APIC Active Pharmaceutical Ingredients Committee

Considerations on biological APIs extracted from material of human and animal origin

London, May 2018

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APIC Active Pharmaceutical Ingredients Committee

Contents of the presentation

- Introduction
- Sources of variability and control – extracted products versus biotech
- Reflection paper in conjunction with other relevant guidelines
- Considerations for the reflection paper

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Introduction

Underlying assumptions presented in the related EMA reflection paper:

- Assumption of consistency of manufacturing process
- What exactly do we currently compare and what exactly do we want to compare?
- Interplay with process control, specifications, and release testing
- Handling shifts and drifts
- What could be an 'acceptable difference' and can this question be answered without taking clinical consequences into consideration?
- What sample sizes are feasible and what are the implications for applicability of statistical methods?
- Feasibility of random sampling and possible alternatives to ensure representativeness of samples
- Implications of very limited knowledge on sources of variability for biosimilar developers
- How can the impact of batch age adequately be taken into account for similarity assessment?

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Introduction

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CHMP/BWP/429241/2013

Guideline on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products.

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CHMP/BWP/429241/2013

- This guideline addresses:
  - To what extent any variability in the early manufacturing steps is acceptable for non-recombinant biological products and for which flexibility in the sourcing in the biological starting material may be needed, to ensure product supply.
  - Heparins and urine derived products, hCG and urokinase, are explicitly mentioned in this guidance.
  - Variability in sourcing and/or initial manufacturing steps for Heparins and urine derived products has traditionally been allowed in contrast to the well characterized biotechnological products of recombinant origin for which a single manufacturing process starts from a unique and well identified cell bank system.

Heparin and hCG extraction products

Heparin sodium:

- **Heparin is a sulfated glycosaminoglycan polysaccharide**
- **Heparin is extracted from intestinal mucosa from pigs**
- **Complex and polydisperse mixture of molecules constitute the API/INT to LMWH**
- **Manufactured over 60 years**

Human Chorionic Gonadotrophin:

- **hCG is a glycosylated gonadotrope hormone**
- **hCG is extracted from urine from pregnant women**
- **Complex heterogeneous mixture of molecules constitute the API**
- **Manufactured over 70 years**

Heparin and hCG extraction products

Heparin sodium:

- **Extensive sourcing program world-wide is needed for supply**
- **Mucosa collected or processed at slaughter-houses and is transported to the manufacturing site**
- **>600.000 pigs needed for a single API/INT batch**

Human Chorionic Gonadotrophin:

- **>100.000 L of urine is needed for a single API batch**
- **Urine collected at the donor's home and is transported to the manufacturing site**
- **>5000 women donate for a single API batch**

Inherent variability in starting material is present, e.g. due to the nature of the biological origin, the extensive collection program needed, etc.

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CHMP/BWP/429241/2013

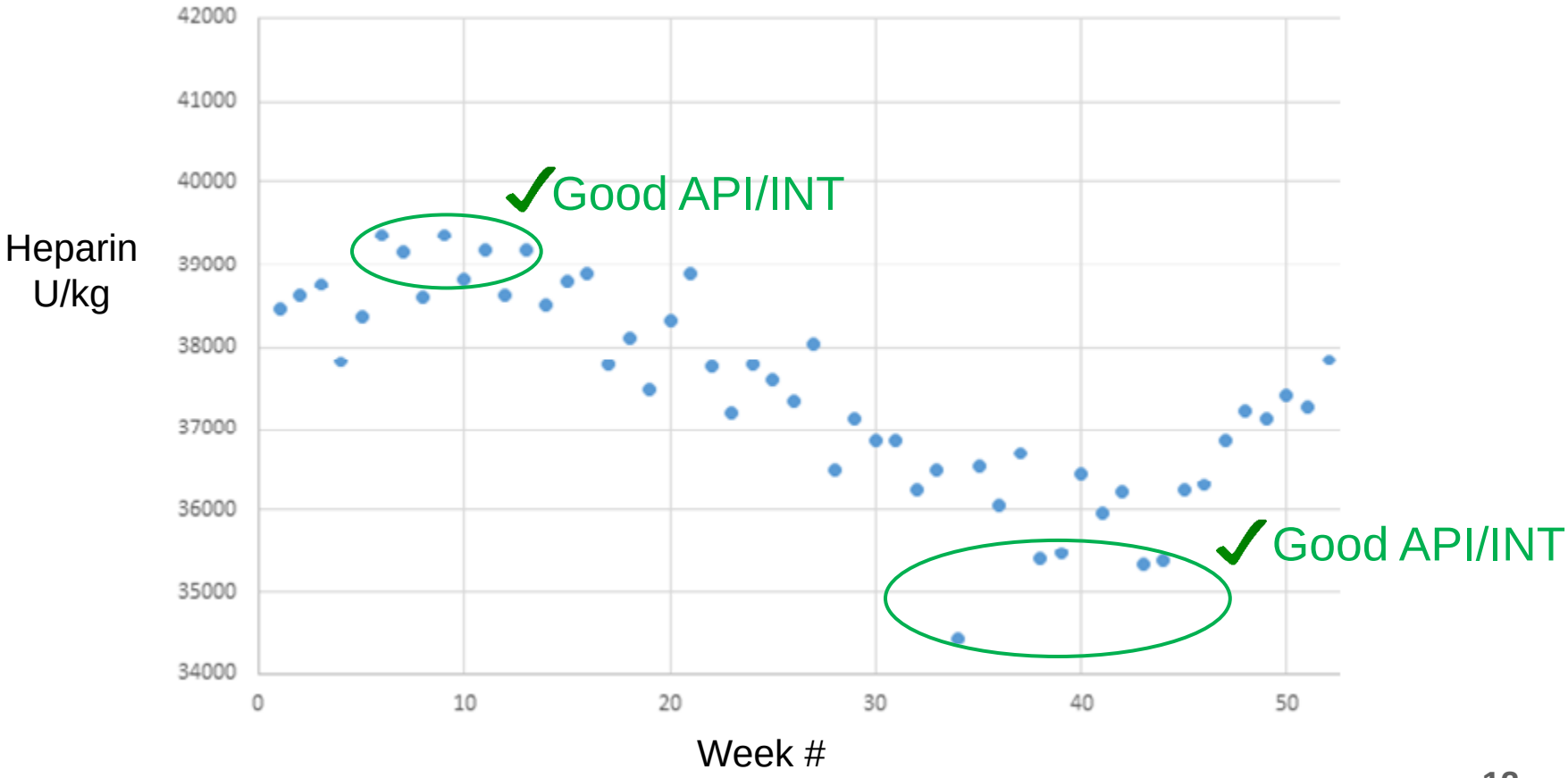
- Heparins and hCG:
  - Pooled porcine intestinal mucosa is defined as the starting material.
  - Pooled human urine should be defined as the starting material for urine derived medicinal products.
  - Where it is not possible to determine the critical quality attributes at the stage of these intermediates, testing for these quality attributes may be performed at a later stage in the manufacturing process.
  - The manufacturing process of the active substance is robust (and validated) and will produce a comparable active substance irrespective of the initial process steps or intermediate used.

CHMP/BWP/429241/2013

- Comparability should also be supported taking into account the principles laid down in guidance [(Note for Guidance for Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (CPMP/ICH/5721/03)] (Q5E).
- The extent of the studies necessary to demonstrate comparability will depend on:
  - (1) the complexity of the biological active substance and
  - (2) how early in the production process different intermediates are introduced.

Seasonal variation of Heparin starting material

Season variability heparin yield in mucosa (2010-2017)



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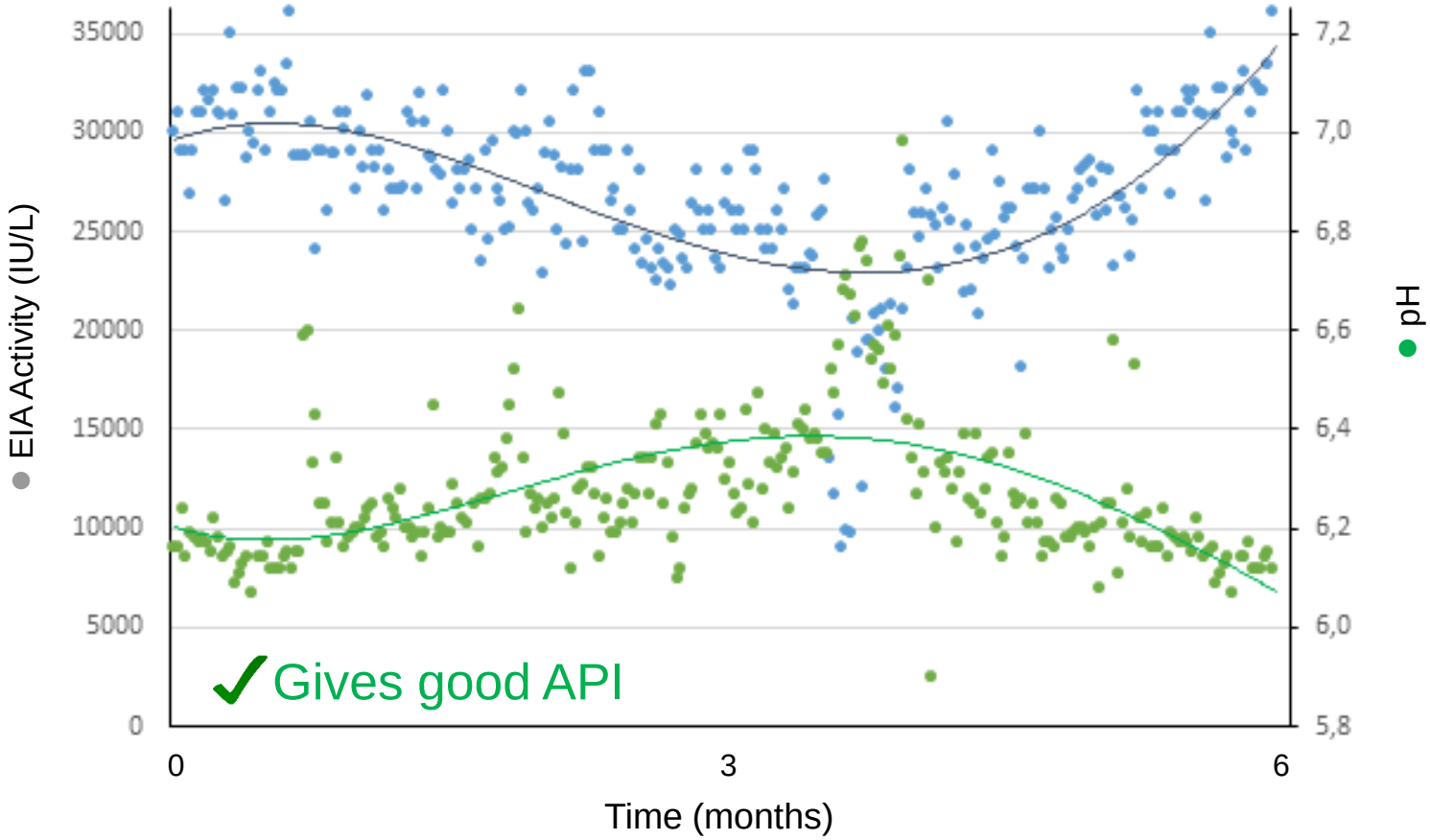
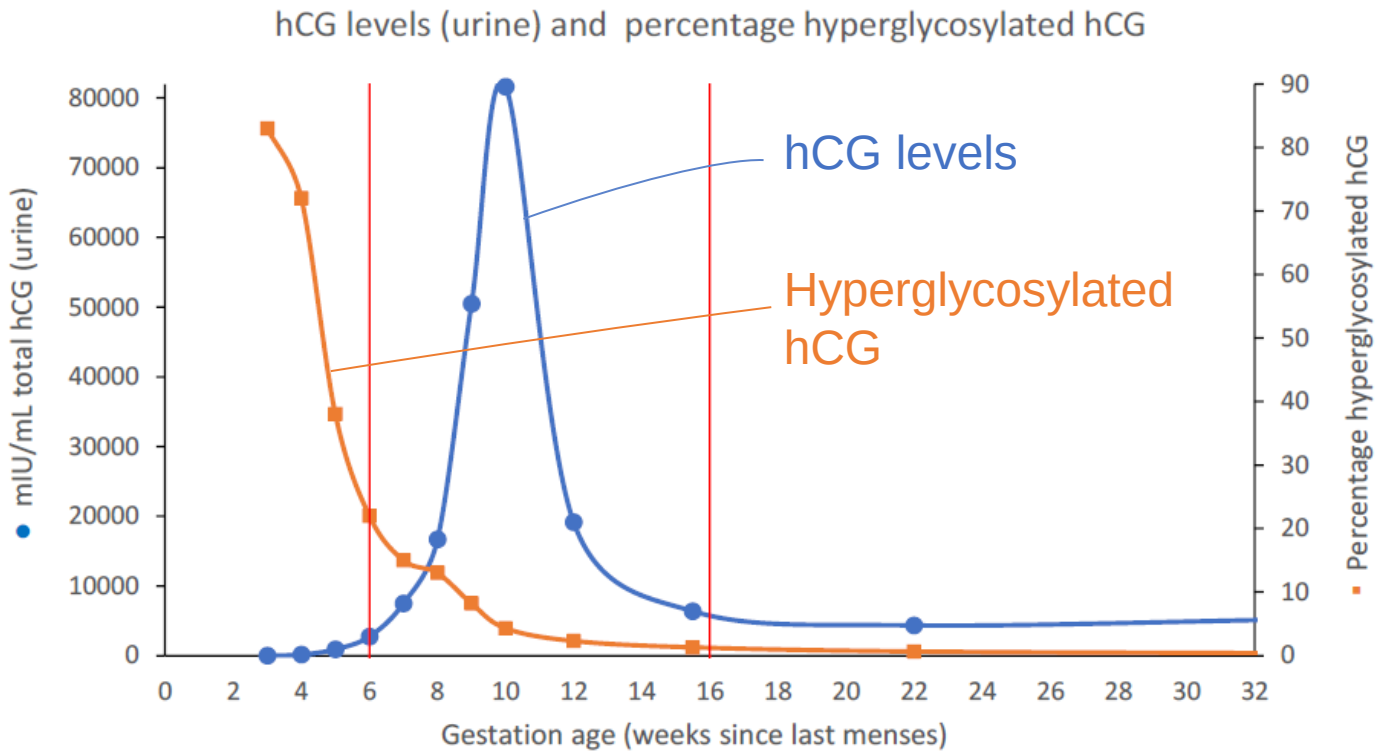
Seasonal variation of hCG starting material

Season variability hCG content of urine (year 2014)



hCG variation per donor per gestation week



Cole, L.A. (2010) Hyperglycosylated hCG, a review, Placenta 31, 653-64.

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hCG variation per donor per gestation week

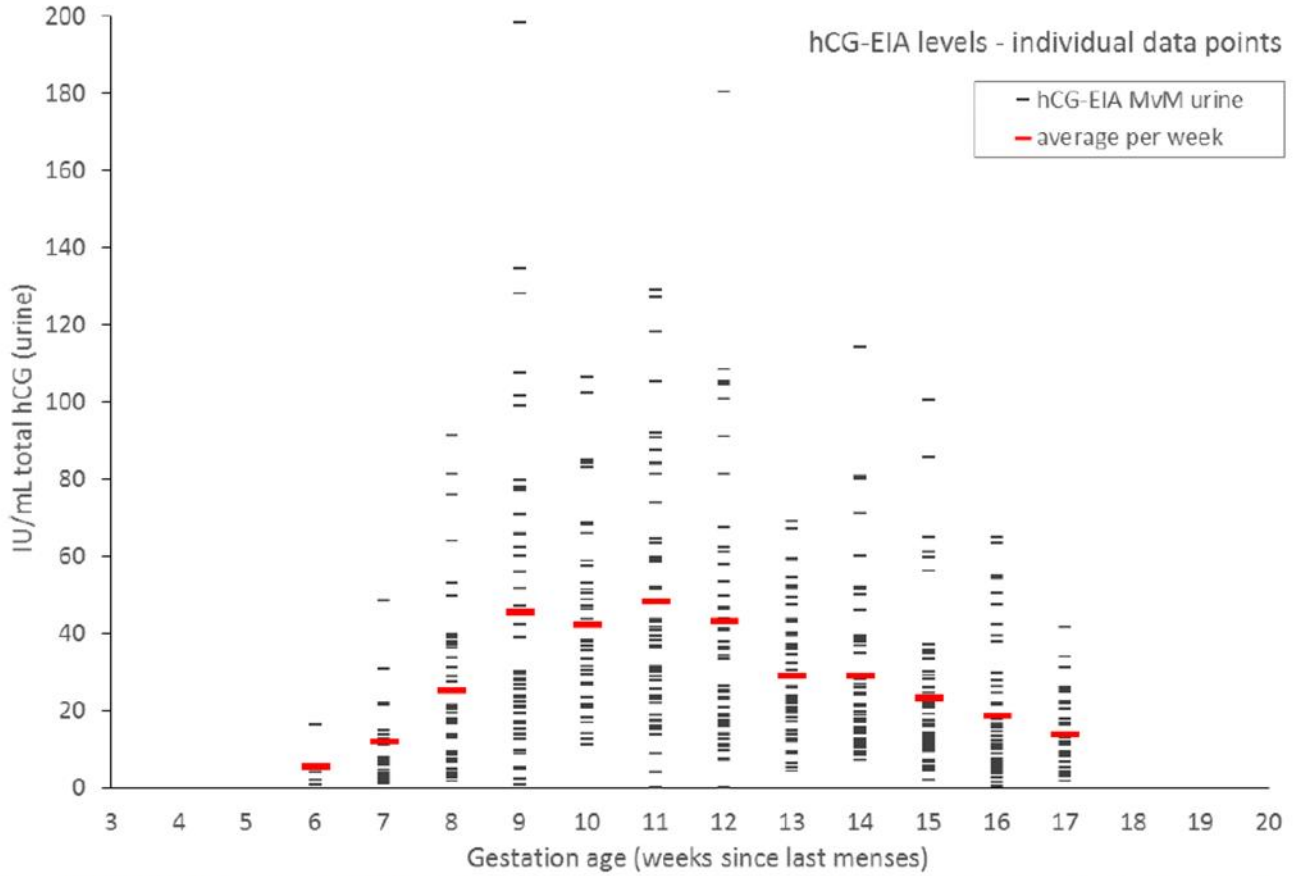

Figure 2. Individual data points hCG-EIA activity in urine (IU/mL) per donor per gestation week (–). The average hCG activity per gestation week is also depicted (—).

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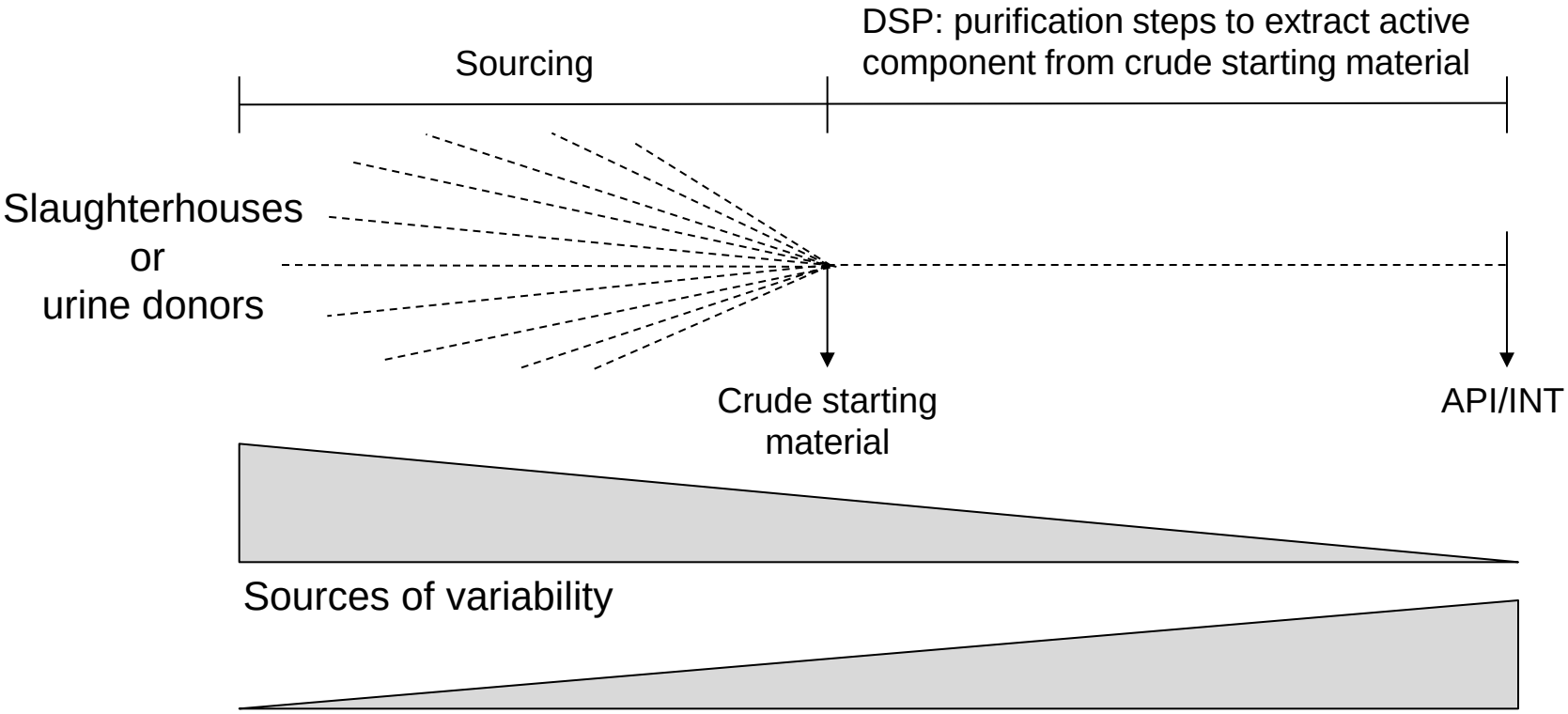
Variation and level of analytical control of extracted products



Impact of variability for comparative assessment for final API/INT quality.
Level of analytical control possible to establish QA for comparability.

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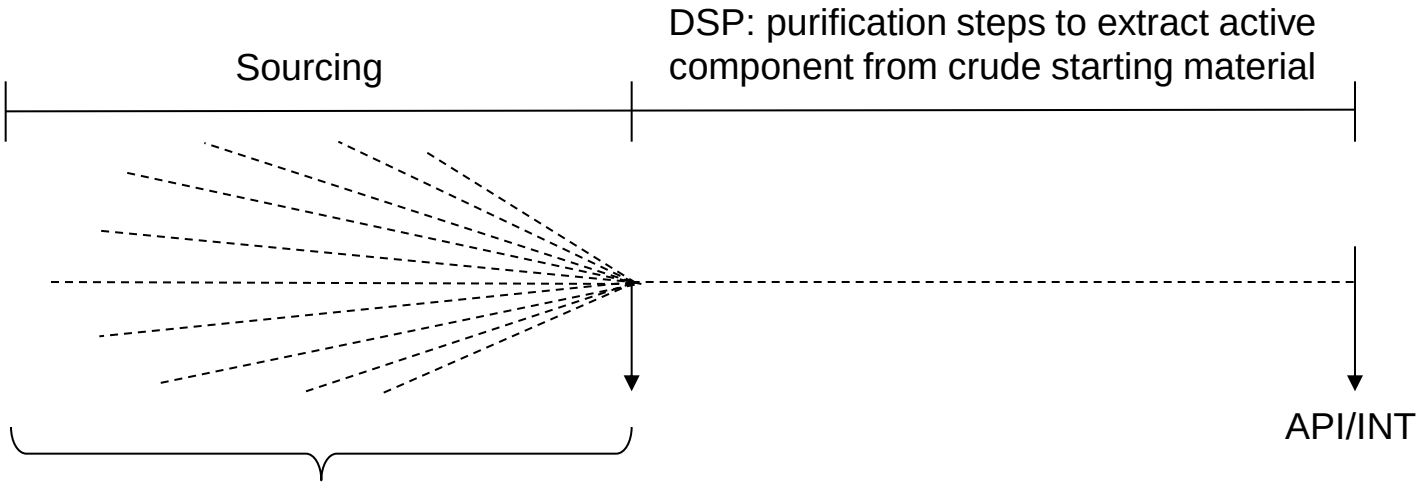
Variation and level of analytical control of extracted products and biotech: sourcing versus upstream process validation

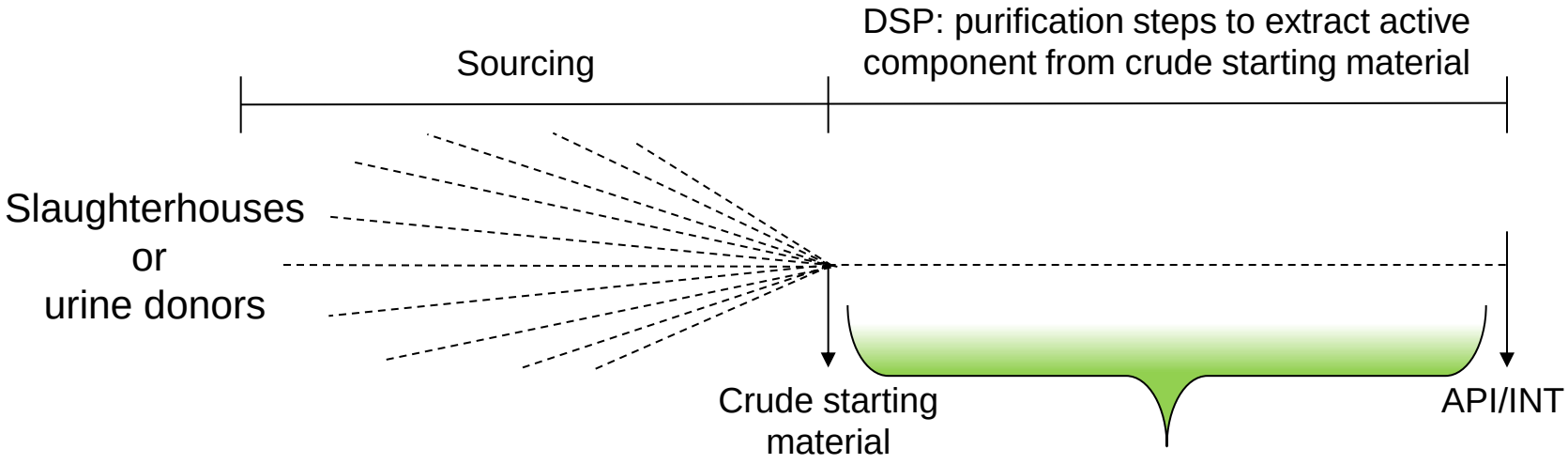


Upstream process validation in biotech*:
- Evaluation of specific cell traits
- Validating cell culture
- Evaluation of any critical conditions for the control of expression of the desired product in the production bioreactor.

Biological variation inherent to biotech as well. Level of analytical control to establish QA for comparability is higher in USP biotech compared to naturally sourced products.

*EMA/CHMP/BWP/187338/2014

Downstream process of extracted products



- Process validation according to guidelines
- Validated Virus/TSE inactivation/removal
- Established process controls (CPPs)
- Results in API/INT of desired quality
- Nonetheless, final u-hCG and rec-hCG differ
- Recombinant manufacturing of Heparin not possible

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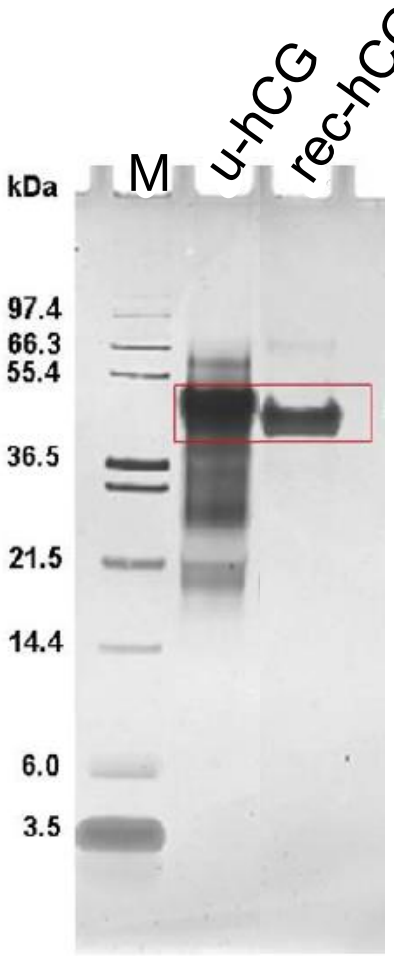
Differences naturally extracted hCG versus recombinant hCG



hCG heterodimer

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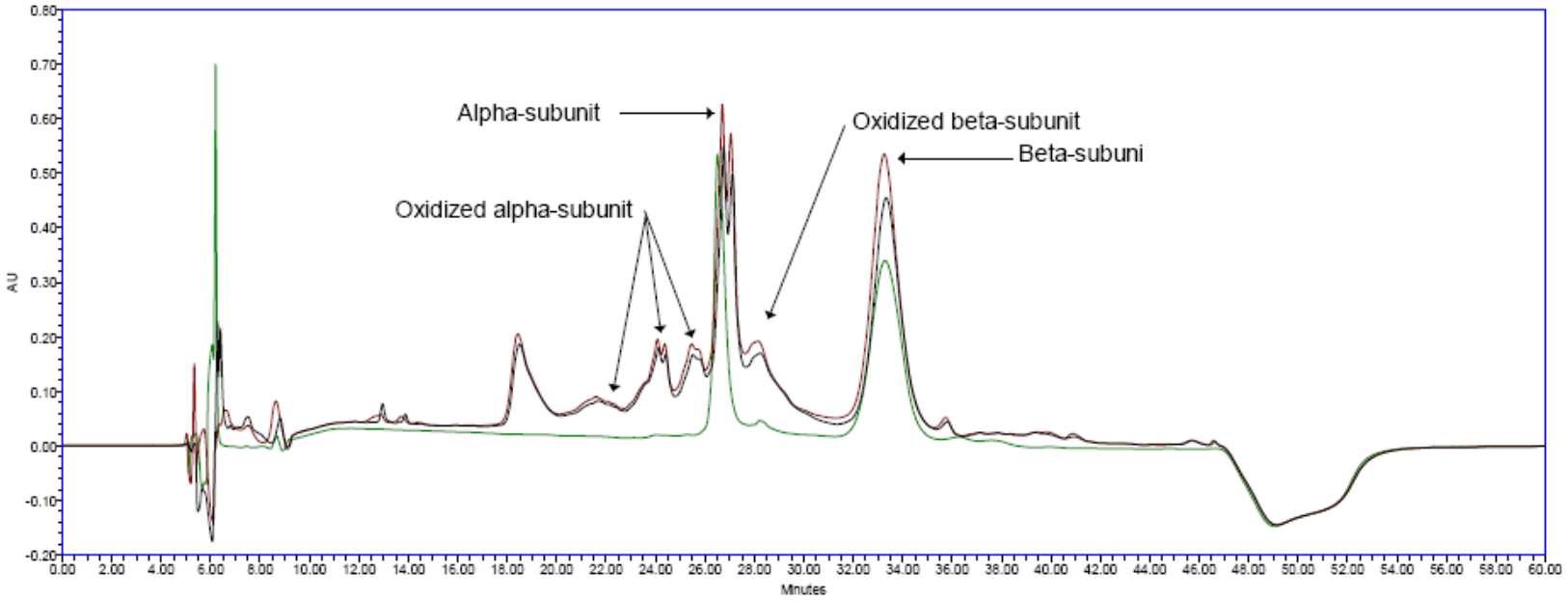
Differences naturally extracted hCG versus recombinant hCG



Overlay chromatogram of non-oxidized u-hCG (black) (5000 IU), non-oxidized u-hCG (brown) (1500 IU) and Ovitrelle rec-hCG (green) samples.

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Sources of variability and control – extracted products versus biotech

- Understanding of the potential sources of variability is difficult for (crude) intermediates.
- Inferential statistics may also become limited if identification of potential sources of variability is limited.
- The impact of differences at the quality level on safety and efficacy is difficult to impossible to assess or quantify for changes on the (crude) intermediate level and not that relevant.
- With variant sourcing a random sampling plan for comparison of QAs might not be feasible as not all sources of variability are fully understood for (crude) intermediates.

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Reflection paper in conjunction with other relevant guidelines

- ICH guideline Q5E: Note for guidance on biotechnological/biological products subjected to changes in their manufacturing process (CPMP/ICH/5721/03)
- Has in paragraph scope that the principles adopted and explained in this document apply to:
  - Proteins and polypeptides, their derivatives, and products of which they are components, e.g., conjugates. These proteins and polypeptides are **produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized** using an appropriate set of analytical procedures.
  - Also, The principles outlined in this document **might also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids**. Manufacturers are advised to consult with the appropriate regional Regulatory Authority to determine applicability.

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Reflection paper in conjunction with other relevant guidelines

- ICH guideline Q11: development and manufacture of drug substances (chemical entities and biotechnological/biological entities, EMA/CHMP/ICH/425213/2011)
- Has in paragraph scope:
  - This guideline is applicable to drug substances as defined in the Scope sections of ICH Guidelines Q6A and Q6B.
  - Q6B scope:
    - Apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates) **produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized** using an appropriate set of analytical procedures.
    - The principles outlined in this document **may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids**.
    - States not to cover several products, including Heparins.

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Reflection paper in conjunction with other relevant guidelines

- Guideline on similar biological medicinal products (CHMP/437/04 Rev 1)
- Has in paragraph application of the biosimilar approach:
  - The biosimilar approach is more likely **to be successfully applied to products that are highly purified and can be thoroughly characterized** (such as many biotechnology-derived medicinal products). **The biosimilar approach is more difficult to apply to other types of biological medicinal products, which by their nature are more difficult to characterize, such as biological substances arising from extraction from biological sources** and/or those for which little clinical and regulatory experience has been gained.

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Reflection paper in conjunction with other relevant guidelines

- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) (EMA/CHMP/BWP/247713/2012)
- Has in paragraph scope:
  - This guideline addresses quality aspects of **the demonstration of biosimilar comparability for similar biological medicinal products containing recombinant DNA-derived proteins and derivatives** to support a Marketing Authorisation Application. Nevertheless, as the biosimilar approach is accessible to any biological medicinal products, **the principles explained in this document could apply to other biological products on a case by case basis**.

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Considerations for the reflection paper

- Industry concern on how to apply comparability for extracted products given the scope of the current RP.
  - Comparability on an (early) intermediate level is less informative due to variation in QAs available. Large number of batches will be needed. Availability?
  - As a consequence, this necessitates a comparability on the API level, which is less pure than a biotech product (hCG).
  - What does comparability than say for a change at the (early) intermediate level? Differences found do not need to be clinically relevant and here detailed analytics can always show differences.
  - Statistics do not always help given the data. Inferential statistics may also become limited if identification of potential sources of variability is limited.

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Considerations for the reflection paper

- Industry concern on how to apply comparability for extracted products given the scope of the current RP.
  - Emphasis should be placed on process robustness, validation status and API comparability instead of (early) intermediate comparability.
  - Relevance of QAs for comparability versus the CPP known from practical experience.
  - Company experience to show that validated DSP, with CPPs and appropriate release specifications will give compliant API material of desired quality, as obtained from variant crude starting material as input.
    - Maintaining safety and efficacy of the product.

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Considerations for the reflection paper

- Industry concern that RP does not take into account the position of extracted products as addressed in other EMA guidance.
  - Include exemptions for extracted products as is effective in other EMA guidance?
  - Exclude extracted products from RP?
  - Draft a separate RP for extracted products?

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