My Potency Assay is Quantitative But is it Quantitative of Potency?

Christopher A Bravery
CBRAVERY@ADVBIOLS.COM

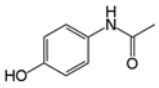
INTRODUCTION

This talk will attempt to discuss....

- What is potency?
  - Potency v Efficacy
- Quantifying potency or just a [distantly] related analyte?
  - Is the measurand even measuring potency?
- Setting and Justifying potency specifications
  - Quality v Clinical Qualification

INCREASING COMPLEXITY

To a point where the structure cannot be defined



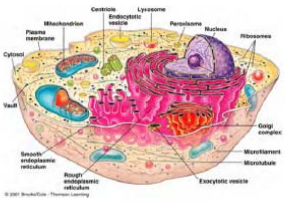
Acetaminophen
(paracetamol)
Ø 1 nm

mAb
Ø 10 nm

Multiple MoA likely, these might even differ between patients.

Filgrastim, G-CSF

Ø 20-4[illegible]m



Eucaryotic cell

Recombinant virus

Ø 10,000-100,000 nm
(10-100 µm)

MoA relates to gene construct.
Note: transduction efficiency is not potency but will impact potency

POTENCY

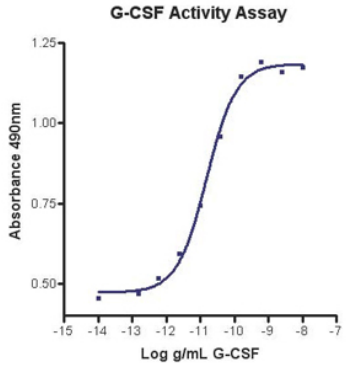
ICH Q6B*

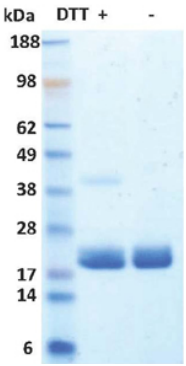
- The measure of the **biological activity** using a suitably **quantitative biological assay** (also called potency assay or bioassay), based on the attribute[s] of the product[/active substance] which is [are] linked to the **relevant biological properties** [of the active substance/product].

Note: Potency is NOT efficacy

*Specifications : Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products (ICH Q6B) 1999

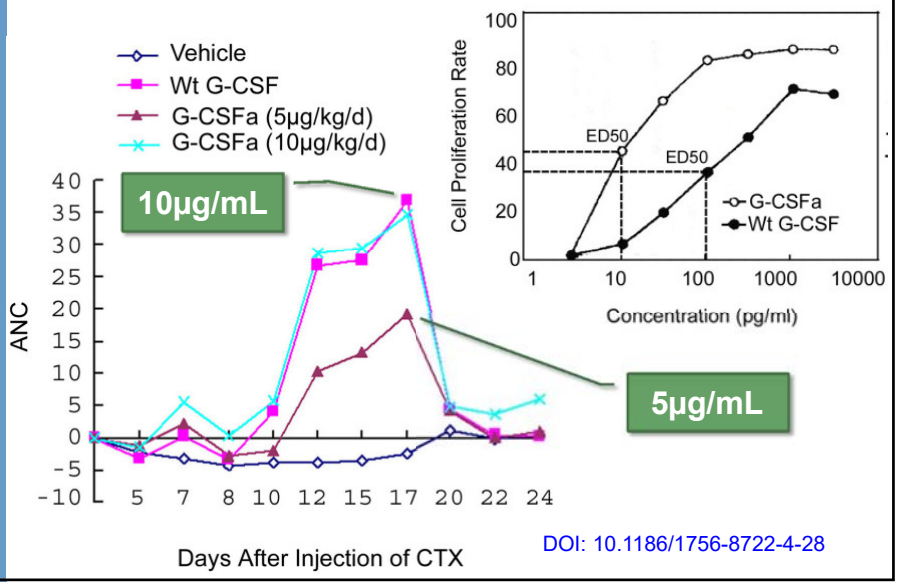
Potency assays for proteins are quantitative
G-CSF potency assay





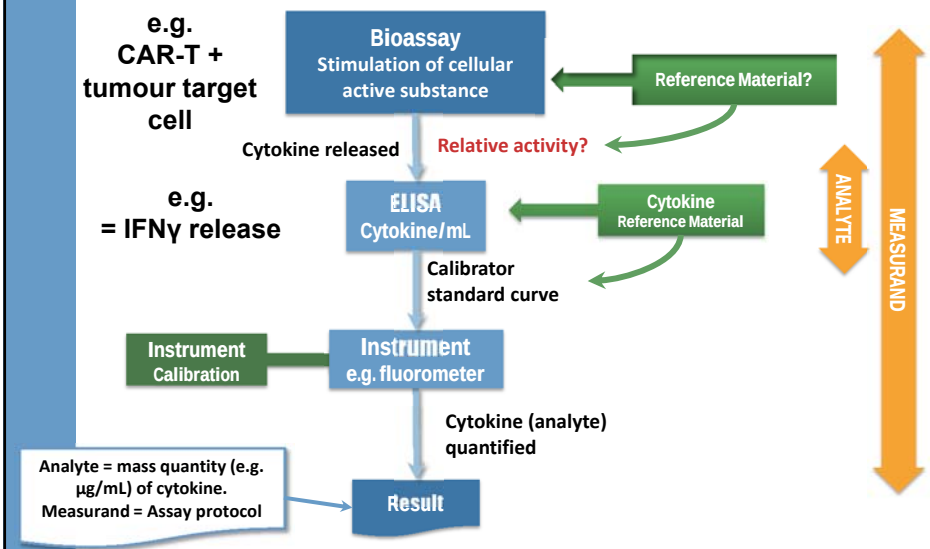
- Cell proliferation with a clear dose-response effect.
- Batch-to-batch the potency per mg would be consistent
- Assay normalised day to day with an in-house reference material, itself calibrated to an international reference standard (WHO)

And can be quantitative for potency
Both *in vitro* (potency) and *in vivo* (monkey)



DOI: 10.1186/1756-8722-4-28

ANALYTE V. MEASURAND
EXAMPLE OF A COMPLEX BIOASSAY



POTENCY ASSAYS
WARNING

Just because your potency assay is **quantitative for an analyte doesn't mean it is quantitative of potency**.

- The *measurand* (overall bioassay) may also not directly correlate to potency
- Potency determination may need to be multi-parameter
- Relationship between mRNA copy number and gene product (protein) concentration can be complex
- Relationship between protein concentration and clinical effect can be complex
- Multiple inter-relationships may exist, e.g. co-signalling etc

HOW DOES THE MEASURAND HELP WITH VALIDATION?
Linearity for example….

- BUT linearity of the bioassay is more complex:
- Lets assume the cellular active substance is pure (~100%, e.g. MSC preparation)
  - i.e. whole population is potent
  - In keeping with the idea of potency/mg with a protein
  - Think of potency/cell
- You need to have cell populations that differ in potency
  - Likely approach is to titrate non-potent cells into potent cells
  - How to get non-potent cells?
    - Non-viable?
    - Arrested, blocked etc?
    - Different cell?

HOW DOES THE MEASURAND HELP WITH VALIDATION?
Which leads to lots of other questions

- What of the cell product isn't 'pure'
  - Or worse 'purity' varies quite a lot?
  - Should I add cells to potency assay based on total cell count, viable cell count, or purity?
  - What if product is frozen?
    - Do I allow cells to recover?
    - Do I remove DMSO?
- Viral vectors are typically not that pure
  - full/empty particles
  - infectious/non-infectious particles etc.
- To identify just a few of the questions……

SPECIFICATIONS
EMA/BWP-Industry Workshop on Specifications for Biotech (Sept 2011)

- Setting specifications cannot be based on mathematical models only – statistical approaches should be used as supportive
- Clinical justification is the **most** important factor when setting acceptance criteria for cQAs [*potency should be a cQA*]
  - How to define "clinical justification"?
  - How many patient should be exposed, is one enough?
  - How about data from lots used in phase I and II?
  - Any use of data from preclinical lots?
  - In addition, sometimes only few batches have been used in the clinical trials (e.g. orphan drugs, biosimilars) and these may not cover the full span of normal production variability

SPECIFICATIONS
Setting specifications

- Approach varies for different tests
- For potency you'd normally expect a range (if it correlates with efficacy)
  - But most ATMP developers use a threshold, e.g. > X or ≥ X.
- At approval (if not before) will need to use a combination of;
  - process capability (i.e. batch data)
  - Clinical qualification
- Regulators will ask;
  - Is there a relationship between the potency measured and clinical outcome?
  - Can your potency assay detect sub-/non-potent product?
    - How to answer this?

EUROPEAN PUBLIC ASSESSMENT REPORTS
Example Issues Raised During MAA Review

- Hyalograft C (2012) Withdrawn
  - "The potency assay is not sufficiently correlated to biological activity of the product….."
- OraNera (2011) Withdrawn
  - "…..correlation between potency testing, biological function and clinical efficacy has not been established. Potency assay not sufficiently validated to represent regenerative capacity of the sheet."
- Provenge (2012) Approved
  - "…CD54 used as a surrogate marker for potency, but unclear whether acceptance criteria set by MAH are relevant and able to detect sub-potent batches…."

(date submitted to EMA)

EUROPEAN PUBLIC ASSESSMENT REPORTS
Example Issues Raised During MAA Review #3

- ChondroCelect (2007); Approved
  - "The mouse ECFA assay was originally central on the one hand in validating the potency assay, and on the other hand in correlating the potency data with the cartilage repair in clinically relevant setting, i.e. implantation to knee. Since a direct correlation between the potency and the cartilage repair in patients could not be demonstrated, the animal data would have been invaluable in providing evidence for this interrelationship. Since the Applicant has later developed a new functional assay to follow potency of the Medicinal product during characterisation and process validation studies, the problems related to the validity of the ECFA assay in bridging the potency and clinical efficacy data is no more an issue."

(date submitted to EMA)

EUROPEAN PUBLIC ASSESSMENT REPORTS
Example Issues Raised During MAA Review #4

- Heparesc (2014); Refused
  - "Additional clarification requested with respect to the acceptance limit and suitability of the potency test to discriminate sub-potent batches."
- MACI (2011); Approved
  - "It has been requested that this newly developed potency assay be further validated against ability to form functional cartilage. . Until the new potency and identity assays are validated the applicant should monitor new patients for safety and efficacy which could be linked with lack of validation of these parameters."

(date submitted to EMA)

EUROPEAN PUBLIC ASSESSMENT REPORTS
Example Issues Raised During MAA Review #5

- Spherox (2012); Approved
  - "The applicant has also addressed the issue concerning the relevance of the limit the potency marker As no efficacy data are present for the validation lots from 2015 these lots have been compared with data from lots used in clinical studies."

(date submitted to EMA)

EUROPEAN PUBLIC ASSESSMENT REPORTS
Example Issues Raised During MAA Review #6

- Zalmoxis (2014); Approved
  - "A major concern was also related to the control of the finished product in particular the potency. To address these concerns, the applicant has performed additional tests to demonstrate the functionality of the T-cells."
  - "To evaluate safety and functional properties of MM-TK, the Applicant developed an integrated approach which included both in vivo pharmacodynamic, toxicology and kinetic data concurrently obtained taking advantage of two different immunodeficient mouse models for Graft versus Host Disease (GvHD) based on the Non-Obese Diabetes/Severe Compromised Immunodeficient (NOD/SCID) mouse system, as well as series of in vitro laboratory tests mainly aimed at an in-depth investigation of the product."

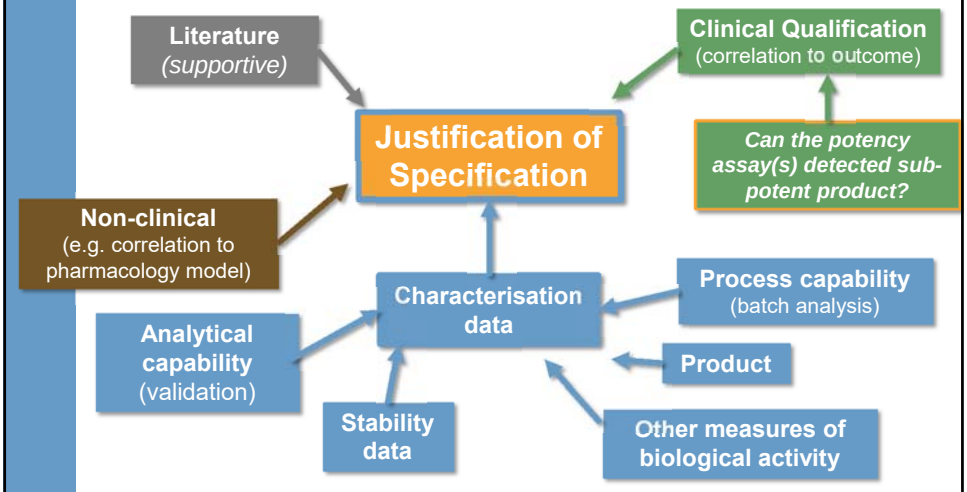
(date submitted to EMA)

EUROPEAN PUBLIC ASSESSMENT REPORTS
Example Issues Raised During MAA Review #7

- Strimvelis (2016); Approved
  - "In vitro functional activity: GSK3336223 supernatant (3 lots) was tested for the ability to transfer ADA into murine lineage negative (ADA-/-) progenitor cells from ADA-deficient mice. There was no ADA activity in untransduced cells; however, one week after transduction, ADA activity was detected (15% to 36% of normal BM ADA). Additionally, CD34+ cells from the BM of ADA-SCID patients were transduced with the GSK3336223 vector. ADA expression, measured by intracellular fluorescence activated cell sorting (FACS) analyses, was detectable (20% to 39%) in transduced CD34+ cells after short-term in vitro culture and absent (as expected) in un-transduced cells."

(date submitted to EMA)

JUSTIFICATION OF POTENCY SPECIFICTION
Summary Considerations



SUMMARY
KEY MESSAGES

- Consider carefully whether your potency assay is quantifying potency or merely quantifying an analyte
  - E.g. do you have a range or a threshold?
- Be prepared at approval to be able to address the following questions:
  - Is there a relationship between the potency measured and clinical outcome?
  - Can your potency assay detect sub-/non-potent product?
    - How to answer this?

END

THANK YOU

POTENCY STRATEGY

Overview