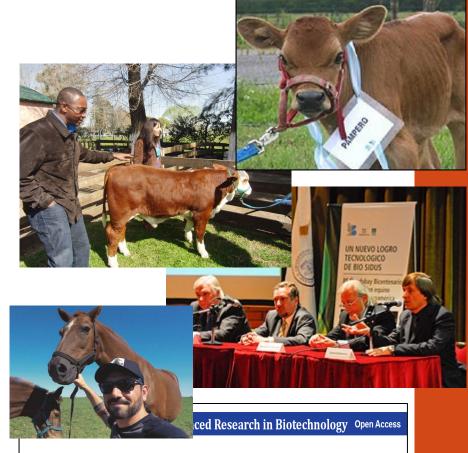
State of Knowledge and Research Needs Regarding Heritable Genomic Modification in Food Animals

Session 2. Horizon scan – A view from Argentina



Development and regulation of animal ag-biotech in Argentina

- 2003: first FT of a transgenic animal (molecular pharming).
- 2011: First International Workshop on the Food and Environmental Safety Assessment of Genetically Modified Animals.
- 2012: GM milking cow for "humanized" milk.
- 2017: Regulatory criteria for gene-edited animals and first regulatory applications.
- 2018: First locally developed GEd animals were born.
- 2019: Full pathway for the commercial approval of GM animals.



Gene Editing: Do not forget about Animal Agriculture

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Horizon scanning

Representative examples of current local projects in Uruguay, Brazil and Argentina

(primarily) Non-food animals

Sportive animals:

- "Natural" \psi myostatin (increased strength) in polo horses (SDN2)
- Sex change (to female) in polo horses.
- (\psi myostatin) in race camels (for UAE).

Human-healthcare related:

- Xenografts: kidney/heart xenograft (GMO: 3 KO + 5Kin); Pancreatic b-cell xenograft (GEd: 4 KO)
- Sheep otoferlin KO (human deafness model)
- Molecular pharming in cattle milk: HGh, lysosomal enzyme.



Food animals

Transgenic:

- Cattle expressing human lactoferrin and human lysozyme ("humanized" milk)
- Sheep expressing cellulase in saliva
- Cattle expressing llama nanoantibodies against rotavirus (functional foods, dairy products).

Gene-edited:

- B-lactoglobulin KO (hypoallergenic milk) in cattle.
- ↓myostatin sheep for meat production.
- Silverside for increased growth rate
- Prion KO in cattle (BSE prevention).

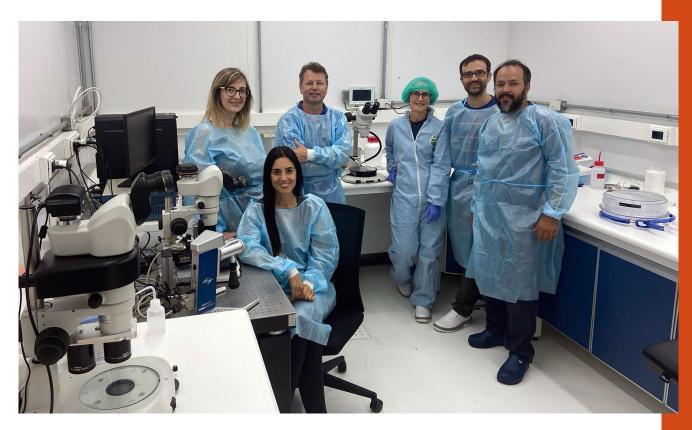




Many proofs of concept without a real commercial intent. Possibly due to the lack of a local partner that could exploit a (relatively) low-added_value/unit trait at a payback scale.

Non-edible animals for agricultural purposes

- Screwworm suppression gene drive
- GM silkworms





Regulatory challenges

Prospective consideration of pending/future issues

Current/future Regulatory issues (in general)

Applicable animal welfare rules:

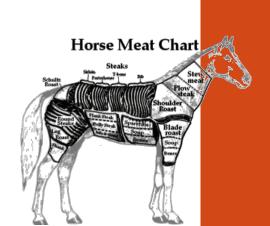
- Ordinary rules for ag animals vs. special considerations for ad hoc facilities and/or husbandry conditions in case of certain non-food purposes.
- Case-by-case (trait-related) assessment, when necessary (e.g., increased udder): estimating/measuring "unwelfareness" and setting ethical boundaries.

Food use of animals developed primarily for non-food uses:

- Coping with different husbandry conditions (e.g., vaccination).
- Ambiguous situations (e.g., GEd sportive animals).
- Perception issues (e.g., "humanized milk vs. humanized meat").
- Every other aspect to be dealt with as a "for food" animal.
- Industry requests "to test the waters".

Others:

• Parallel assessments of GM/GEd animal cell lines for cultured meat.



...re gene editing (non transgenic)

State of the art in SDN off-target effects:

- Can it be "accumulated" (e.g. with plant SoA)?
- Moving target

Considerations for ruling out unintended insertion:

- Sources: purposely introduced nucleic acids, DNA from adjuvant material, unintended "cisgenesis"
- Techniques: WGS vs. Southern vs PCR... (esp. for LADs*)
- Thresholds (size, non-coding regions, etc.)
- Intermediate treatment for inconsequential insertions

State-of-the-art in somaclonal variation, large offspring syndrome, etc:

- How comparable to other ARTs in commercial use?
- If quali/quantitative equivalent, no oversight?



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Regulatory Assessment of Off-Target Changes and Spurious DNA Insertions in Gene-Edited Organisms for Agri-Food Use

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Abstract

Worldwide, an increasing number of regulatory systems have begun to consider applications for the authorization of activities involving geneedited organisms for agri-focul use. Although a handful of countries have made advances in establishing regulatory criteria and gathering practical experience in this regard, there is still a general need for regulatory cooperation concerning capacity building and development of harmonized criteria. Consequently, many biotechnology regulators need to quickly become more acquainted with the numerous technological possibilities concluded under the concept of "gene editing", and to incorporate criteria for their regulatory assessment. This article contains a simplified introduction to the state of the art in genome editing, described from a regulatory perspective. In particular, two issues of higher practical importance are covered in detail, namely, off-target effects and unintended DNA insertions. The detailed review of current evidence regarding those issues serves as the basis for proposing concrete regulatory criteria to address them.

*Less-Advantaged Developers

...re transgenic animals

Food safety assessment:

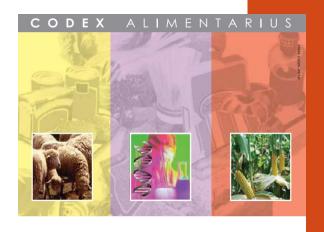
• Codex Guideline CXG 68-2008 for the "Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals" suffice (also for gene-edited animals, when necessary). But more OECD consensus documents (on food composition and biology) are warranted.

Environmental risk assessment:

- unlikely to be an issue for highly domesticated farm animals.
- Significant for other animals, but preliminary experiences (e.g. Aquadvantage Salmon) suggests it does not require extraordinary guidance or regulatory criteria.

Risk management if segregation is proposed for certain cases (speculative):

- Expression of foreign, known allergenic proteins
- Altering disease/stress resistance in a way that creates potential counterbalancing weaknesses (re further breeding)
- "non-food" animals' tracing.



Foods derived from modern biotechnology

Second edition





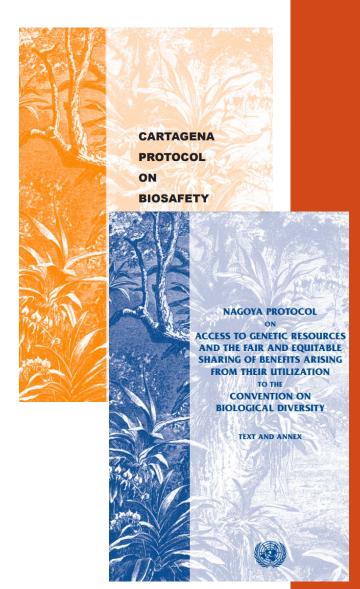
Finally, crosscutting issues

Regulators' measures to avoid trade disruption:

- Trade impact assessments
- Sworn statements (e.g. CPB "may contain", food labeling, exportation of reproductive material).
- Official and improvised detection methods.

FTO and benefit sharing:

- Intellectual property re the animals themselves.
- · Nagoya Protocol.



Truly thanks for your attention

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(online profile including publications and other relevant content)