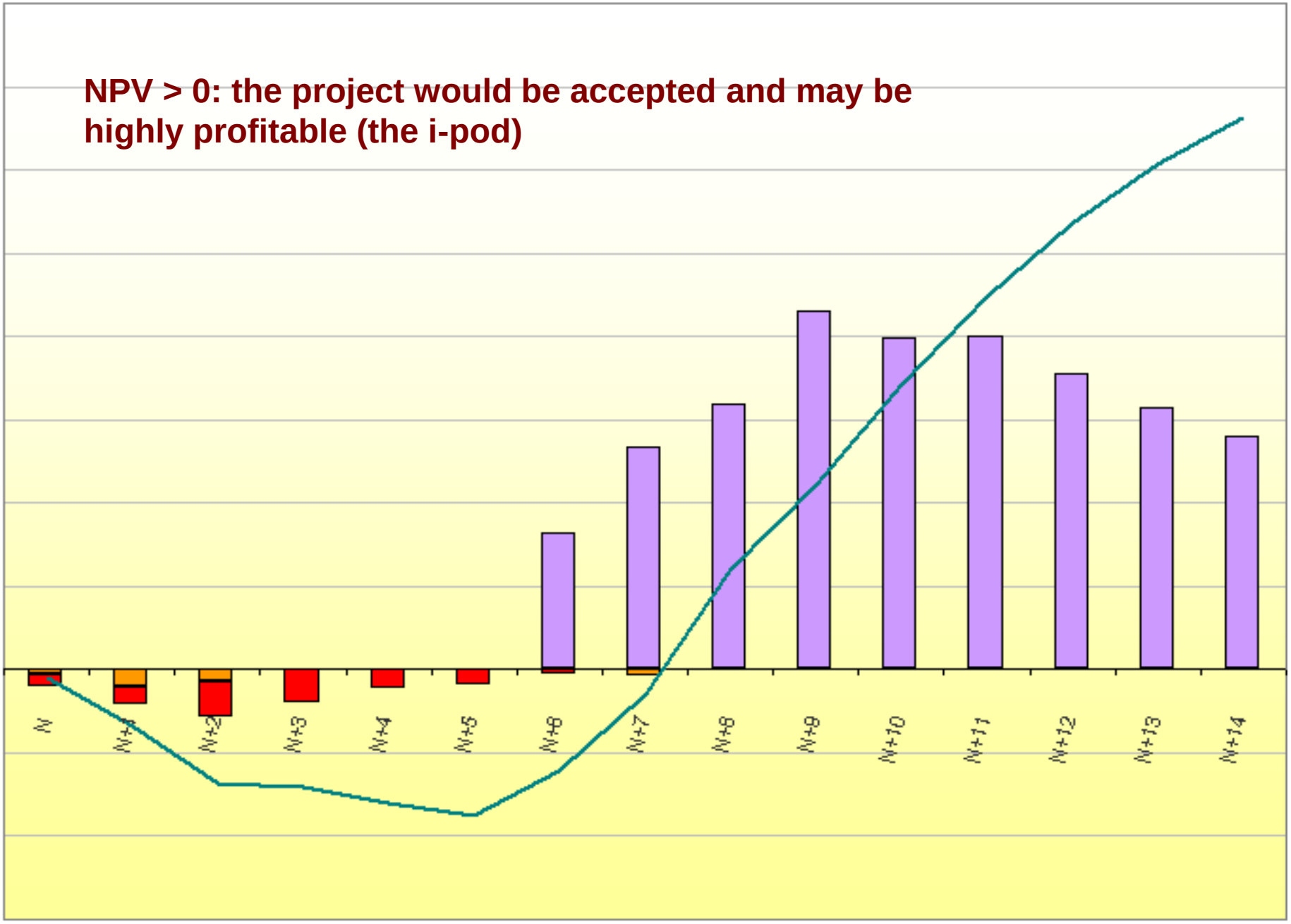
What is a « Proof Of Concept »?

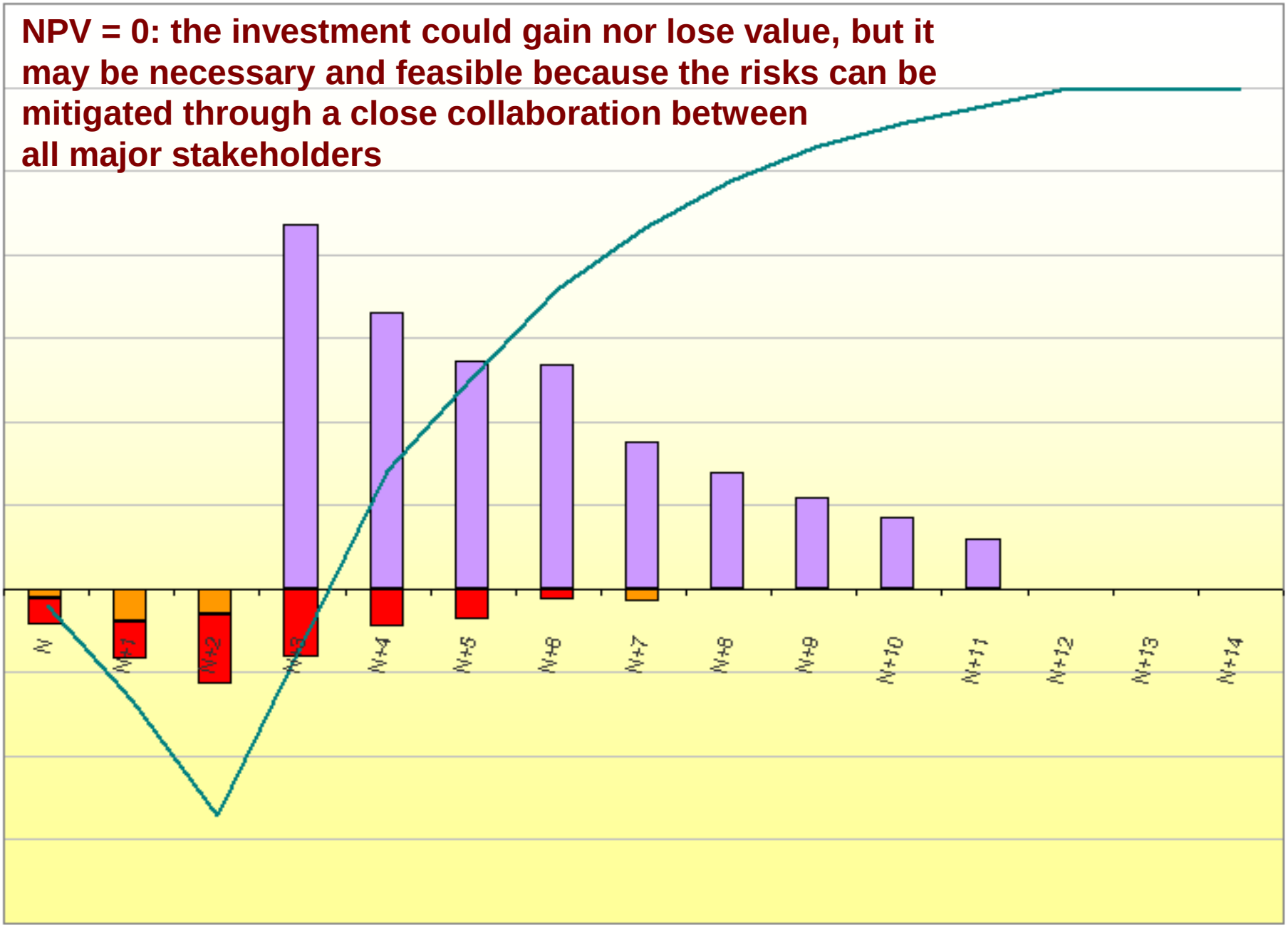
- **Proof of concept** is a realization of a certain method or idea to demonstrate its feasibility, or a demonstration in principle, whose purpose is to verify that some concept or theory has the potential of being used. A proof of concept is usually small and may or may not be complete.
- A sacred covenant between the various R&D functions to set a common definition of POC
- Often not aligned with other scientific bodies and partners


NPV < 0: the project should be rejected
N
N+1
N+2
N+3
N+4
N+5
N+6
N+7
N+8
N+9
N+10
N+11
N+12
N+13
N+14

NPV > 0: the project would be accepted and may be highly profitable (the i-pod)



NPV = 0: the investment could gain nor lose value, but it may be necessary and feasible because the risks can be mitigated through a close collaboration between all major stakeholders



NPV evaluation

Market potential	Geographical areas and countries	Populations concerned	Persistence of the problem	Achievable Market Share
Return on investment	R&D costs	Capital expenditures	Revenues	Operating expenses
Environmental risks	Vaccine need	Control policies	Veterinary capacities	Budget
Technical feasibility	Technical proof of concept	Intellectual property	Available laboratories	Regulatory strategy

This is what is (sometimes) brought from the typical potential external public partner

Pre-development

Development

8 to 12 years

Generic

…years

R1 Opportunity Evaluation

R2 Proof of Concept

…nanagement

…ans …ns MA …gilance

Stop MA

- Preliminar…
- Preliminar…
- Laborator…
- Process definition
- First blends and formula
- Analytical tests definition
- Preliminary stability
- RA strategy
- …

- Manufacturing process (outlines)
- In process and release control tests
- Stabilities
- RA process
- ….

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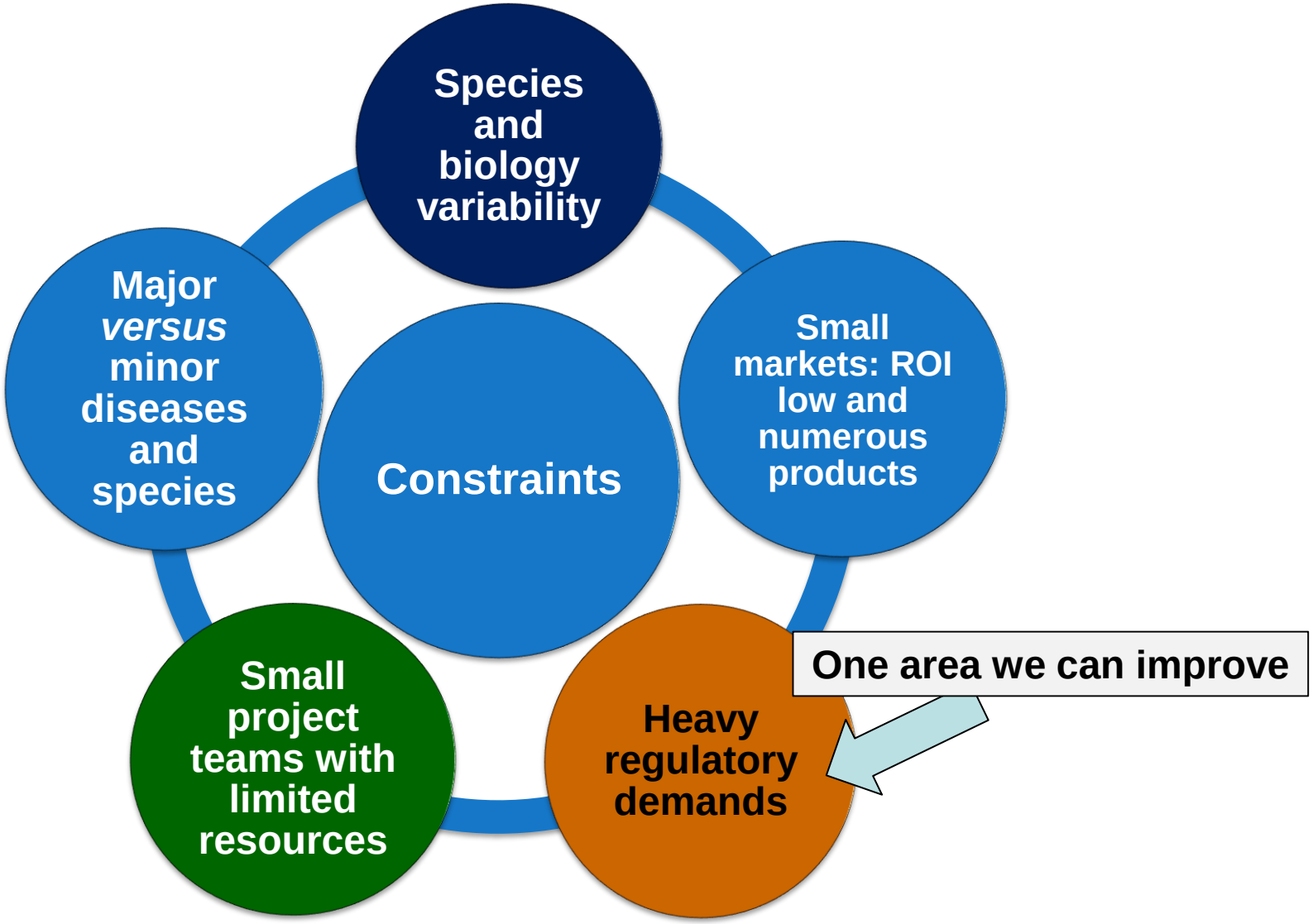
Pharma and bios are different

The differences are especially important in veterinary medicine

- Pharmaceutical product development starts with a known molecule and follows a very tightly pre-defined path
  - Limited possibility to reformulate the compound
  - The final success is very dependent on the initial choice of the "right" molecule
- Biological product development is a selective process which starts with a very large array of possible choices and progressively narrows them down towards (a) workable target(s)
  - Iterative process with many feedback loops
  - The success depends from the adaptability and expertise of the project team, and the ability to make the "good" choices many times along the way

What constraints can we alleviate?



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Why do we need Regulatory Authorities?

- Only the medicines with Marketing Authorization (MA) granted by Competent Authorities can be put in the markets
- Protection of the “patient/animal”, the environment and the public against the “bad” medicines
- Regulatory demands establish the criteria for the evaluation of the medicines by the Authorities ➔Regulatory texts
- Granting **“Marketing Authorization” or license to sell**

Europe = 28(7) countries & 23 languages

Others countries not part of EU, closely following:

Norway and Iceland

(2 other languages),

Liechtenstein

Switzerland

The Regulatory bodies

- **National Authorities in each EU country**

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000167.jsp

  - Ex: France: ANMV (Anses)

- **Multinational Institutions**

  - Ex: European Union: European Medicines Agency (EMA) composed of several specific committees
    - Coordination of the scientific evaluation of the MA requests
    - Publication of guidelines for EU harmonization of requirements
  - Ex: VICH Trilateral (EU-Japan-USA)

    Program aimed at harmonizing technical requirements for veterinary product registration

Status of the regulatory texts

Several levels of legislation in EU

- **International**: International Pharmacopoeia (WHO)
- **Council of Europe**: European pharmacopoeia and country pharmacopoeia
- **European Union**: Directives, European regulations, EMA Guidelines
- **Member States**: National requirements, Official communications

NB: Non-EU legislations: other legislators, other legislations

- USA: FDA/USDA/EPA, act/CFR/guidances
- Japan: PMDA/MAFF, regulatory texts in Japanese

What is a marketing authorization?
(Directive 2001/82/EC)

- In order to be placed on the European Community market for sale and supply, a veterinary medicinal product must be granted a **Marketing Authorization** (MA) by a competent authority
  - For this purpose, an **application dossier**, containing supporting data for **quality**, **safety** and **efficacy** carried out on the veterinary medicinal product, must be submitted
  - A product only receives a MA if **its benefits outweigh any risks, the benefit/risk balance**
  - Not all products for which MA applications are submitted are subsequently granted a MA: a**pplications may be refused due to insufficient and/or inadequate data**

How long is a MA valid for?

- A MA is **initially valid for 5 years** from the date of first authorization
- Then it will be subject to **renewal**
  - **After an assessment to ensure the benefit/risk balance remains favorable**
  - **Takes into consideration any further information obtained about the product from the experience in the field, *e.g.* pharmacovigilance data**
- Following this review, the MA will be valid **indefinitely** (or the Marketing Authorization Holder (MAH) will be asked to submit another renewal in a further five year's time on justified grounds relating to pharmacovigilance)
- **MA can be removed/suspended** in case of issues or no sales

IFAH-Europe's priority suggestions for reduced requirements (1)

- Change of the licensing process: instead of 'one stop', a step-wise procedure
- Abandoning the requirement for field efficacy studies
- Establishing guidance for (more) acceptance of long term experience with a product to compensate for data sets that are not completely up to nowadays' standards
- Acceptance of laboratory or field studies from regions where (GoodxPractices) GxP is not required, but 'GxP-like' standards are implemented (e.g. USA)

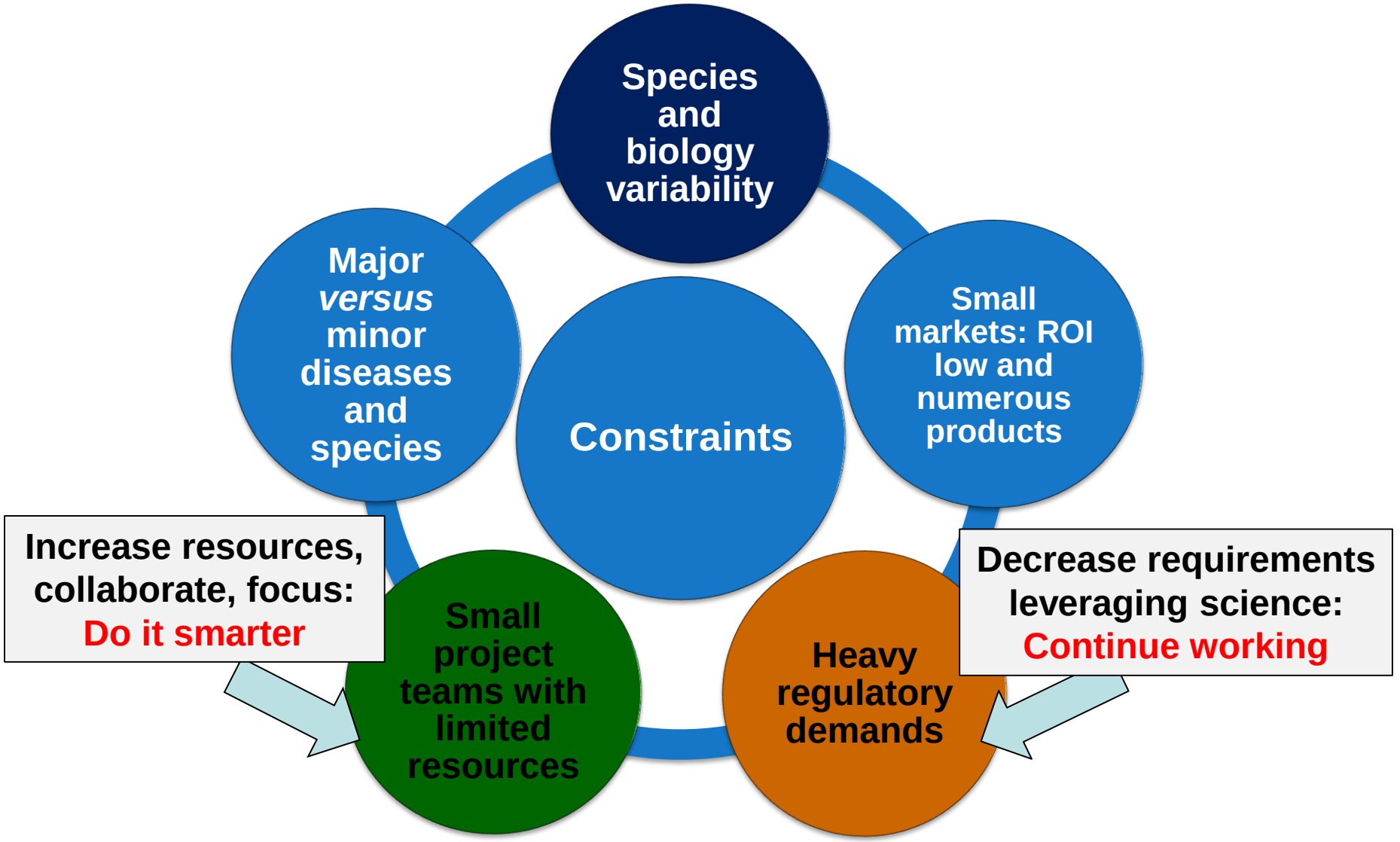
IFAH-Europe's priority suggestions for reduced requirements (2)

- Handling MUMS* applications as initially intended, *i.e.* with more flexibility and not requiring commitments to provide a full package later
- Establishing guidance for replacing challenge by serology to prove efficacy
- Acceptance of data extrapolation/less stringent requirements where sufficient experience and proof of no risk is present
- Assessor training

* "Minor Use Minor Species" include animals such as zoo animals, ornamental fish, parrots, ferrets, guinea pigs, sheep, goats, catfish, game birds, honey bees…

- The veterinary medicine sector in EU is submitted to a **very high administrative burden** :
  - It represents an estimated 13% of the industry's annual turnover, **the double** that of the human medicines market
  - Compliance with labelling rules constitutes 34% of the total administrative burden
  - It has contributed to a 20% recent drop in the innovation rate, and lower product availability, especially for minor species and smaller countries

What constraints can we alleviate?



Gap analysis: DISCONTOOLS

- Development of the most effective tools to control infectious diseases in animals
- EU funded FP7 project, started in 2008, now supported by sponsors (Declan O' Brien, Managing Director)
- Current objectives
  1. To further develop the disease prioritization methodology which has enabled the prioritization of research in order to stimulate the delivery of new or improved diagnostics, vaccines or pharmaceuticals
  2. To further develop the gap analysis for each of the prioritized diseases to identify where research is needed

Group 1: Epizootic diseases

- African Horse Sickness
- African Swine Fever
- Avian Influenza
- Bluetongue
- Contagious Bovine Pleuro Pneumonia
- Classical Swine Fever
- Foot & Mouth Disease
- Peste des Petits Ruminants
- Rift Valley Fever
- Sheep and Goat Pox
- Swine Vesicular Disease
- West-Nile Virus infection
- Zoonotic pox viruses (Parapox and Orthopox)

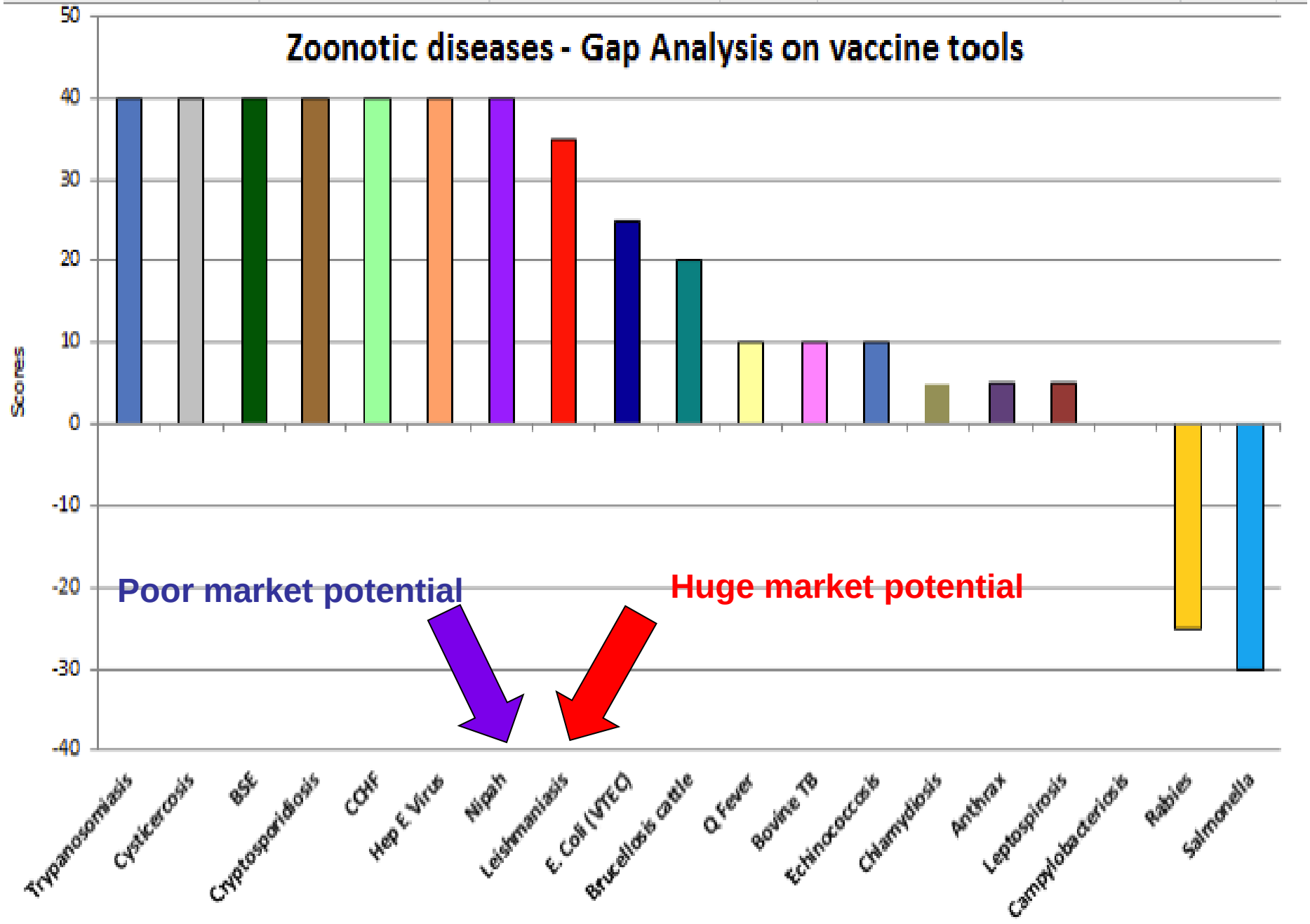
Group 2: Zoonotic diseases

- Rabies
- Nipah virus infection
- Anthrax
- Brucellosis
- Bovine Tuberculosis
- Q Fever
- Trypanosomiasis
- Leishmaniosis
- Leptospirosis
- Chlamydiosis
- Cysticercosis
- Echinococcosis
- Food-borne bacterial:
  - Salmonella
  - E. Coli
  - Campylobacter
- Cryptosporidiosis
- Food-borne viral (Hepatitis E. Virus)
- Bovine Spongiform Encephalopathies
- Crimean Congo Haemorrhagic Fever

Group 3: Major food-producing animal disease complexes

- Paratuberculosis (Johne's)
- Parasitic gastro-intestinal diseases:
  - Liver Fluke
  - Coccidiosis
  - Nematodes
- Mastitis:
  - Staphylococcus areus mastitis
  - Environmental/Streptococcal mastitis
  - Small ruminant mastitis
- Swine respiratory:
  - PRRS – CG3 + HN
  - PCV II
  - SIV
  - A. Pleuropneumonia
  - Swine Mycoplasma
- Bovine respiratory:
  - BVDV
  - BRSV
  - BHV-1 (IBR)
- Mycoplasma bovis
- Theileria

- **Every one is different**
- **All of them are interesting**
- **The list is not final…**


Zoonotic diseases - Gap Analysis on vaccine tools
Scores
50
40
30
20
10
0
-10
-20
-30
-40
Poor market potential
Huge market potential
Trypanosomiasis
Cysticercosis
BSE
Cryptosporidiosis
CCHF
Hep E Virus
Nipah
Leishmaniasis
E. Coli (VTEC)
Brucellosis cattle
Q Fever
Bovine TB
Echinococcosis
Chlamydiosis
Anthrax
Leptospirosis
Campylobacteriosis
Rabies
Salmonella

Collaborations

- The Innovative Medicines Initiative (IMI) is working to **improve global health** in EU by **facilitating collaboration** between all key healthcare players
- It is a **partnership** between the **European Union** (represented by the **European Commission**) and the European **pharmaceutical industry** (represented by **EFPIA**, the European Federation of Pharmaceutical Industries and Associations)
- IMI is the **world's biggest public-private partnership** in life sciences with a **€3.3 billion** budget for the period **2014-2024**
- **ZAPI (Zoonotic anticipation and preparedness initiative)** is a IMI project that brings together experts in human and animal health to create new platforms and technologies that will facilitate a fast, coordinated response to new infectious diseases as soon as they emerge
- http://www.imi.europa.eu/content/zapi

Conclusions

Common understandings are critical

We must get smarter

Thank you for your attention

Questions?

Sources and further readings

- http://www.simv.org/
- http://www.ifaheurope.org/
- http://healthforanimals.org/our-industry/about-us/
- http://www.discontools.eu/
- http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=
- http://online.pheur.org/EN/entry.htm
- http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/04/WC500186281.pdf