

# The Predictive Value of Accelerated & Forced Degradation Data: A Case Study

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# How industry feels about regulations...



"Who gets to be the SOB who quotes us  
the regulations?"

# Overview

- General principles and perspectives regarding the value of accelerated and forced degradation studies
- Case study highlighting the importance of such stability studies and the consequences of not undertaking them at the earliest opportunity
- Key messages and follow up for both regulatory agencies and industry

# General Principles and Perspectives

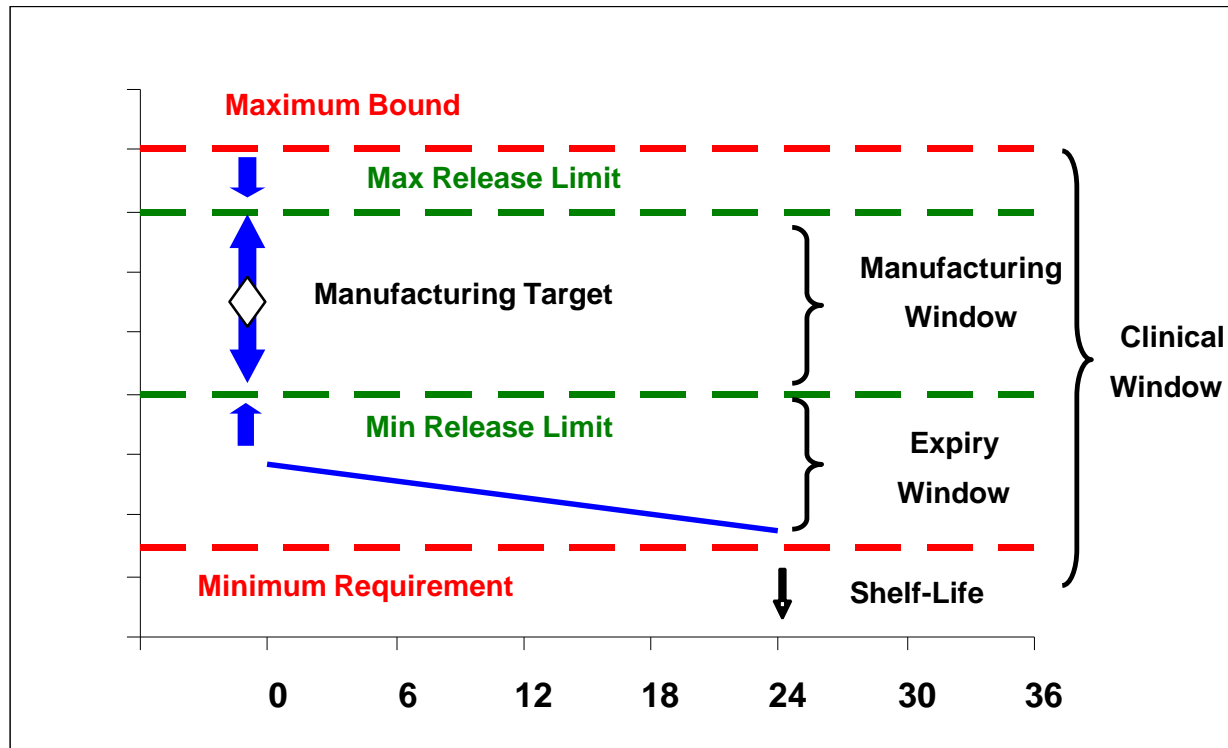
- The importance of early stability characterization can not be overstated. A “*pay me now or pay me later*” situation can be the result, as will be seen in the case study.
- Accelerated versus forced degradation conditions; is there an advantage to either option? The later should be favoured, provided the conditions are biologically relevant.
- When determining what specific conditions should be assessed, don't let compliance be your guide. Have a clear logic and rationale for what you are doing **and why**.
- Select optimized times and temperatures to favour degradation and not polymerization in stability studies.
- Note that current standard temperature conditions relate to Arrhenius kinetics, which are relevant to small molecule drugs, but are not generally applicable to biologics.

# General Principles and Perspectives Cont'd

- Beyond temperature, what other stability conditions should be modeled? Considerations should be product specific and manufacturing process related (e.g., light sensitivity, oxidation *via* peroxide with disinfection procedures, potential for aggregation and impact on potency/safety etc.)
- Are the assays in use fit for purpose. Are you “seeing” what you think you are? This will be highlighted in the case study and there are also non-biologics examples as well (e.g., a embarrassing airport security situation, where a test could detect plastic explosives but not gun powder).
- Are there more appropriate non-compendial assays that are stability-indicating, or would the use of a battery of assays be more informative than the conventional or compendial assay? Is the data you have meaningful?

# Manufacturing Stability & Product Release Models

Stability release models combine clinical, quality and process information, with assay variability to control risks



*Tim Schofield: IABS Vaccine Stability Workshop Oct. 2008, Geneva*

# H1N1 Pandemic Flu Case Study

- The 2009 H1N1 flu pandemic provides insights to best practices related to problematic assumptions, missed opportunities and the value of appropriate forced degradation data. The lessons apply to all biologics at the time of product approval, and also suggest a more efficient approach for the assessment of post-approval manufacturing changes in terms of shelf-life decisions.
- These insights have implications for manufacturers and regulators.

# The Unique World of Flu Vaccines

- Each year flu vaccine typically includes a new strain for one of the 3 or 4 strains in the product.
- The annual process from strain selection, manufacturing and lot release is a highly compressed schedule and a challenge for all involved.
- Full real-time stability data is not available at the time of approval. The previous year's data (often with at least one different strain) is often considered as key supportive data. This is necessary but problematic.
- The 2009 monovalent H1N1 vaccine was proposed as a strain change from the H5N1 monovalent mock vaccine, but how similar were they?
- The Potency Assay for inactivated Flu vaccine is the **legacy** Single Radial Immunodiffusion (SRID) Assay.



# The Case Study Overview

- During the 2009 H1N1 pandemic, some but not all vaccine manufacturers of both non-adjuvanted and adjuvanted vaccines experienced stability issues with their products. (Note: The adjuvants were oil emulsion-based not Alum)
- The Case Study involves mock stability SRID assay data sets for H5N1 and H1N1 products initially intended to support a proposed 24 month shelf-life for flu vaccines from manufactures A, B and C. The data presented mimics the general events experienced but is not from any specific product or manufacture.

# The Case Study Overview Cont'd

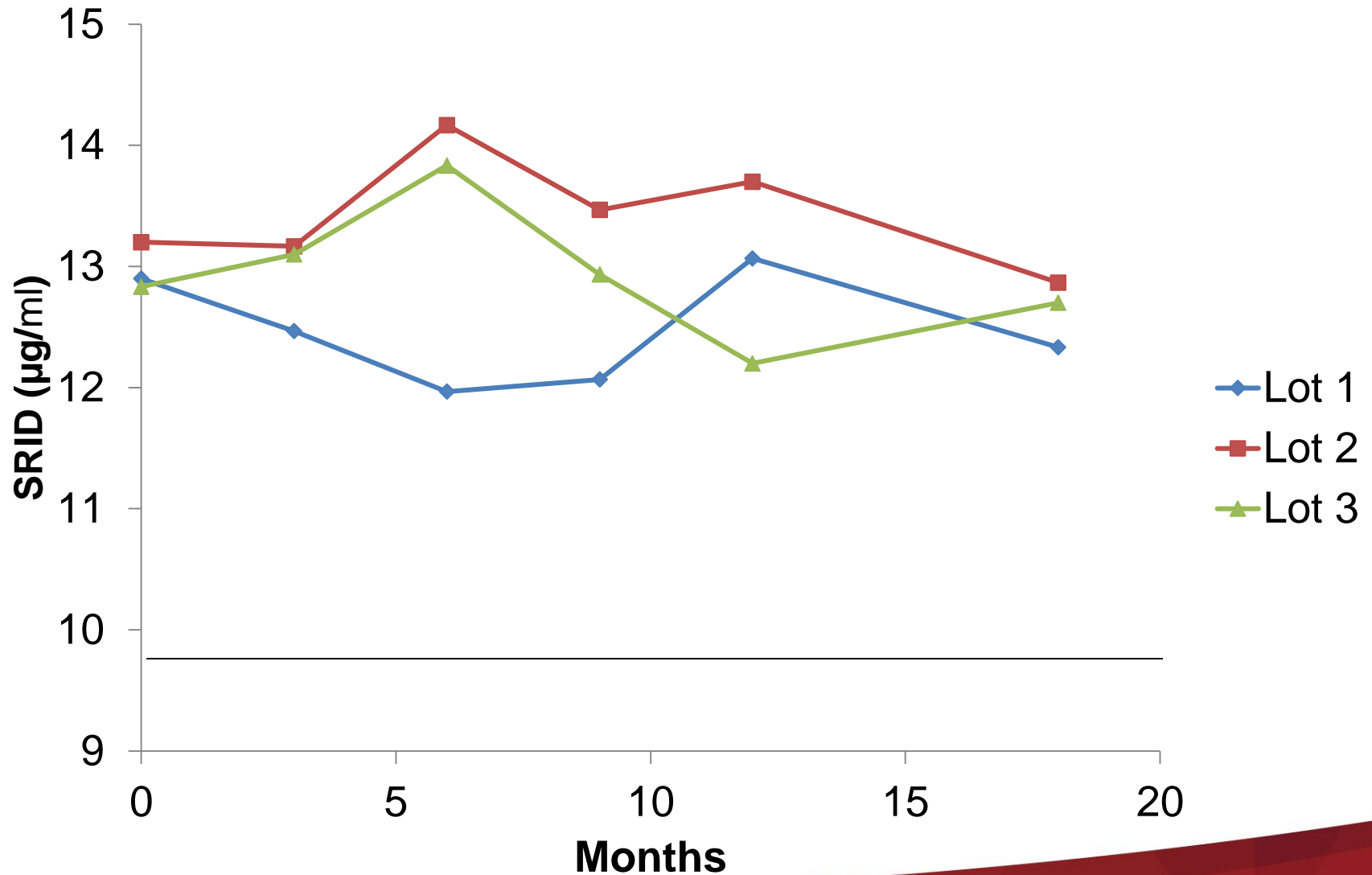
## Manufacturers Vaccine's:

- A: Adjuvanted H5N1 & H1N1 Vaccines with a SRID-based label claim of 10 µg/ml. Lower bound specification at 80% was 8 µg/ml. Liquid vaccine is combined with an equal volume of liquid emulsifying adjuvant. The final antigen content was 2.5 µg/dose.
- B: Adjuvanted H5N1 and H1N1 Vaccines with a SRID-based label claim of 12 µg/ml. Lower bound specification at 80% was 9.6 µg/ml. Liquid vaccine is combined with an equal volume of liquid emulsifying adjuvant. The final antigen content was 3 µg/dose.
- C: Non-Adjuvanted H5N1 Vaccine with a SRID-based label claim of 120 µg/ml. The lower bound specification at 80% was 96.0 µg/ml. The final antigen content was 60 µg/dose.
  - also,
- C: Non-Adjuvanted H1N1 Vaccine, SRID-based label claim was 30 µg/ml. The lower bound specification at 80% was 24 µg/ml. The antigen content was 15 µg/dose.

**Note the antigen sparing offered with the use of adjuvant and the immunogenicity differential between H5N1 versus H1N1. The latter is most evident with Manufacturer C's products, where H1N1 is far more immunogenic.**

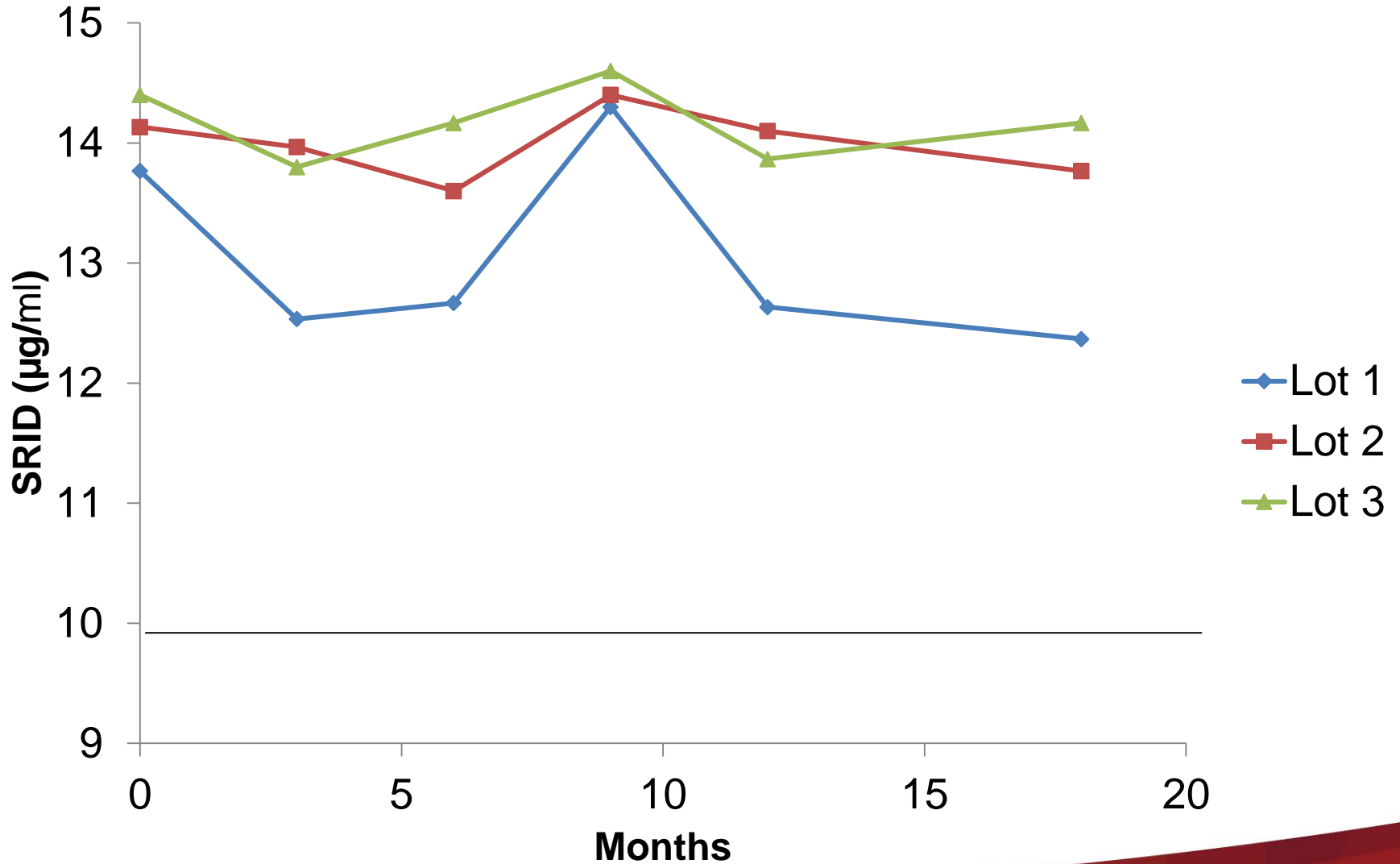
# First Data Submitted to Agencies

## Manufacture A: H5N1 Adjuvanted Vaccine at 5°C



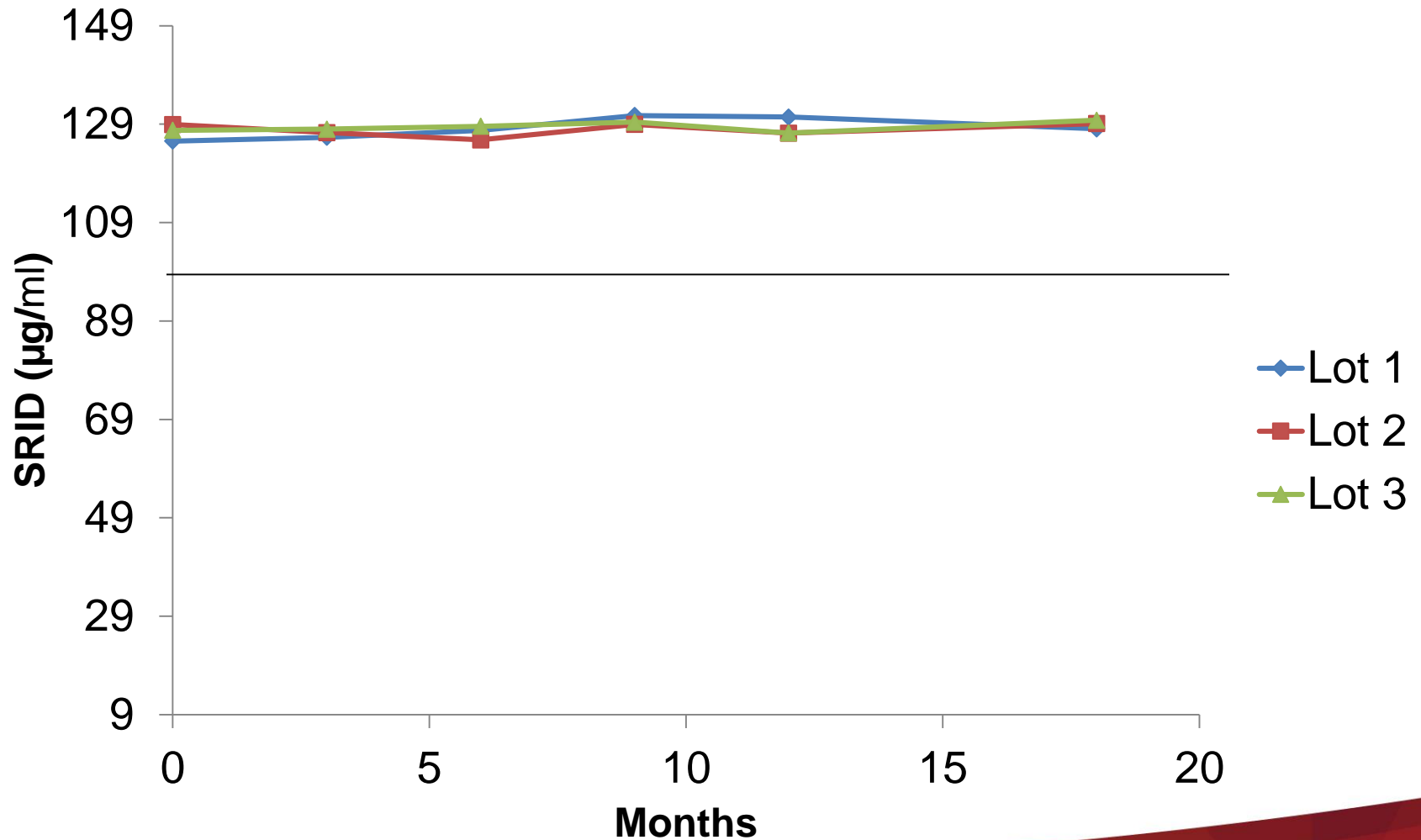
# First Data Submitted to Agencies

## Manufacture B: H5N1 Adjuvanted Vaccine at 5°C



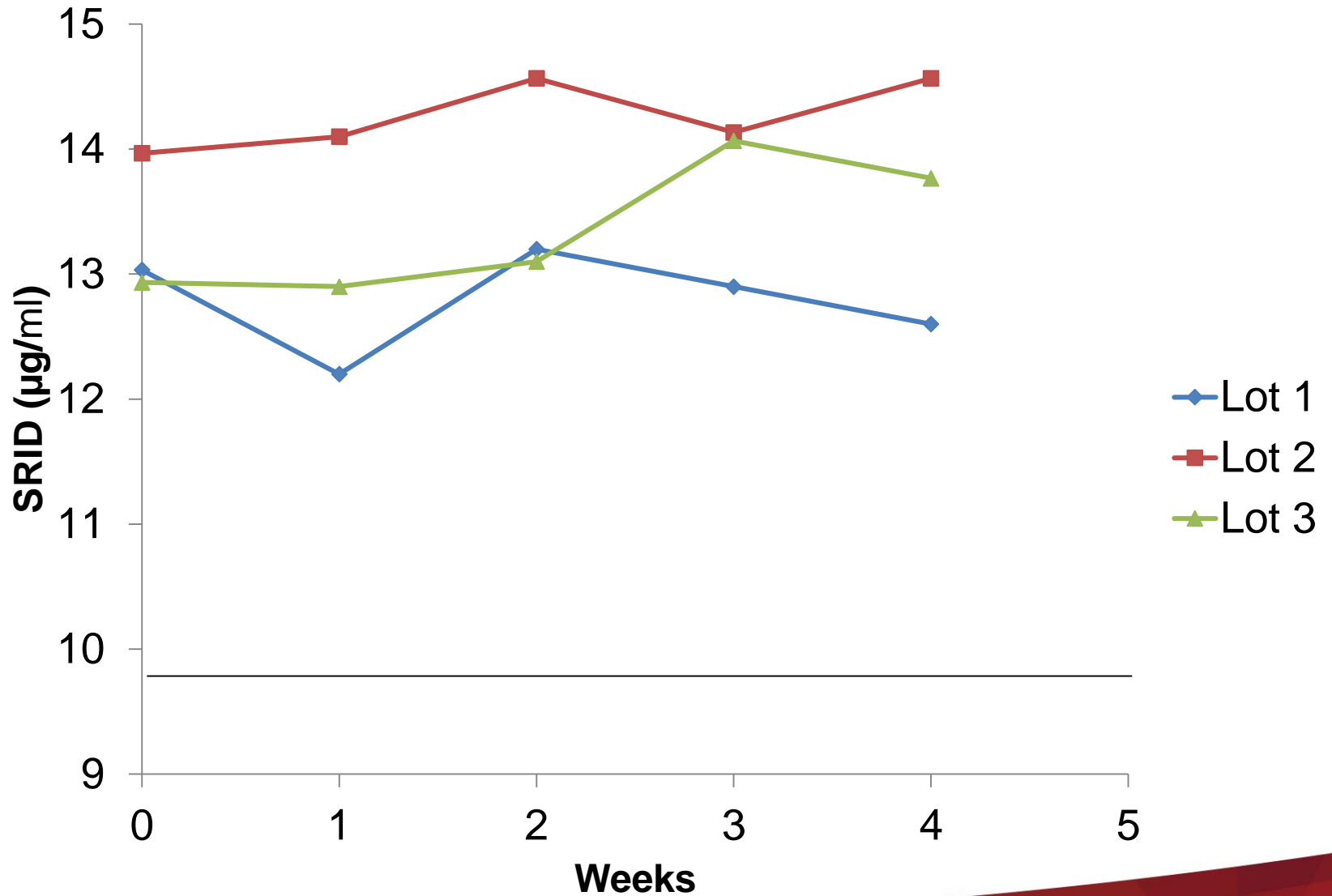
# First Data Submitted to Agencies

## Manufacture C: H5N1 Non-Adjuvanted Vaccine at 5°C



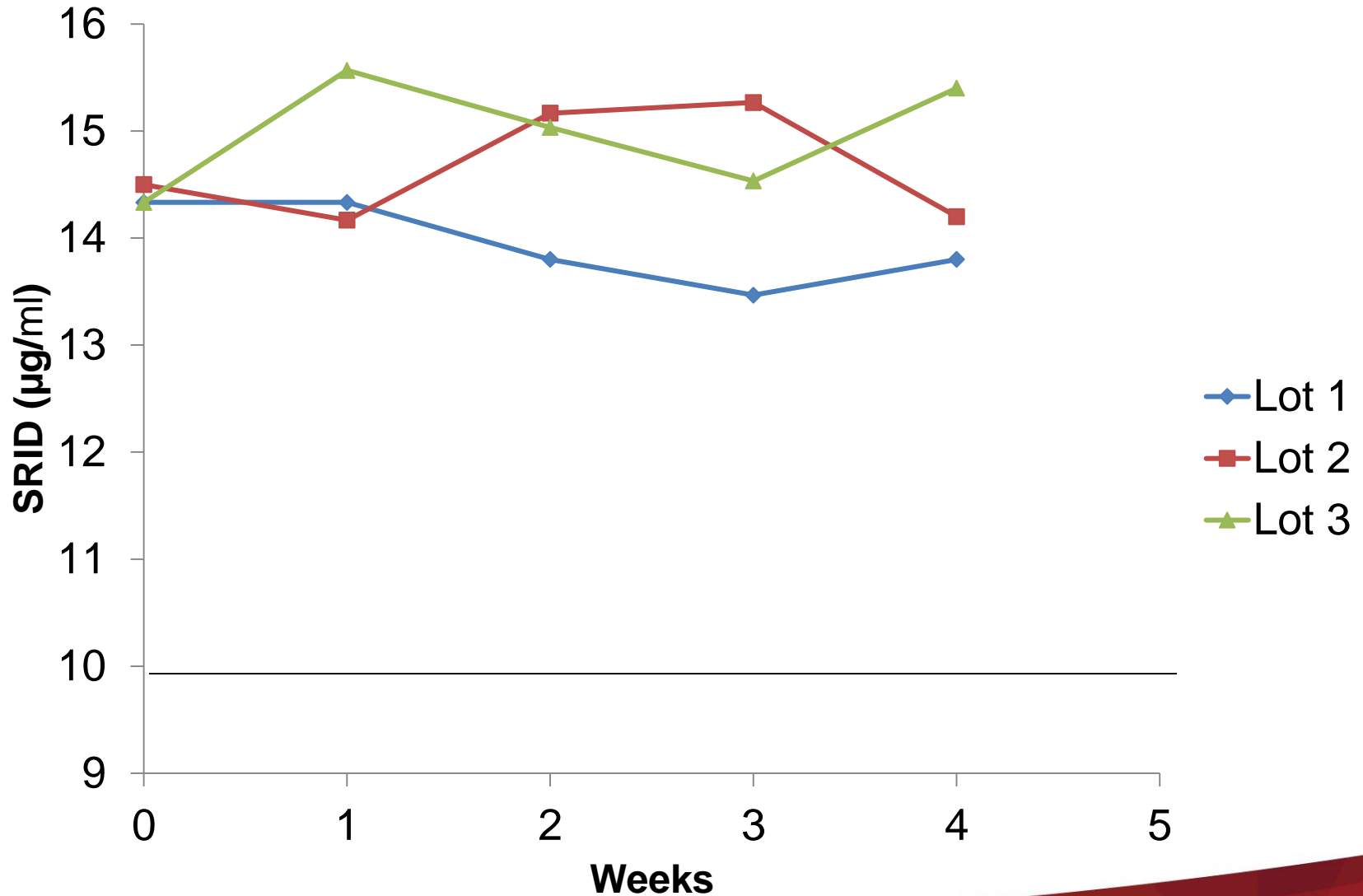
# First Data Submitted to Agencies

Manufacture A: H5N1 Adjuvanted Vaccine at 37°C



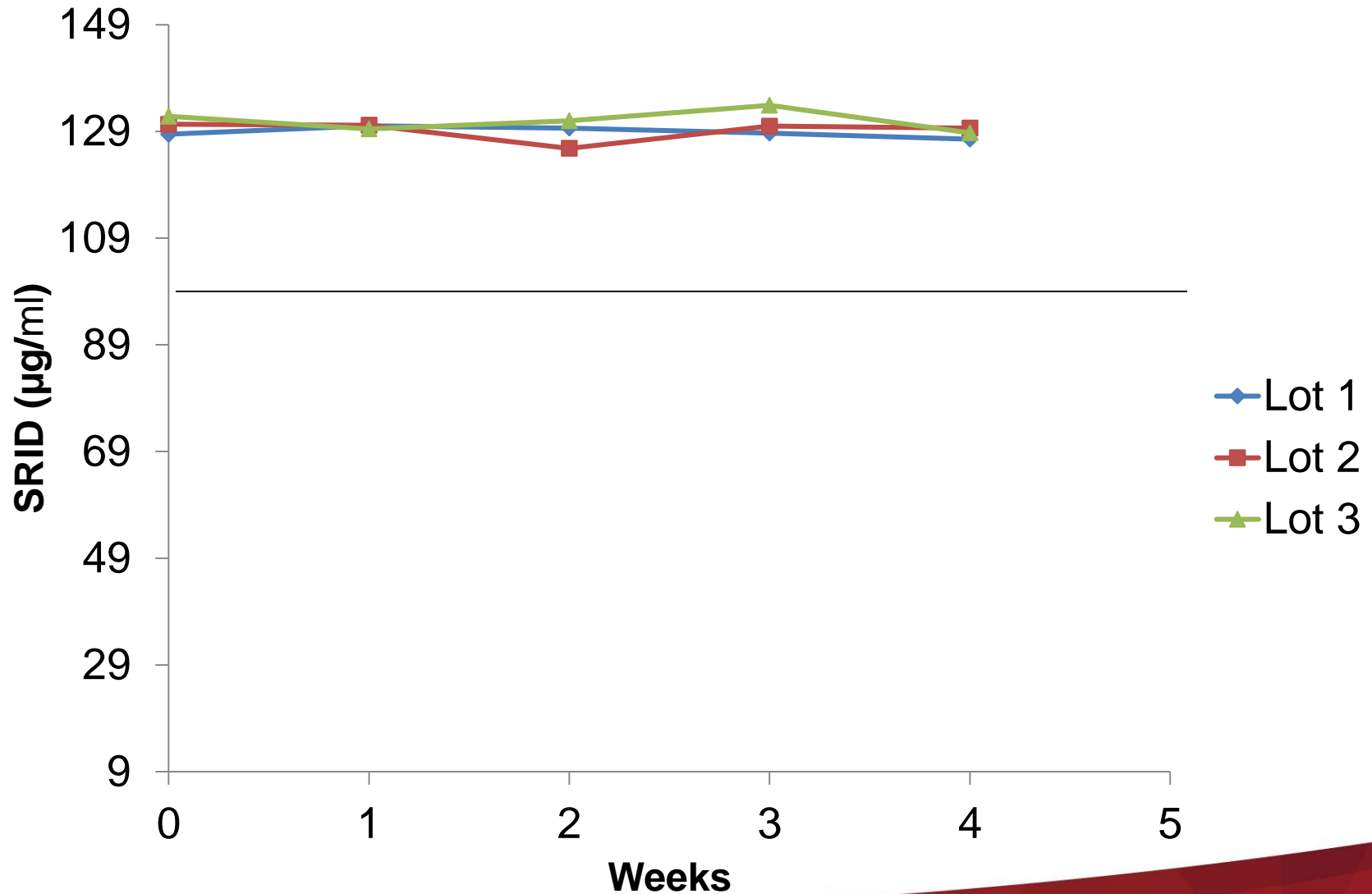
# First Data Submitted to Agencies

Manufacture B: H5N1 Adjuvanted Vaccine at 37°C



# First Data Submitted to Agencies

Manufacturer C: H5N1 Non-Adjuvanted vaccine at 37°C





Initial conclusions, questions and options?

# First H1N1 Specific Data For Vaccines at 5°C

## Vac A: SRID values in µg/ml

Months	Lot 1			Mean	STD
0	12.2	13.4	11.9	12.5	0.793725
3	10.1	12.9	9.8	10.9	1.709776
Months	Lot 2			Mean	STD
0	14.9	13.8	12.8	13.8	1.050397
3	10.7	12.3	11.5	11.5	0.8
Months	Lot 3			Mean	STD
0	13.1	12.1	13.7	13.1	0.80829
3	12.5	11.5	12.6	12.2	0.608276

## Vac B: SRID values in µg/ml

Months	Lot 1			Mean	STD
0	14.5	15.2	13.9	14.5	0.650641
3	14.1	14.8	14.6	14.5	0.360555
Months	Lot 2			Mean	STD
0	13.9	12.5	14.5	13.6	1.02632
3	14.6	13.5	13.6	13.9	0.608276
Months	Lot 3			Mean	STD
0	16.2	14.4	15.1	15.2	0.907377
3	15.4	13.8	14.3	14.5	0.818535

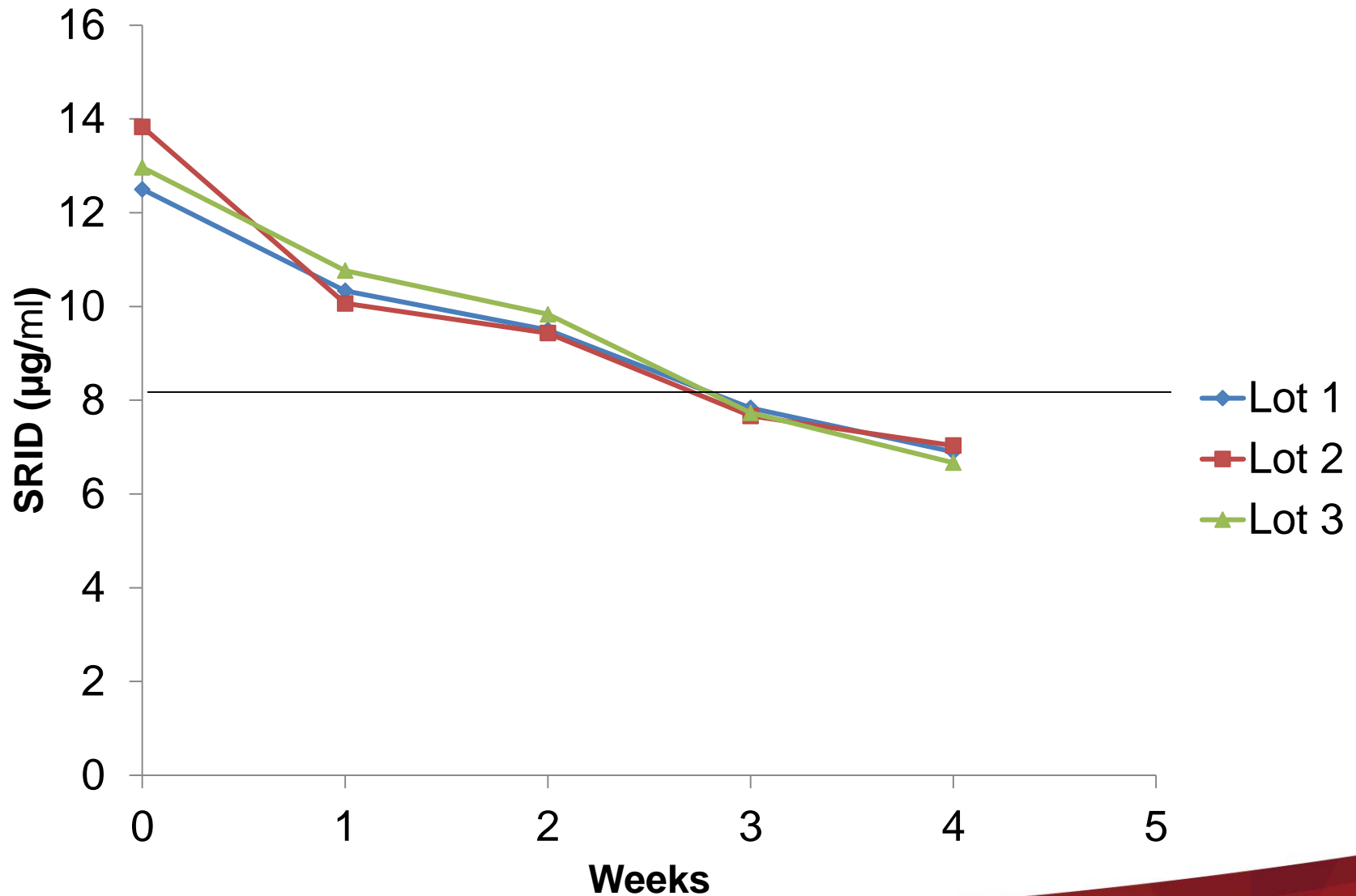
## Vac C: SRID values in µg/ml

Months	Lot 1			Mean	STD
0	35.3	32.2	34.4	34.0	1.594783
3	28.2	27.2	30.3	28.6	1.582193
Months	Lot 2			Mean	STD
0	31.1	37.4	32.3	33.6	3.345146
3	27.3	28.4	29.6	28.4	1.150362
Months	Lot 3			Mean	STD
0	35.2	34.2	32.2	33.9	1.527525
3	29.4	28.4	29.2	29.0	0.52915

# Conclusions, questions and options?

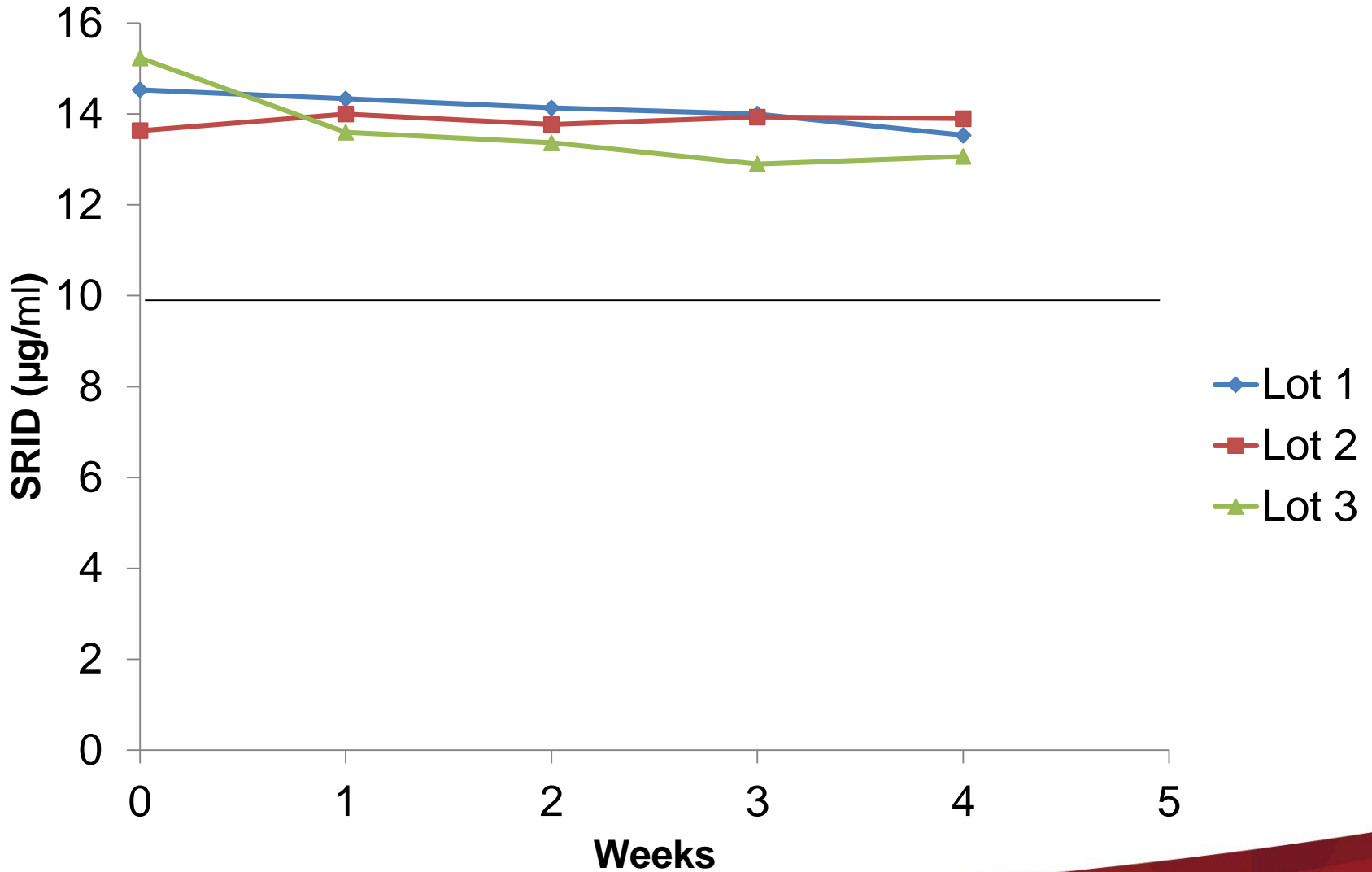
# Agency Request for Accelerated Data

Manufacture A: H1N1 Adjuvanted Vaccine at 37°C



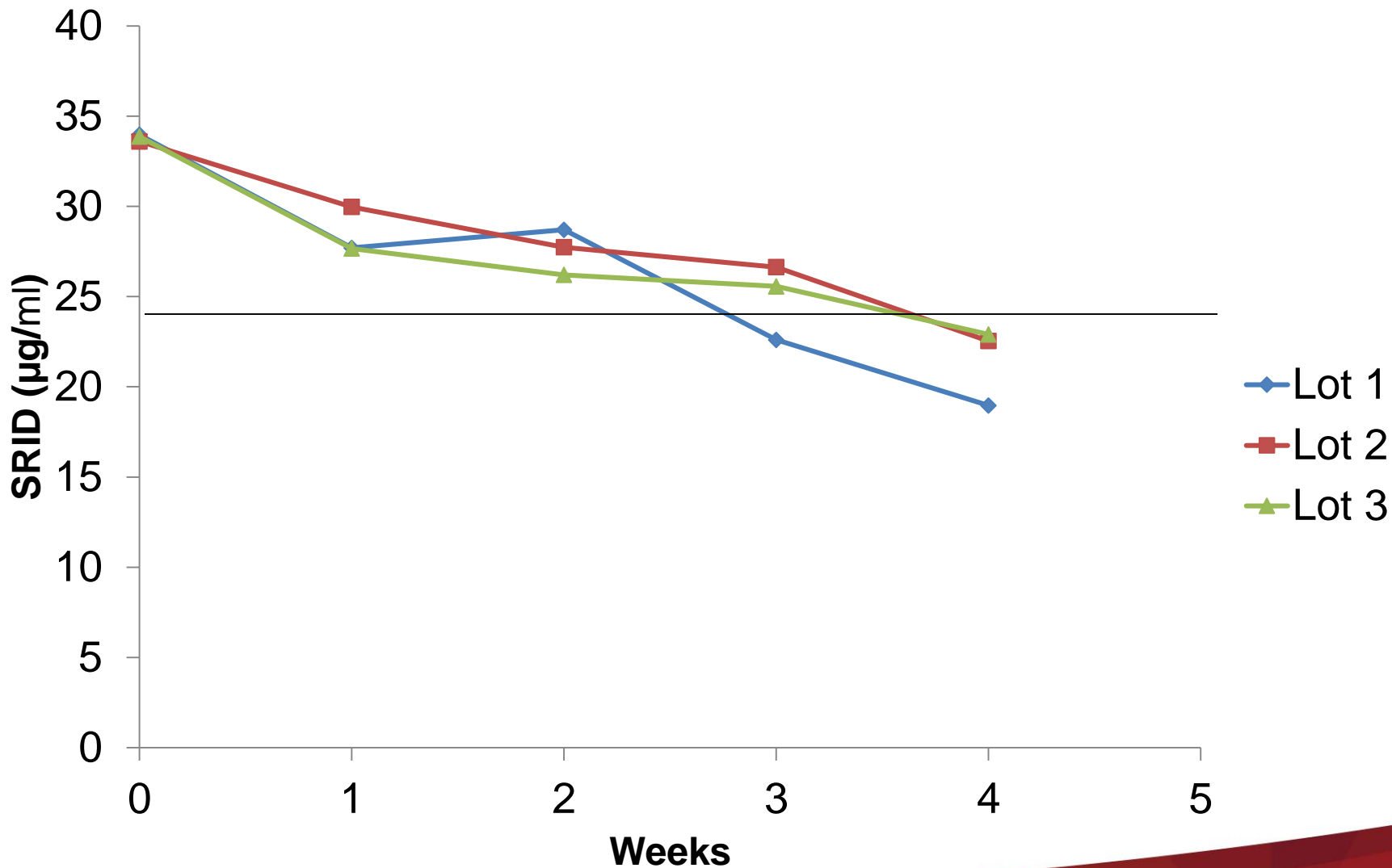
# Agency Request Accelerated Data

Manufacture B: H1N1 Adjuvanted Vaccine at 37°C



# Agency Request Accelerated Data

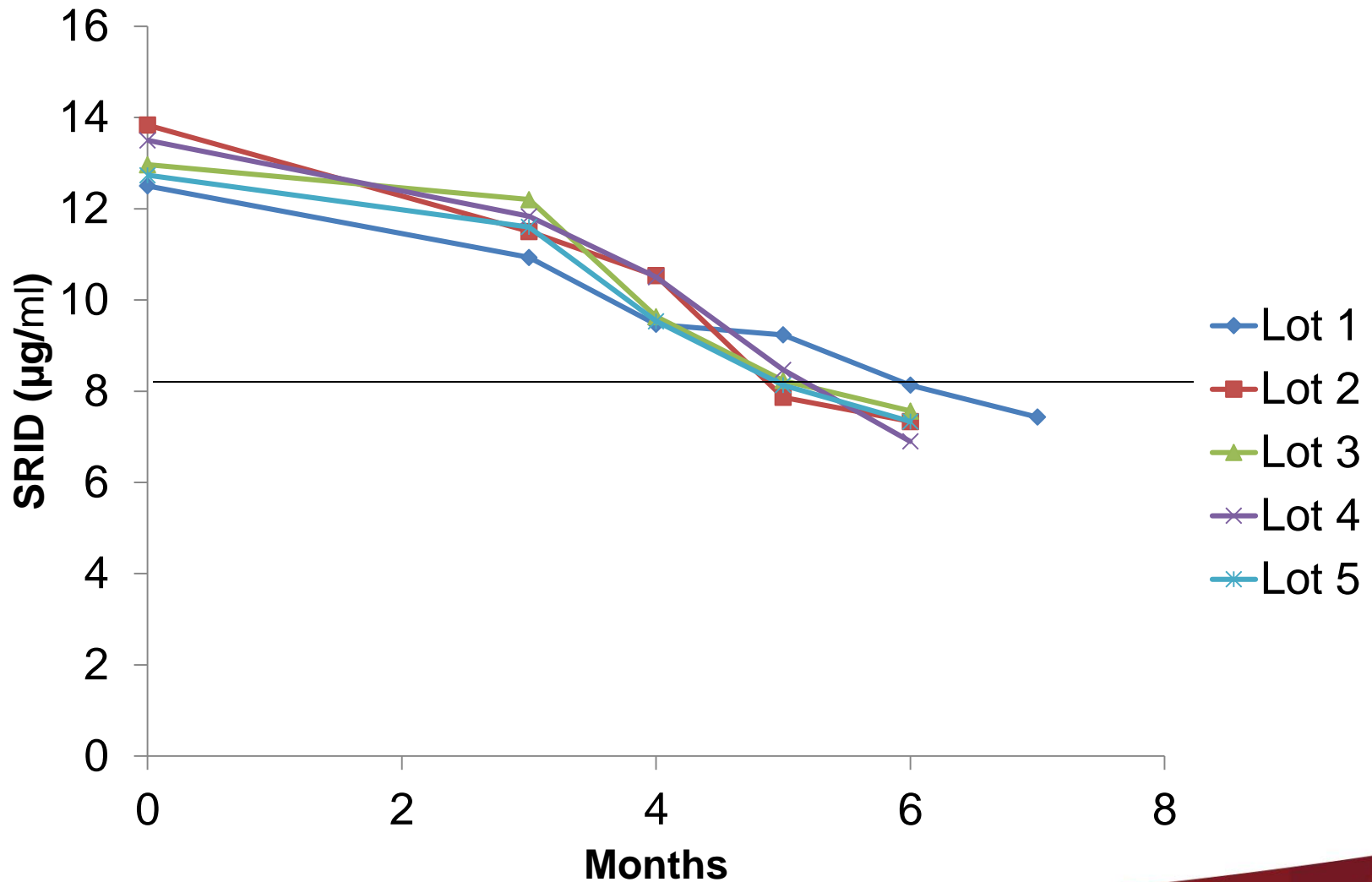
Manufacture C: H1N1 Non-Adjuvanted Vaccine at 37°C



# Conclusions, questions and options?

# Real-Time Stability Data At 6 Months

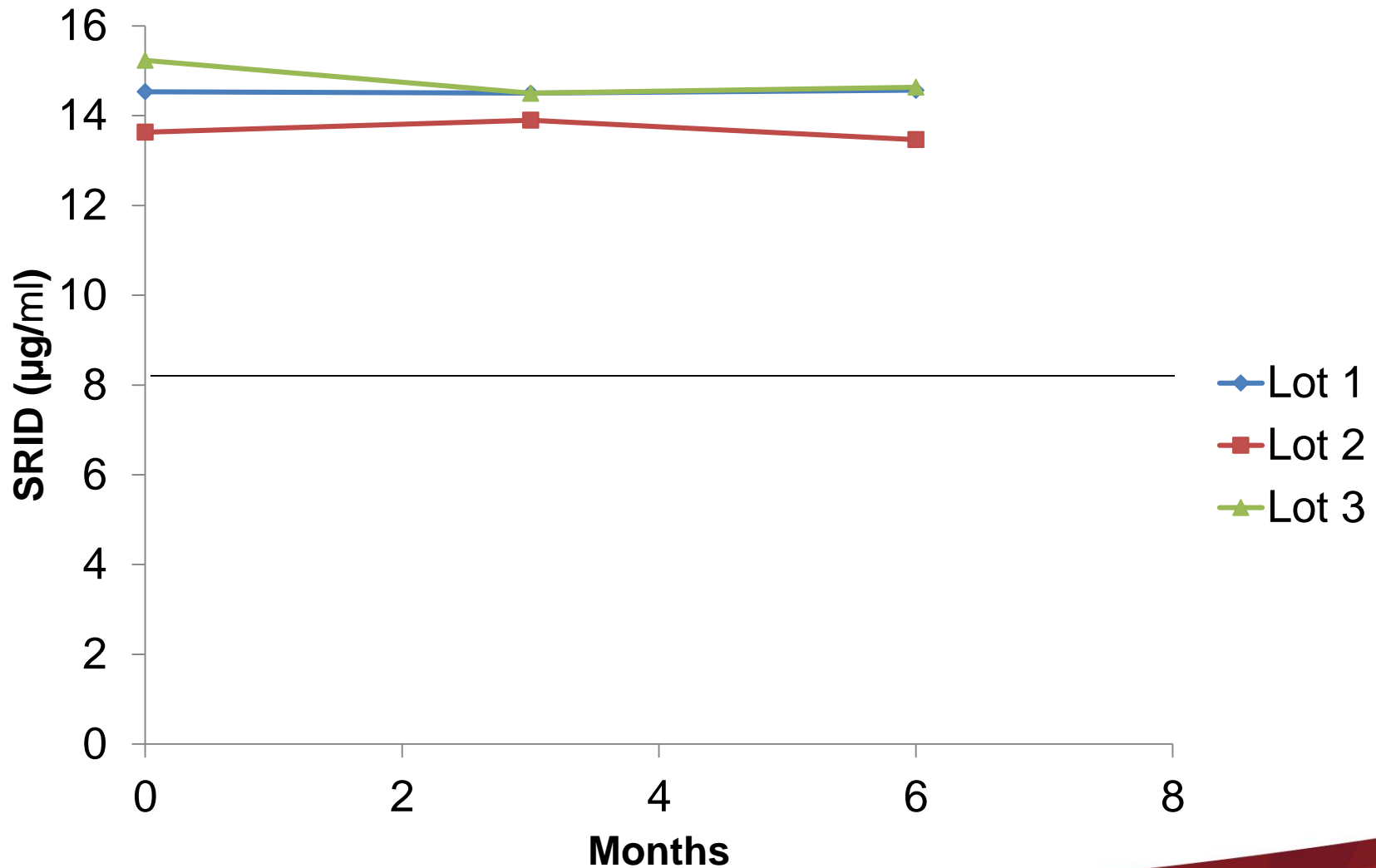
## Manufacture A: H1N1 Adjuvanted Vaccine at 5°C





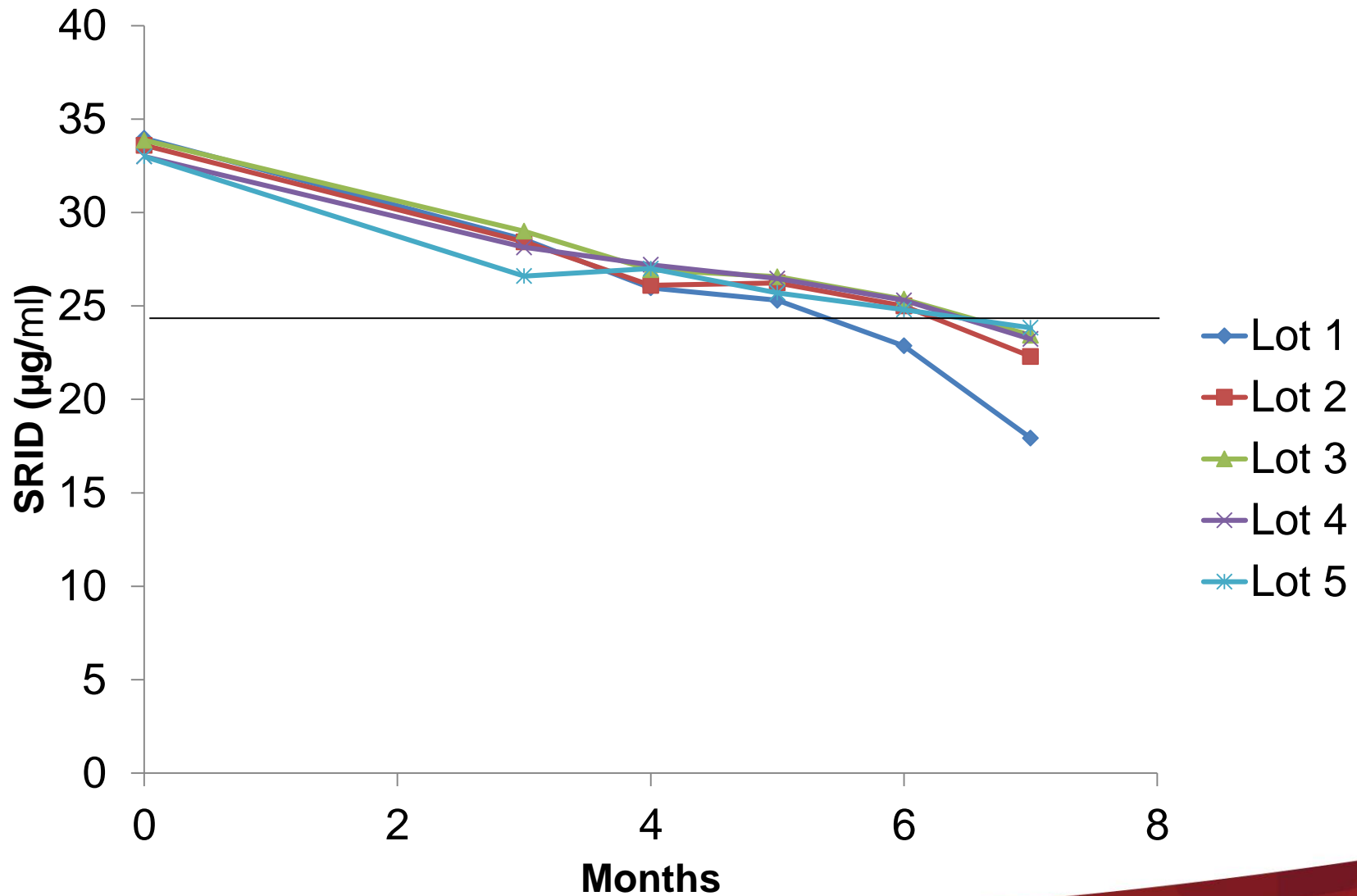
# Real-Time Stability Data At 6 Months

## Manufacture B: H1N1 Adjuvanted Vaccine at 5°C



# Real-Time Stability Data At 6 Months

Manufacture C: H1N1 Non-Adjuvanted Vaccine at 5°C



# Conclusions, questions and options?

# Consequence and Follow-Up Studies

- At Health Canada, for those vaccines that had an apparent reduction of antigen content over time, the shelf-life was reduced on a lot-by-lot bases. The revised shelf-life was based on a statistical analysis of the potency rate of decay, as defined by the SRID assay, and the minimum required potency.
- Follow-up studies by some manufactures demonstrated that the apparent loss of antigen content was due to antigen aggregation, and that there was an underestimate of the actual “potency” or immunogenicity using the the SRID assay. Protection studies in the Ferret animal model indicated that the immunogenicity of certain of these vaccines was maintained or even enhanced in spite of their low SRID assay results.

# Key Messages For Biologics Regulation

- Accelerated and forced degradation studies (e.g., at elevated temperature generally below 40°C) are generally not predictive of real time stability for biologics at 2 to 8°C, but can provide extremely valuable information and can predict relative stability.
- Early forced degradation stability data, when combined with initial real-time data and other product characterization data, should permit more rapid regulatory decisions as full confirmatory real-time data is accumulated. This applies to post-approval manufacturing changes as well as for seasonal flu strain changes.
- Know the limitations of the assays that stability studies depend on.
- In general stability studies can provide insight into:
  - Kinetics of degradation
  - Degradation products
  - Stability influencing parameters (e.g., pH, moisture, etc.)
  - Determine if an assay is “stability-indicating”
  - Supportive data for establishing shelf-life
  - Assess stability under accidental or planned excursions in extreme conditions (i.e., Extended Controlled Temperature Conditions)
  - Used for comparative purposes (e.g., different formulations, scale-up)

# Acknowledgements

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