MERCK MILLIPORE

Comprehensive PEGylation services.

Optimize your protein therapeutics and reduce your time to market.

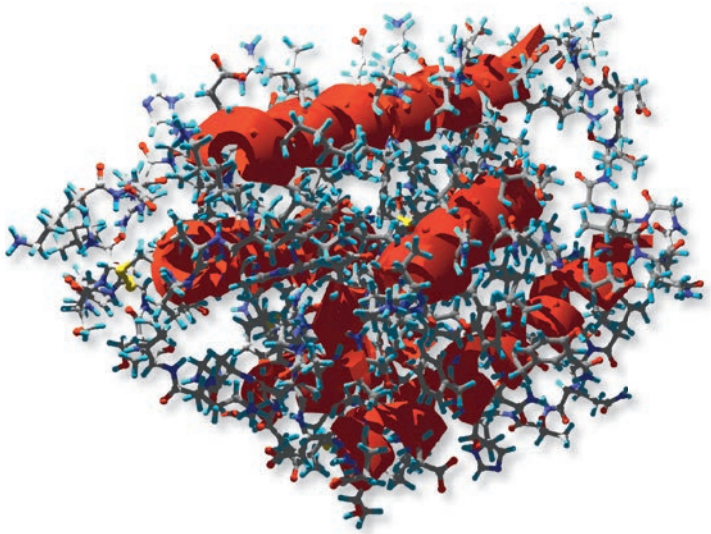
Merck Millipore
is a business of MERCK

High-quality PEGs and expertise in one place

PEGylation of therapeutic proteins is becoming increasingly essential to assuring bioavailability, given that it is an established method for the delivery of biopharmaceuticals. In many cases, modifications with PEG (polyethylene glycol) can not only significantly improve the physico-chemical properties, but it can also modify the pharmacokinetics and pharmacodynamics of a drug.

As a global partner, we can supply commercial quantities of high quality funtionalized PEGs that are essential for your PEGylated therapeutic proteins. Our offering includes high-purity raw materials, reagents, and process materials for use in investigational products in every phase of clinical development and in commercialized products.

We also offer services that leverage our broad range of functionalized PEG products of different molecular weight and activation chemistry.



These services include:

- PEGylation feasibility studies
- Process development of PEG-drug conjugate manufacturing
- Development of analytical methods
- Pilot production of PEG-drug conjugate
- Development of PEGylated biosimilars

For more information, visit **www.merckmillipore.com/pegylationservices**

PEGylation feasibility studies

We perform feasibility studies for the PEGylation of biopharmaceuticals. These studies allow you to determine a suitable PEGylation strategy for your biopharmaceutical drug. Please note that 25-50 mg of the biopharmaceutical is required for this service.

Scope of work

- Investigation of PEGylation strategies
- Screening of different PEG reagents
- Development of reaction conditions
- Development of basic purification method
- Preparation of PEG-drug conjugates
- Analytical characterization of PEG-drug conjugates

What we offer

- 1-2 mg PEG-drug conjugate for *in-vitro* testing
- Certificates of Analysis for conjugates
- Final report

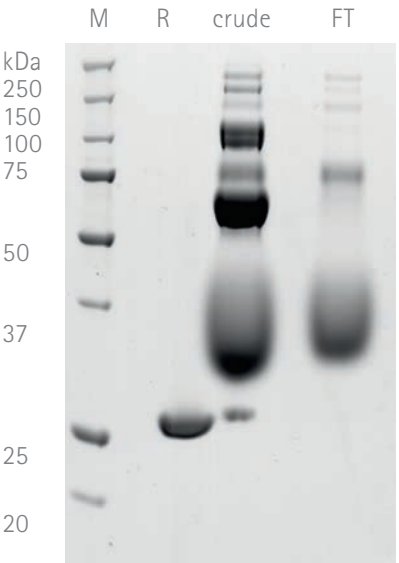
Workflow

Set-up
- Time/resource planning
- Initial analytics
- Assay establishment

PEG screen
- Established test program
- Selection of lead conjugates
- Initial process optimization

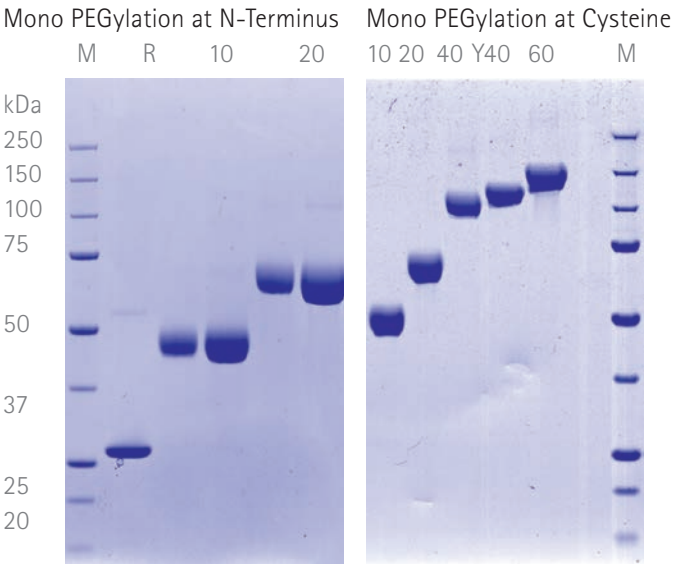
Sample preparation
- Purification development
- Preparation of conjugates
- Release analytics

Purification



SDS-PAGE of crude conjugate and IEX fractions. M = marker; R = unmodified protein; FT = Flow.

Test samples



SDS-PAGE of final PEG-drug conjugates. M = marker; R = unmodified protein; Numbers indicate MW of PEG in kDa.

Process development of PEG-drug conjugate manufacturing

PEGylation of a biopharmaceutical and purification of the resulting conjugate is a challenging process. Efficiency and reproducibility of PEGylation and product purification is crucial for the overall quality of the process.

We offer several processes for the preparation of PEGylated biopharmaceuticals from early stage to preparation of preclinical material. Our capabilities facilitate the development of robust and scalable methods that are transferrable to a CMO for the supply of drug substance and product. Please note that 0.5-1.0 g of the biopharmaceutical is required for this service.

Scope of work

- Optimization of PEGylation conditions
- Development of purification process
- Scaling and standardization of process
- Establish SOPs for manufacturing process
- Test preparations (3 x 100 mg)
- Verification of product quality

What we offer

- SOPs for process
- Three lab-scale batches of conjugate
- Development report

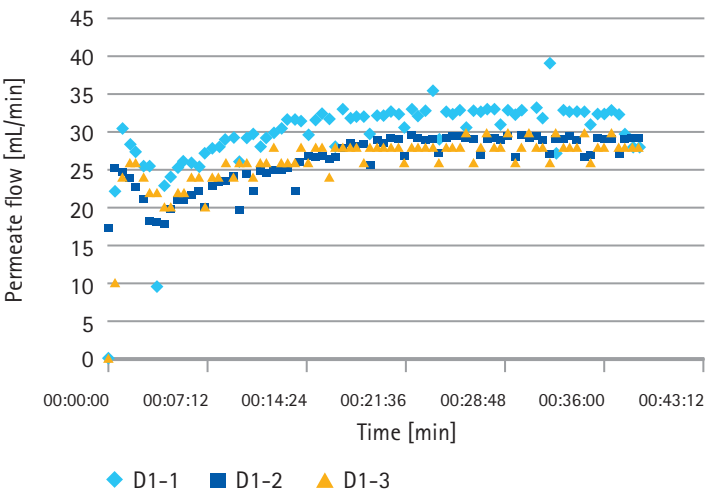
Workflow

PEGylation
- Process optimization
- Robustness testing
- SOP development

Purification
- Chromatography
- UF/TF conditions
- Process scaling

Verification
- Test preparations
- Conjugate characterization
- Determination of yield

Purification



Reproducible UF/TF as demonstrated by comparison of permeate flow and process time chart for three 100 mg preps.

PEGylation

PEGylation at a 10 L scale. Reactions are temperature controlled.

Development of analytical methods

PEGylation has a strong impact on the physico-chemical properties of a biopharmaceutical. Consequently, a new set of methods needs to be developed to facilitate the full characterization of a PEGylated biopharmaceutical.

We have access to state-of-the-art analytical tools and qualified equipment for the development of all analytical methods related to PEG and PEGylated drugs. Analytical methods will be validated according to the ICH guideline Q2 and may be used when filing for regulatory submission. Please note that 20 mg of reference material is required for this service.

Scope of work

- Establishment of basic methods
- Development of HPLC/UPLC methods
- Identification of PEGylation sites
- Quantification of deamidation/truncations
- Determination of potency
- Validation of methods according to ICH Q2

What we offer

- Development report
- Method SOPs
- Validation report

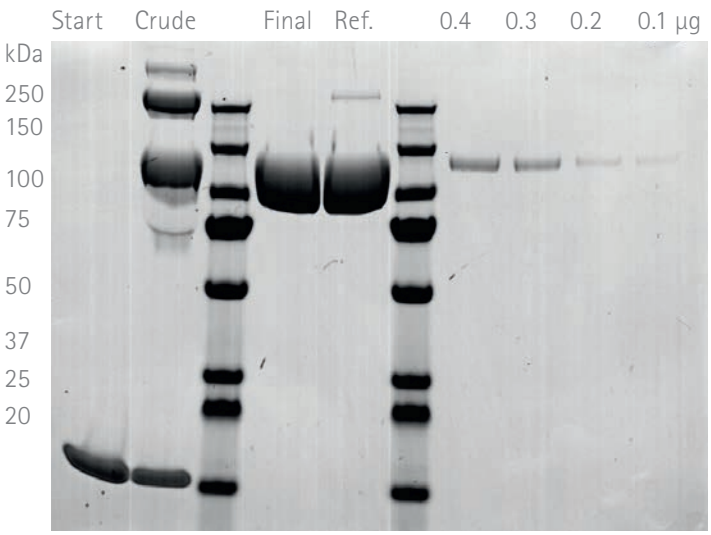
Workflow

Parameters
- Physico-chemical
- Purity, impurities, quantity
- Biological activity

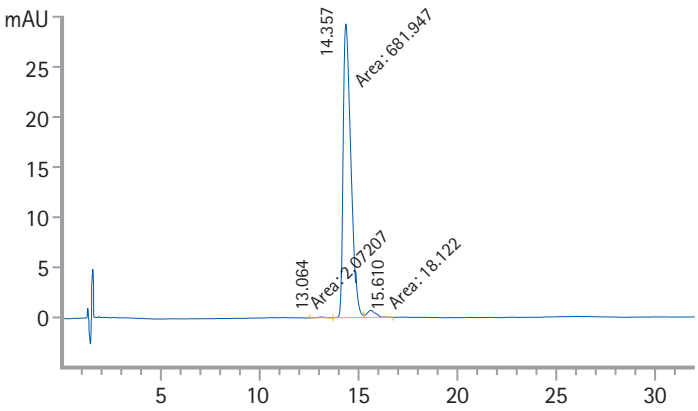
Development
- MS, NMR, IR for ID testing
- HPLC/UPLC methods
- Bioassays, ELISA

Validation
- Qualified equipment
- According to ICH
- Full documentation

Purification



SDS-PAGE analysis of mono-PEGylated protein.
No HMW impurities observed in the final product.



Quantification of deamidated forms by RP-HPLC.

Pilot production of PEG-drug conjugate

Process up scaling, adaption to pilot equipment and manufacturing of a PEGylated biopharmaceutical can be performed at our facilities in scales ranging from 500 mg to 20 g. Material from these productions can be used as reference material for future productions, initial stability testing or animal experiments.

Manufacturing procedures are established and verified in consistency runs and all results are summarized in a technical information package (TIP). We also support the transfer of the final process to a CMO for the supply of drug substance and product. Please note that 5-100 g of the biopharmaceutical is required for this service.

Scope of work

- Adaptation of process to pilot scale
- Set points and manufacturing controls
- Establishment of manufacturing instructions
- Verification of process in consistency runs
- Receipt of conjugate
- Full characterization of bulk product

What we offer

- Manufacturing instructions
- Technical information package (TIP)
- GMP-like conjugate, i.e. process ready for transfer into GMP environment

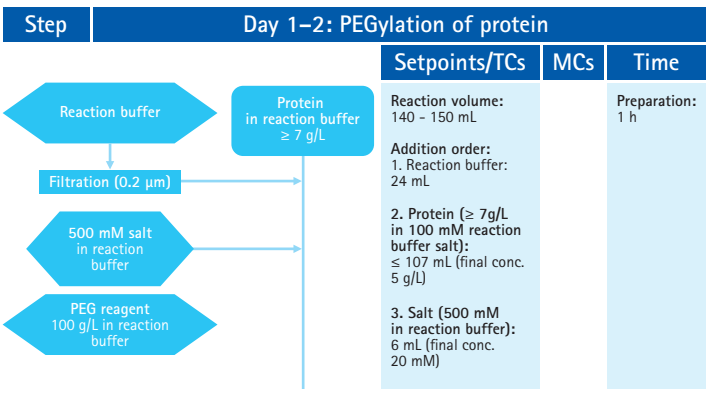
Workflow

Consistency
- Determination of set points
- Manufacturing instructions
- 3 x gram scale production

Pilot production
- Tech batches
- GMP-like production
- Reference conjugate

Tech transfer
- TIP
- On-site training
- Method transfer

Tech transfer



Process flow scheme for PEGylation process (consistency runs).

Development of PEGylated biosimilars

We have unparalleled experience in the development of PEGylated biosimilars and provide full development for your protein-conjugate starting with the native protein and ending with the transfer of a robust manufacturing process to a CMO. Please note that 5 g of protein starting material is required for this service.

Scope of work

- Development of manufacturing process
- Development of analytical methods
- Establishment of manufacturing instructions
- Verification of process in consistency runs
- Comparability study with originator's product
- Process transfer to CMO

What we offer

- Manufacturing instructions
- Technical information package (TIP)
- Full set of analytical methods (SOPs)

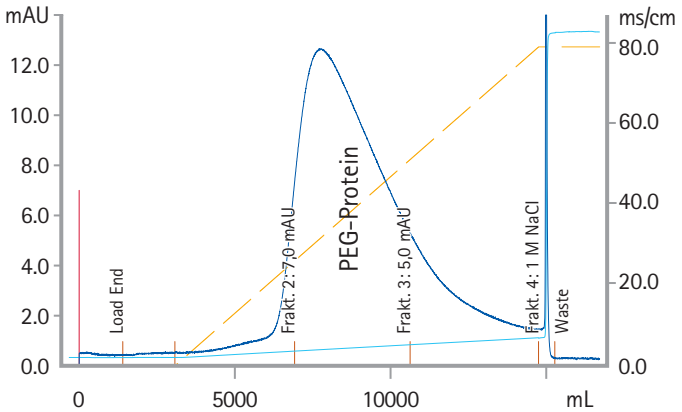
Workflow

Process
- PEGylation development
- Purification development
- Consistency batches

Analytical methods
- Method development
- Method validation
- Development report

Tech transfer
- TIP
- On-site training
- Method transfer

Process



Purification of PEGylated protein by ion-exchange chromatography.

Analytics

22 May 2014
EMA/CHMP/BWP/247713/2012
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)

5.3. Analytical considerations

Extensive state-of-the-art characterization studies should be applied to the biosimilar and reference medicinal products in parallel, to demonstrate with a high level of assurance that the quality of the biosimilar is comparable to the reference medicinal product.

Title and requirements for biosimilar development are defined in EMA guideline EMA/CHMP/BWP/247713/2012.

The typical technical data above serve to generally characterize the product. These values are not meant as specifications and they do not have binding character. The product specification is available separately, from the website: www.merckmillipore.com

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.

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