A company strategy for immunogenicity testing of peptide drugs

Birgitte Buur Rasmussen, Director, Bioanalysis

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Ferring Pharmaceuticals is a research-driven, specialty healthcare company, which is a leader in Reproductive Medicine and Women’s Health, and in specialty areas within Gastroenterology and Urology.

Traditionally, Ferring’s R&D activities have been focused on the development of therapeutic peptide and protein drugs.

The portfolio is currently expanding into more modalities, including therapeutic antibodies (Mabs) and small molecule drug candidates.

This talk will focus on the peptide development projects.
Ferrings current portfolio

- **Therapeutic proteins (> 30,000 Da)**
  - Sex hormones for fertility treatment

- **Large peptides (4000-6000 Da)**
  - Gastroenterology
  - (Orthopaedics)

- **Small peptides (1000-1700 Da)**
  - Urology
Probability of an immunogenicity reaction

- **Size of molecule**
  - Protein > polypeptide > oligopeptide

- **Similarity to endogenous compound**
  - Foreign > endogenous
  - Non-human > humanised > human

- **Product specific characteristics**
  - Structure, glycosylation pattern,
  - Stability, aggregation, impurities

- **Dosing regimen**
  - Repeated dosing > single dosing
  - Prolonged dosing > short dosing period
  - Intermittent dosing > continuous dosing

- **Route of administration**
  - Subcutaneous > intramuscular > intravenous

- **Patient status**
  - Disease, immune status
  - Previous exposure
Ferring Immunogenicity testing strategy

- **High risk drugs (hormones with endogenous counterparts):**
  - Immunogenicity testing (ADA, NAb) from first clinical study (SAD)
  - Most often online testing (FDA request)

- **Medium risk drugs (large peptides; proteins with no endogenous counterpart):**
  - Immunogenicity testing (ADA) from first repeated dose study
  - Typically NAb in phase III

- **Low risk drugs (small peptides)**
  - Case by case evaluation of intended clinical use (eg. dosing regimen and period)
  - All from no testing at all, testing in phase 3 only, no NAb etc

Inform and get confirmation from the authorities whenever possible
Examples - small peptides

Building on oxytocin and vasopressin (9-10 amino acids, 1000-1500 Da)

Oxytocin

Vasopressin

Building on gonadotropin releasing hormone (GnRH, 10 aa, 1200-1700 Da)

GnRH
Small peptides (1000-1700 Da)

- **Characteristics**
  - Small synthetic peptides containing non-natural amino acids
  - Some for acute dosing and some for chronic
  - Most often for SC administration

- **Immunogenicity risk assessment**
  - Case-by-case based on above
  - Always confirmed with authorities before clinical program
  - Typical FDA request at PreIND:
    “Address the immunogenicity potential of FE XXX”
Interaction with authorities

- Never sell your self by suggesting too much!!

"Due to the limited size of FE XXX (1xxx g/mol), the lack of an endogenous counterpart and due to the fact that FE XXX only will be used for a short duration of treatment (2 weeks), no immunogenicity testing will be implemented in the clinical program"

or

"Due to the limited size of FE XXX (1xxx g/mol) and no endogenous counterpart immunogenicity is not believed to be an issue. However, as FE XXX is intended for chronic use immunogenicity testing (binding antibodies) will be included in phase 3"

- Most often accepted
Case story - Degarelix

- **Degarelix**
  - GnRH antagonist developed for the treatment of advanced hormone-dependent prostate cancer
  - Synthetic peptide building on the natural GnRH peptide, MW 1633 Da
  - Consist of 4 natural and 6 non-natural amino acids

- **Immunogenicity risk assessment**
  - Small size and with no endogenous counterpart → low risk
  - Chronic dosing → increase risk
  - Product is depot-forming by gel-formation → potential risk for aggregation in SC depot

Requested by authorities to conduct immunogenicity testing in phase 3
Case story - Degarelix

- **Immunogenicity testing**
  
  - All patients tested every 6 months in phase 3 studies in Caucasians (up to 5.5 years of treatment), Japanese (1 year of treatment) and Chinese (1 year of treatment) by a validated RIA assay

- **Data evaluation and conclusion**
  
  - 12-29% of patients developed anti-degarelix antibodies after 1 year of treatment, reaching a plateau of approx. 40% after 3 years
  
  - Antibodies were low titered
  
  - Presence of antibodies did not impact safety
  
  - Presence of antibodies had no impact on efficacy as evaluated by correlation to testosterone levels (a validated biomarker for prostate cancer treatment)
  
  - Cell based assay for neutralising antibodies was not developed
Case story - Degarelix

- Authority interaction and filing
  - The lack of correlation between the presence of anti-degarelix antibodies and safety or efficacy was demonstrated statistically.
  - Data were presented to authorities in “Clinical evaluation of Immunogenicity” reports.
  - Data were accepted by FDA, EMA, PMDA and are currently under evaluation by SFDA.
  - No requests for neutralising antibody analysis have been received.
  - The product is currently registered in 74 countries as FIRMAGON/GONAX.
Large peptides (4000-6000 Da)

- **Characteristics**
  - Building on natural peptides with some amino acid substitutions
  - Intended for long time dosing or depots

- **Immunogenicity risk assessment**
  - Immunogenicity testing (ADA) in repeated dose studies
  - NAb in phase 3 (dependent on presence of endogenous counterpart)
Case story - AMPLEX

- AMPLEX
  - A combination of osteoconductive ceramic granules and B2A, a synthetic peptide that triggers bone formation
  - Inserted surgically in joint and intended for enhancing bone repair in foot and ankle
  - 45 amino acids, most natural - some non-natural
  - Contains amino acid sequences building on an endogenous protein
Case story - AMPLEX

- Immunogenicity risk assessment
  - One-time insertion inside joint, with no expected leakage to blood = low risk
  - In theory, patients can be operated more than once = increase risk
  - Contains endogenous amino acid sequences = increase risk

Requested to conduct immunogenicity testing (ADA/NAb) in clinical program

- Direct ELISA assay and cell-based NAb assay developed
- Testing currently ongoing in a phase 3 study
- As expected, no antibody positives seen so far
A technical note…

- Bridging format is most often not feasible for peptide ADA assays due to steric hindrance
  - Direct format more useful
  - Important to assure that all (most) subclasses are detected
  - We use a mixture of protein A/G and protein L as detection component