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CVB Potency Assay Policy Development Overview

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5CFR §2635.101

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Core

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Core

- ***Data-driven***
- ***Consistent***
- ***Coherent***

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Historical Background

2003

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Archaic hodge-podge ⟶ Unified framework

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Historical Background

Example

§ 113.206 Wart Vaccine, Killed Virus.

(d) *Potency and efficacy*. The efficacy of wart vaccine has been demonstrated to the satisfaction of Veterinary Services as being a valuable biological product. The inherent nature of the product precludes the possible development of serial to serial potency tests and none is required: *Provided*, That,

[40 FR 14084, Mar. 28, 1975, as amended at 40 FR 23989, June 4, 1975; 40 FR 30803, July 23, 1975. Redesignated at 55 FR 35562, Aug. 31, 1990, as amended at 56 FR 66786, Dec. 26, 1991]

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Don't bother, we know it works.

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Efficacy?

Don't bother, we know it works.

Potency?

Don't bother, you couldn't do it anyway.

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- ***Data-driven*** – The specific methods should set testing criteria based on experimental and observed data, rather than arbitrary standards.

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  e.g.
  throughout-dating spec for live vaccines
  fixed constant
  not based on data

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- ***Consistent*** – The general principles should be consistent across all classes of assays and products.

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  e.g.

  throughout-dating spec for live vaccines

  fixed constant

  2X for count assays

  5X for titration assays

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- ***Consistent*** – The general principles should be consistent across all classes of assays and products.

e.g.

throughout-dating spec for live vaccines

	fixed constant
~~*bacterial vaccines*~~	2X for count assays
~~*viral vaccines*~~	5X for titration assays

vid. e.g. 9 CFR §113.71, 9 CFR §113.330

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Core

- ***Consistent*** – The general principles should be consistent across all classes of assays and products.

Consistent principles ≠ Inflexible application

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- ***Coherent*** – The various elements of a potency testing system must work together in a coordinated way.

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  e.g.
  No ***assay validation*** requirement before mid-2008

  - Approximately 75% products licensed before validation
  - Many of the 25% licensed since then have been grandfathered in with existing assays

Overview of Potency Assay Policy Development

Approximately

1,850 licensed products

700 distinct antigenic fractions

90 validated potency assays

(many more incrementally improved)

e.g.

No ***assay validation*** requirement before mid-2008

- Approximately 75% products licensed before validation
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Core

- ***Coherent*** – The various elements of a potency testing system must work together in a coordinated way.

Immortal vaccine licenses

Contemporary science

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Core

- ***Data-driven*** ***Criteria***
- ***Consistent*** ***Principles***
- ***Coherent*** ***System***

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Ideal – Current – Proposed

Lot release specifications

(aka serial release)

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Ideal – Current – Proposed

Lot release specifications

(aka serial release)

- Potency-efficacy relationship
- Targeted potency
- Acceptance criteria

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Potency-Efficacy Relationship

Ideal

Establish functional relationship between the potency measurement and the efficacy response.

The potency-efficacy relationship can only be properly estimated from a set of studies that is designed for that purpose.

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Potency-Efficacy Relationship

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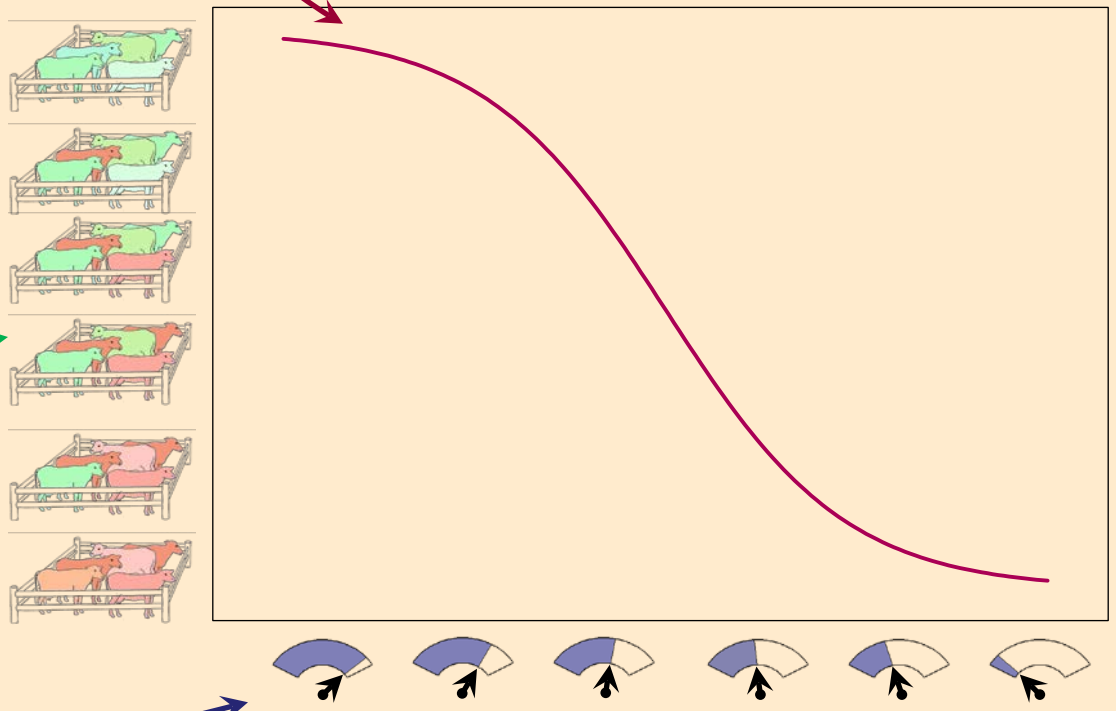
Establish **functional relationship** between the **potency measurement** and the **efficacy response**.

The potency-efficacy relationship can only be properly estimated from a set of studies that is designed for that purpose.



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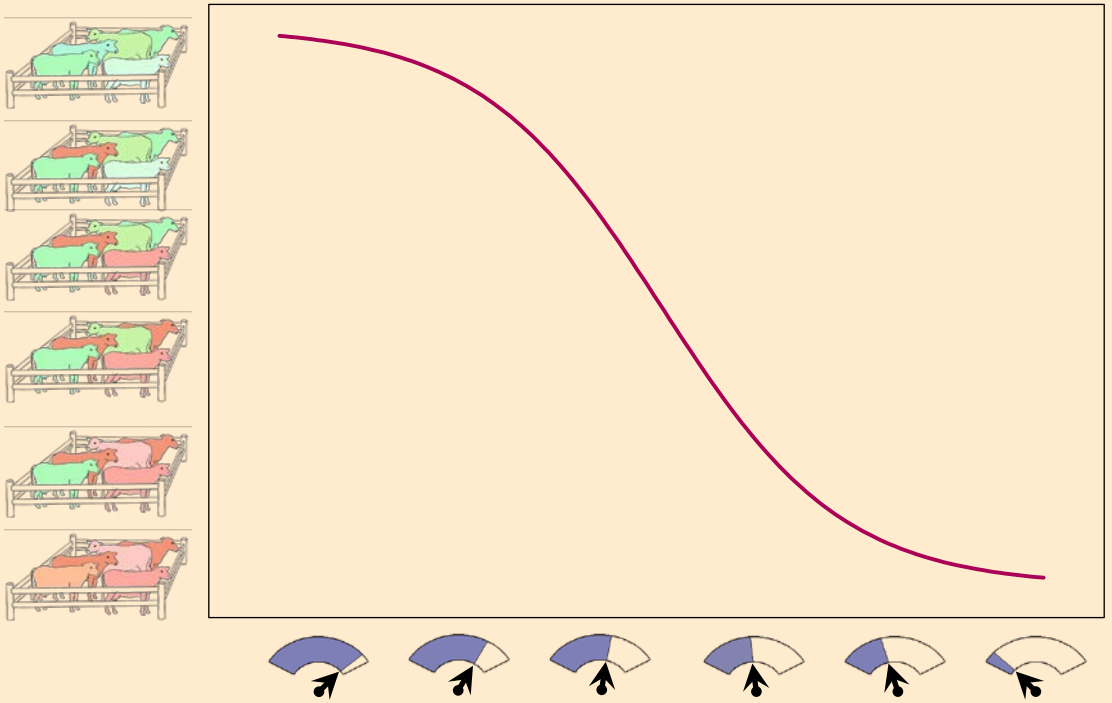

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Potency-Efficacy Relationship

Ideal	Current
Establish functional relationship between the potency measurement and the efficacy response.	Assume there is a relationship of some kind between the potency test and efficacy.
The potency-efficacy relationship can only be properly estimated from a set of studies that is designed for that purpose.	Potency measurement not explicitly associated with a specific level of efficacy - no basis for quantitative conclusions.

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Potency-Efficacy Relationship

Ideal	Current	Proposed
Establish functional relationship between the potency measurement and the efficacy response.	Assume there is a relationship of some kind between the potency test and efficacy.	Show a plausible conceptual presentation of the relationship, but not a mathematical characterization.
The potency-efficacy relationship can only be properly estimated from a set of studies that is designed for that purpose.	Potency measurement not explicitly associated with a specific level of efficacy - no basis for quantitative conclusions.	First step in potency assay validation according to VSM 800.112.

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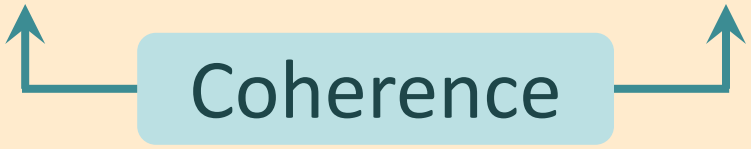
Which guidance applies: old or new?



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Targeted Potency

Ideal

If a functional potency-efficacy relationship exists and is well described, it can be used to mathematically relate a measurement of potency to a level of efficacy.

Cf. VSM 800.209 and Draft 122 describe such methods.

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Targeted Potency

Ideal	Current
If a functional potency-efficacy relationship exists and is well described, it can be used to mathematically relate a measurement of potency to a level of efficacy.	Take the observed potency of the vaccine formulation used in the pivotal efficacy study and add a standard quantity to it.
Cf. VSM 800.209 and Draft 122 describe such methods.	

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Targeted Potency

Ideal	Current	Proposed
If a functional potency-efficacy relationship exists and is well described, it can be used to mathematically relate a measurement of potency to a level of efficacy.	Take the observed potency of the vaccine formulation used in the pivotal efficacy study and **add a standard quantity** to it.	Take the observed potency of the vaccine formulation used in the pivotal efficacy study and **add an amount based on data** observed in potency testing rather than an arbitrary amount.
Cf. VSM 800.209 and Draft 122 describe such methods.		

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Acceptance Criteria

Ideal

Formulated so that a specified fraction of a lot meets a minimum specification.

Large enough sample of the vials in each lot tested to reasonably depict the distribution of potencies among them.
Acceptance sampling system makes it possible to formulate explicit probability statements about the vaccine.

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Acceptance Criteria

Ideal	Current
Formulated so that a specified fraction of a lot meets a minimum specification.	Varies; often based on arbitrary quantities unrelated to manufacturing or assay performance.
Large enough sample of the vials in each lot tested to reasonably depict the distribution of potencies among them. Acceptance sampling system makes it possible to formulate explicit probability statements about the vaccine.	Lot release based on single test of single vial. Biased retesting of unsatisfactory test results, but not satisfactory ones. No probability statements warranted.

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Acceptance Criteria

Ideal	Current	Proposed
Formulated so that a specified fraction of a lot meets a minimum specification.	Varies; often based on arbitrary quantities unrelated to manufacturing or assay performance.	**Target** based on potency test performance to account for assay precision and manufacturing consistency. **Release** above target by an amount estimated from average potency loss during storage.
Large enough sample of the vials in each lot tested to reasonably depict the distribution of potencies among them. Acceptance sampling system makes it possible to formulate explicit probability statements about the vaccine.	Lot release based on single test of single vial. Biased retesting of unsatisfactory test results, but not satisfactory ones. No probability statements warranted.	Rewarding precise assays and consistent manufacturing gives the manufacturer greater degree of control over its potency specifications.

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Ideal – Current – Proposed

Large type version

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Potency-Efficacy Relationship

Ideal	Current	Proposed
Establish functional potency-efficacy relationship	**Assume** there is a relationship of some kind between potency and efficacy	**Show plausible** conceptual potency-efficacy relationship
The potency-efficacy relationship can only be properly estimated from a set of studies that is designed for that purpose	Potency measurement not explicitly associated with a specific level of efficacy - no basis for quantitative conclusions	First step in potency assay validation according to VSM 800.112

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Targeted Potency

Ideal	Current	Proposed
potency-efficacy relationship exists and is used to relate potency measurement to efficacy level	add a **standard amount** to observed potency in pivotal efficacy study	add an **amount based on data** to observed potency in pivotal efficacy study
Cf. VSM 800.209 and Draft 122 describe such methods.		

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Acceptance Criteria

Ideal	Current	Proposed
Specified fraction of a lot meets a minimum specification	Varies; often based on arbitrary quantities	**Target** – potency test performance **Release** – average potency loss in storage
Must sample enough vials in each lot to depict the distribution of potencies among them. Can make **explicit probability statements** about the lot.	Release based on single test of single vial. Biased retesting of unsatisfactory test results. **No probability statements warranted**.	Rewards precise assays and consistent manufacturing; **manufacturer control** over potency specifications.

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Ideal – Current – Proposed

Why is proposed less than ideal?

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Ideal – Current – Proposed

Why is proposed less than ideal?

- Regulatory pragmatism
- Number of product licenses
- Historical inertia
- Manufacturer reluctance

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Comparison of Regulatory Systems

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Comparison of Regulatory Systems

"The current concept of the quality assurance of vaccines is based on the overall consistency of production, involving several in-process controls, rather than being based simply on a single lot release assay. The adherence to good manufacturing practices is therefore of critical importance…"

WHO Annex 3; also vid. 21 CFR §211.100(a)

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Comparison of Regulatory Systems

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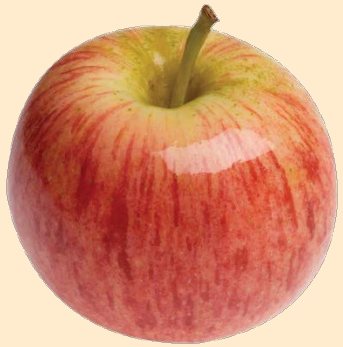
Comparis[illegible] of Regulatory Systems



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Guidelines for Potency Assays

	EMA	CVB
Active substance	Correlation between potency and efficacy	Crude association
Adjuvant	Adjuvant testing for quality and quantity	Adjuvant testing not required
Production	GMP and process validation	No GMP or process validation
Assay validation	Follow VICH guidelines	VSM 800.112, June 2008

EMA/CVMP/IWP/582970/2009, EMA/CVMP/IWP/206555/2010

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Guidelines for Setting Potency Specs

	ICH/VICH	CVB
Clinical	Specifications linked to preclinical and clinical studies	Tenuous link
Assay	Specifications linked to analytical procedures	Not yet (Draft 440)
Manufacturing	Specifications linked to manufacturing process	Not yet (Draft 440)
Stability	Specifications account for stability	Informal (Draft 155)

ICH Q6B

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Guidelines for Stability

	FDA, ICH, VICH	CVB
Stability-Indicating Assay	Stability-Indicating assay required "Validated quantitative analytical procedure that can detect changes …"	Not yet (Draft 155)
Stability Protocol	Many characteristics including potency, physicochemical measurements, pH, bioburden, pyrogenicity, moisture if lyophilized, stability following reconstitution if lyophilized, stability through freeze-thaw if frozen, …	Potency only (Draft 155)
Stability Monitoring	On-going stability monitoring	Draft 155

ICH Q1A(R2), ICH Q1E, VICH GL3(R), VICH GL51; FDA Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for Vaccines

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Number of Products

	FDA-CBER	USDA-CVB
Vaccines	79	1,211
Antibody	49	54
Diseases	26	220

- 20 of 79 CBER vaccines are influenza
- 1,211 CVB vaccines does not include 145 FFMs

Data accessed 2015.02.27
http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm
http://www.fda.gov/downloads/BiologicsBloodVaccines/UCM149970.pdf

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Risk Assessment – Decision Analysis

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Risk Assessment – Decision Analysis

Example

Sub-potent Serial	
Vaccine Manufacturer	
Low, because all vaccine is gone long before end of dating.	
(But don't shorten my dating period, because we need it to market the product.)	

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Risk Assessment – Decision Analysis

Example

Sub-potent Serial	
Vaccine Manufacturer	Vaccine User
Low, because all vaccine is gone long before end of dating.	**High**, because vaccine is used throughout its dating period.
(But don't shorten my dating period, because we need it to market the product.)	(Check your medicine cabinet tonight.)

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Risk Assessment – Decision Analysis

Events

Value

Action

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Risk Assessment – Decision Analysis

Events	Probability Distribution	
Value	Utility Function	(Cost / Benefit)
Action	Decision Rule	(Optimization)

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Risk Assessment – Decision Analysis

Events	Probability	Same for All
Value	Utility Function	Different for Each
Action	Decision Rule	Different for Each

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Terminology

Potency is a quantitative measure of the activity of a vaccine lot as measured in a validated potency assay.

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- Activity may be measured in various ways
  - Immunochemical
  - Cellular
  - Clinical
  - Component concentration

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Terminology

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- Activity may be measured in various ways
  - Immunochemical
  - Cellular
  - Clinical
  - Component concentration

- Ideally related to efficacy

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Terminology

Potency is a quantitative measure of the activity of a vaccine lot as measured in a validated potency assay.

- Often assumed to be a function of a single input for simplicity
- Vaccine activity may actually be a function of several inputs, e.g.
  - Antigenic epitopes
  - Innate immunity stimulants
  - Adjuvants

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Core

- ***Data-driven*** ***Criteria***
- ***Consistent*** ***Principles***
- ***Coherent*** ***System***

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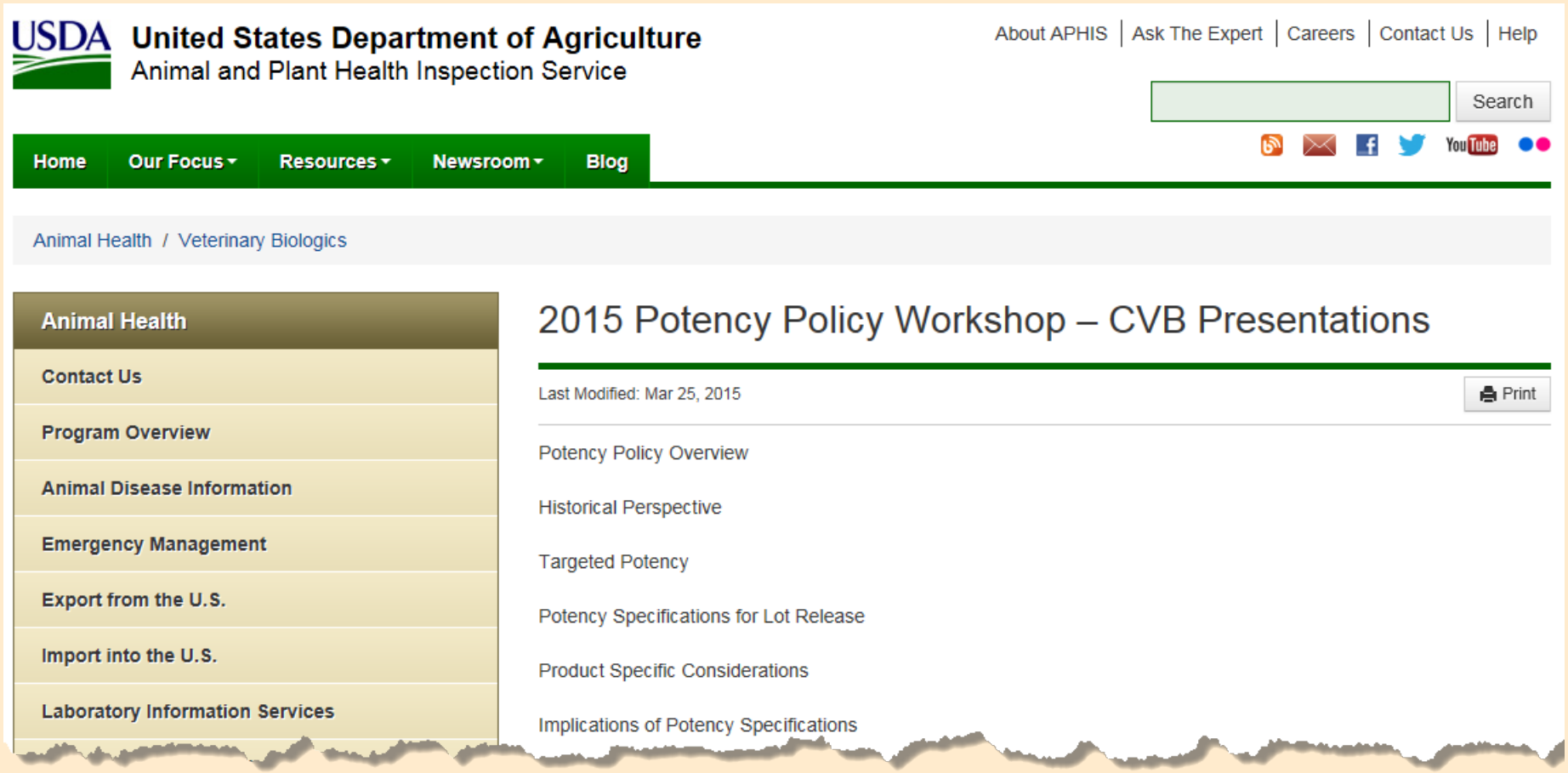
Summary

- ***Core***
- Context – framework
- Ideal-Current-Proposed
- Other regulatory systems
- Risk assessment
- Potency

Overview of Potency Assay Policy Development



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