Terms of Sale

Belyntic GmbH

Terms of Sale

1. Subject Matter, Scope

1.1 Belyntic GmbH ("**Belyntic**") is a manufacturer of chemical linker molecules ("**PEC-Linker**"). The main purpose of the PEC-Linker is the purification and modification of chemically synthesized peptides. Belyntic offers the PEC-Linker in the form of packed kits ("**Kits**" or "**Product**"). Kits include related chemical products and goods which are resold by Belyntic ("**Related Goods**"). The individual components of the Kits are not offered for sale separately.

1.2 Belyntic offers the Product to purchasers that are either entrepreneurs, legal persons under public law or special funds under public law within the meaning of Sec. 310 para. 1 German Civil Code (BGB) only. Such purchasers may be professional research institutions or manufacturing customers with a focus on the chemical, pharmaceutical, biotechnology, cosmetics, food and diagnostics industries. Belyntic does not offer its Products to consumers.

2. Contract Conclusion

2.1 Belyntic's quotations are not binding offers but must be seen as invitations to submit a binding offer. The contract is concluded by purchaser's order of the Products (offer) and by Belyntic's acceptance of this order. An order shall not be regarded as accepted until Belyntic has sent to the purchaser a confirmation of order ("**Confirmation of Order**"). In case the acceptance differs from the offer, such acceptance constitutes a new non-binding offer of Belyntic.

2.2 The contract between Belyntic and the purchaser is governed exclusively by these Terms of Sale. Belyntic shall sell and provide all Products, as well as any associated supplies or services, to the purchaser on the basis of these Terms of Sale only. Differing or contrary terms shall not apply except if expressly agreed upon by the parties in writing. These Terms of Sale shall also govern all future transactions between the Parties and shall also apply if Belyntic performs delivery despite its knowledge of differing or contrary terms.

3. Scope of Order, Product Quality and Safety

3.1 Belyntic shall sell to the Purchaser the Products listed in the Confirmation of Order.

3.2 Any use of Belyntic's Products requires and presupposes professional knowledge about the handling, storage and disposal of chemical substances. Subject to such knowledge, and unless expressly agreed in writing otherwise, the nature, quality and intended uses of the purchased Products and their individual components, e.g. potential peptide purification advantages, limitations and sources of contamination are exclusively defined by the respective description in the product description set forth in **Annex 1** ("**Product Description**"). It is the sole responsibility of the purchaser to evaluate whether the quality of the results of the application of the Product meet the requirements of the purchaser's own purposes. Therefor the purchaser might need to perform a suitable analysis and take appropriate measures for further processing and utilization, e.g. by additional purification using chromatographic methods.

3.3 The purchaser recognizes that in order to achieve the potential advantages of the applications of the Product referenced in the Product Description, it is in principle necessary to follow the instructions and use the components as described in detail in the respective manual in its latest version ("**Manual**"). To this end, and considering the Manual is subject to change, the purchaser shall always only use the latest version of the Manual which can be retrieved at

www.belyntic.com/products. Without prejudice thereof, the current version of the Manual at the time of delivery will be enclosed in the shipment of the purchased Products. The Manual may require the use of other chemicals and consumables which are not included in the purchased Kits and must be procured separately by the purchaser. In case of any questions about the applicable version or content of the Manual, the purchaser shall immediately contact Belyntic before proceeding.

3.4 Furthermore, the purchaser recognizes that the Product Description might mention applications of the Product for which the Manual does not contain any instructions or descriptions; with regard to these applications, the purchaser is solely dependent on his own knowledge and skills to achieve their potential advantages.

3.5 Safety instructions and fields of application for the purchased Products are set forth in the relevant safety data sheets in their latest version ("**Safety Data Sheets**"). As the Safety Data Sheets are subject to change, the purchaser shall always only refer to the most recent version of the Safety Data Sheets. Information about the most recent version of the Safety Data Sheets can be found at www.belyntic.com/products. The current version of the relevant Safety Data Sheets at the time of delivery will be enclosed in the shipment of the purchased Products. Belyntic will provide updated Safety Data Sheets in accordance with the applicable law and besides that provide updated Safety Data Sheets upon the purchaser's request. In case of any questions about the applicable version or content of the Safety Data Sheets, the purchaser shall immediately contact Belyntic before proceeding.

4. Prices and Payment

4.1 Prices for the Products are exclusive of any applicable statutory VAT and exclusive of costs for shipment, except as otherwise expressly agreed upon.

4.2 The purchase price is due and payable net within thirty (30) days from the date of the invoice. From this due date, default interest in the amount of nine (9) % above the respective base interest rate within the meaning of Sec. 247 German Civil Code (BGB) p. a. shall accrue. Belyntic reserves all rights to claim further damages for delay.

5. Offset (Aufrechnung), Retainer (Zurückbehaltungsrecht)

5.1 The purchaser shall be entitled to offset only insofar as his counterclaim is acknowledged, undisputed or assessed in a legally binding judgement.

5.2 The purchaser is entitled to claim retainer rights only to the extent such rights are based on the same transaction.

6. Delivery

6.1 Delivery is implemented via shipment to the purchaser and conditioned upon timely and proper performance of all duties of the purchaser. Defences based on non-performance of the contract are reserved.

6.2 In case of default in acceptance or other breach of duties to cooperate by the purchaser, Belyntic is entitled to claim any resulting damage including but not limited to additional expenses, if any. Further damages are reserved. In this case, the risk of loss or damage to the Products passes to the purchaser at the time of such default or breach of duty to cooperate.

6.3 Belyntic's delivery obligations shall at all times be subject to a timely and orderly receipt of the relevant manufacturing parts and other ordered products from Belyntic's own suppliers.

7. Passing of Risk

The risk of loss or damage to the purchased Products (*Gefahrübergang*) passes to the purchaser upon dispatch of the shipment.

8. Retention of Title (*Eigentumsvorbehalt*)

8.1 Belyntic retains title to the Products until receipt of all payments in full. Subject to the retention of title, the following additional terms apply:

8.1.1 In case of breach of contract by the purchaser including, without limitation, default in payment, Belyntic is entitled to take possession of the Products.

8.1.2 The purchaser shall handle the Products with due care, maintain adequate insurance for the Products and, to the extent necessary, service and maintain the Products.

8.1.3 The purchaser shall immediately inform Belyntic in writing if the Products become subject to rights of third persons or other encumbrances.

8.1.4 The purchaser may resell the Products subject to the retention of title only in the course of his regular business. In this case, the purchaser hereby assigns all his claims (e.g. claims for payment) arising out of such resale to Belyntic. Notwithstanding Belyntic's right to enforce such assigned claims, the purchaser shall remain entitled to receive the payment on the assigned claims. To this end, Belyntic agrees to not demand payment on the assigned claims to the extent the purchaser complies with all his obligations for payment and does not become subject to an application for insolvency or similar proceedings or to any stay of payments.

8.2 Insofar as the securities conferred to Belyntic by means of the retention of title exceed the secured claim by more than 10 %, the purchaser may request Belyntic to, if possible, release such securities upon the purchaser's request.

9. Warranty

9.1 Any warranty claim of the purchaser is preconditioned on the purchaser's full compliance with all requirements regarding inspection and objection established by Sec. 377 German Commercial Code (*Handelsgesetzbuch – HGB*).

9.2 Warranty claims of the purchaser shall become time-barred after twelve (12) months of the passing of risk.

10. Liability

10.1 Belyntic shall be liable only in accordance with the provisions set out under (a) to (e): (a) Belyntic shall be unrestrictedly liable for losses caused intentionally or with gross negligence by Belyntic or its assistants in performance. (b) Belyntic shall be unrestrictedly liable for death, personal injury or damage to health caused with intent or negligence by Belyntic or its assistants in performance.

(c) Belyntic shall be liable for losses arising from the lack of any guaranteed characteristics (Sec. 443 German Civil Code (BGB)) up to the amount which is covered by the purpose of the guaranteed and which was foreseeable at the time the guarantee was given. (d) Belyntic shall be liable in accordance with the German Product Liability Act in the event of product liability. (e) Belyntic shall be liable for losses caused by the breach of its primary obligations by Belyntic or its assistants in performance. Primary obligations are such basic duties which form the essence of the contract, which were decisive for the conclusion of the contract and on the performance of which the parties may rely upon. If primary obligations are breached through simple negligence by Belyntic or its assistants in performance, then Belyntic's ensuing liability shall be limited to the amount which was foreseeable.

10.2 Belyntic shall be liable for loss of data only up to the amount of typical recovery costs which would have arisen had proper and regular data backup measures been taken.

10.3 Any more extensive liability of Belyntic is excluded on the merits.

11. Force Majeure

11.1 Belyntic shall not be responsible for delays in delivery or failure to perform other obligations caused by force majeure. Such events include natural occurrences, wars, strikes, lock-outs, shortages of raw material and energy, obstructions of transportation, breakdowns of manufacturing equipment, fires, explosions, acts of governments and other acts or causes reasonably beyond Belyntic's control (each a "**Force Majeure Event**") and have the effect of exonerating Belyntic, also when they occur in the sphere of a sub-contractor or Belyntic's suppliers.

11.2 Force Majeure Events entitle Belyntic to delay performance for the period in which the Force Majeure Event persists and for an additional reasonable period of preparation for performance. If the aforementioned occurrences last for a period of more than three months, Belyntic is entitled to withdraw from the contract with respect to the part of the contract which could not be performed due to the Force Majeure Event. The purchaser shall not be entitled to damages or compensation in case of such withdrawal.

12. Miscellaneous

12.1 The Confirmation of Order, the Annex 1 as well as the latest versions of the relevant Manual and Safety Data Sheets constitute integral parts of these Terms of Sale.

12.2 These Terms of Sale shall be governed by German law to the exclusion of German international private law and the UN Convention on Contracts for the International Sale of Goods.

12.3 Place of performance and exclusive place of jurisdiction for all disputes arising out of or in connection with these Terms of Sale shall be Berlin, Germany.

12.4 The contract language is English. Any translations are for information only. If an English term in these Terms of Sale refers to a German legal term, the legal meaning of the German term shall, in the event of a contradiction with an English legal term, prevail.

Annex 1: Product Description

1. General

This Product Description applies to packed kits ("**Kits**"), primarily containing novel chemical linker molecules ("**PEC-Linker**") which are manufactured and offered by Belyntic GmbH ("**Belyntic**"). The Kits additionally include related chemical products and goods ("**Related Goods**").

2. Purpose

2.1 The main purpose of the PEC-Linker is the purification and modification of peptides that have been chemically synthesized with Fmoc (Fluorenylmethyloxycarbonyl)-based solid phase peptide synthesis (SPPS).

2.2 Generally, the PEC-Linker may be suitable for the temporary or permanent conjugation of two (bio-) chemical components ("**Component A**" and "**Component B**").

2.3 The use in or for clinical or diagnostic products, applications or services is excluded.

3. PEC-Linkers and principles of the Catch-and-Release technology

3.1 Belyntic's PEC-Linkers are bifunctional, cleavable molecules (see Figure 1).

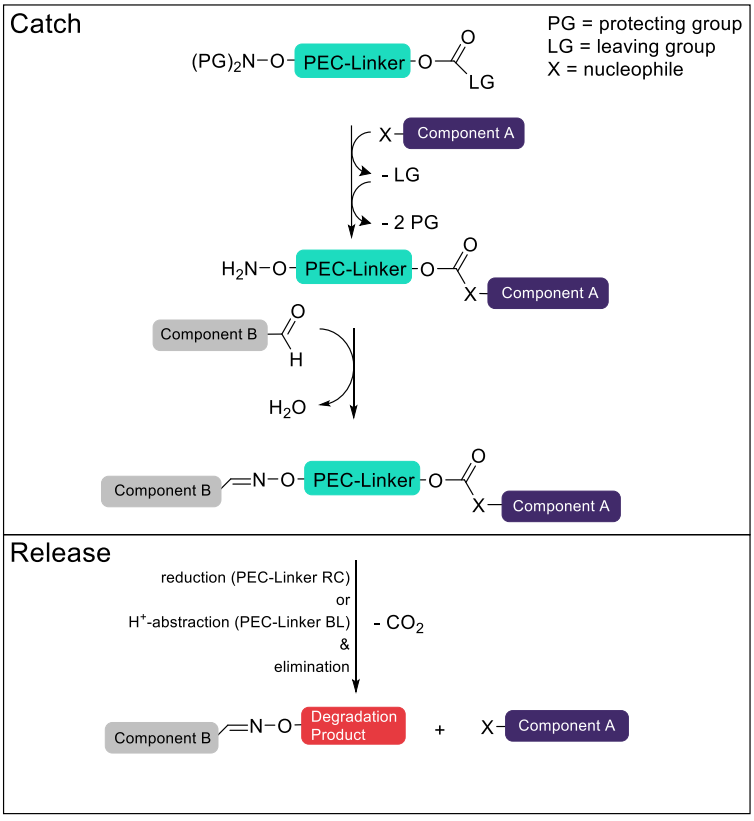

Figure 1: Schematic representation of the basic principle of Belyntic's PEC-Linker.

3.2 Two (bio-) chemical components Component A and Component B can be linked via stable covalent bonds ("**Catch**"): Component A binds with a nucleophilic functional group to the protected PEC-Linker while exchanging a leaving group. After deprotection of the PEC-Linker, a second aldehyde-modified Component B binds via an aminooxy group at the PEC-Linker by forming an oxime bond.

3.3 The PEC-Linker can be cleaved with a suitable cleavage protocol. Component A is thereby recovered in its original form ("**Release**"). A degradation product of the PEC-Linker remains at Component B.

3.4 The full process including Catch and Release is referred to as Catch-and-Release technology ("**Catch-and-Release**").

3.5 The PEC-Linkers are currently available in the following categories (a) and (b): (a) reductively cleavable linker molecules ("**PEC-Linker RC**") and (b) linker molecules cleavable with a base ("**PEC-Linker BL**").

(a) The group of PEC-Linkers RC includes reductively cleavable linker molecules. After reduction, PEC-Linkers RC decompose at controlled pH via elimination, releasing CO_2 and the previously coupled Component A. Hence, reductive conditions lead to the cleavage of the PEC-Linkers RC, while they may furthermore harm Component A or Component B, as for example azides and disulfides are reduced.

(b) The group of PEC-Linkers BL includes linker molecules cleavable with a base. The PEC-Linkers BL decompose in the presence of base, releasing CO_2 and the previously coupled Component A via elimination. Hence, basic conditions lead to the cleavage of the PEC-Linkers BL, while they may furthermore harm Component A or Component B, e.g. by induction of unwanted side reactions. For example, N-terminal threonine or serine in peptides can undergo side reactions, aspartimides can be formed in peptides, or citrulline can be formed in peptides e.g. with arginine-glutamine domains.

4. Activated Filter Material as Component B

4.1 As a variant of Component B, aldehyde-modified solid supports ("**Activated Filter Material**") are used. This allows Component A, which is bound to a PEC-Linker, to be immobilized on a solid support. Possible applications of this combination are the following options (i) to (iii):

(i) The bound Component A can be separated from unbound substances since the Activated Filter Material can be separated from liquid media by centrifugation or filtration (purification).

(ii) The bound Component A can be further modified chemically, physically or biologically on the Activated Filter Material (modification).

(iii) Conjugates of Component A and Activated Filter Material can be used as a hybrid material (application).

4.2 Aldehyde-modified agarose beads are typically employed as a suitable Activated Filter Material. These activated agarose beads are designed for single use and should not be reused.

4.3 Technical information about the Activated Filter Material can be found in Table 1.

Table 1: Technical properties of Activated Filter Material

Name	Agarose100
Geometry, size	Spherical, ≈ 150 µm diameter
Crosslinking	Yes
Functional group	Aldehydes by oxidized diols
Agarose content in settled beads/ %	10
Functional group density / µmol mL^{-1}	80 to 120
Storage media	20% ethanol
Storage temperature / °C	2 to 8
Reuse	No

5. Buffer salts for binding to Component B (Catch)

5.1 The formation of the oxime bond during the Catch step predominantly occurs in acidic medium.

5.2 Corresponding buffers such as citric acid buffer or ammonium acetate buffer can be used.

5.3 A mixture of citric acid and sodium carbonate can be used as a salt to prepare a suitable citric acid buffer.

5.4 The solution in which Component A is linked to Component B via oxime ligation may contain additional organic solvents such as DMSO.

6. Blocking Agents for Component B

6.1 If aldehyde-modified Activated Filter Material is used as Component B, it is recommended to block excess of aldehyde groups after binding the PEC-Linker-modified Component A with a suitable reagent ("**Blocking Agent**") in order to prevent undesired side effects.

6.2 Blocking Agents for aldehyde blocking should be added after formation of the oxime bond and removal of the reaction supernatant.

6.3 L-Cysteine has proven to be a suitable Blocking Agent.

7. Cleavage of the PEC-Linker

7.1 Depending on the design of the individual components PEC-Linker, Component A and Component B as well as the desired purpose, various strategies can be used to cleave the PEC-Linker.

7.2 These strategies can be distinguished between option (a), suitable for reductive cleavage, and option (b), suitable for cleavage with a base.

(a) Using triphenylphosphine (PPh_3) or DL-Dithiothreitol (DTT) as reducing reagents ("**Reducing Agent**"), for example, aryl azides as an embodiment of the PEC-Linker RC (e.g. PEC-Linker RC+) can be reduced to amines. This results in Release of Component A via elimination at a controlled pH. The reagent is not intended for the PEC-Linker BL group.

(b) Using ammonium hydroxide or organic amines such as ethanolamine, cleavage of the sulfone oxide bridge as an embodiment of the PEC-Linker BL can be initiated by abstraction of a proton at the alpha-carbon atom, before Release of Component A occurs via elimination.

8. Kit products

8.1 Belyntic's PEC-Linkers in conjunction with peptides as Component A and Activated Filter Material as Component B form the basis of Belyntic's Kits. Possible applications of this combination are the following options (a) to (c): (a) peptide purification, (b) peptide modification or (c) use of immobilized peptide on Activated Filter Material.

8.2 The linking of the target peptide with the Activated Filter Material by means of the PEC-Linker allows the washing out of unbound substances and/or the selective modification of the bound peptide. The subsequent (optional) cleavage of the PEC-Linker enables Release of the purified and/or modified peptide with a free amino group. The degradation product remains on the Activated Filter Material.

9. Single Kits

9.1 The PEC-Linker BL and PEC-Linker RC may be purchased as single component based on an individual agreement.

9.2 Agarose100 may be purchased as single component based on an individual agreement.

10. Research Kits

10.1 Research Kits are typically suitable for peptide purification and/or peptide modification.

10.2 The Research Kit contains all individual components that are typically not available in the customer's laboratory to be able to perform a defined amount of peptide purifications and/or modifications in timely manner. Other chemicals and consumables which are not included in the Kit must be procured separately from the customer.

10.3 The individual components of the Research Kits are listed in Table 2. The listed products differ in their size as well as in the type of the contained Reducing Agent.

Table 2: Components of Research Kit, Developer Kit and High-Throughput Kit products

Product name	Research Kit			Developer Kit	High-Throughput Kit
Product number(s)	180484004 (for 8x100 µmol) 180484005 (for 8x25 µmol) 180484006 (for 24x10 µmol)	180484007 (for 8x100 µmol) 180484008 (for 8x25 µmol) 180484009 (for 24x10 µmol)	180484020 (for 8x100 µmol) 180484021 (for 8x25 µmol) 180484022 (for 24x10 µmol)	180484000 (including 100 g PEC-Linker) 180484001 (including 50 g PEC-Linker) 180484002 (Including 25 g PEC-Linker) 180484003 (including 10 g PEC-Linker)	180484100 (for 96x10 µmol) 180484102 (for 48x20 µmol)
PEC-Linker	RC+	RC+	BL	RC+ (BL on written request)	RC+
Activated Filter Material	Agarose100, filled in fritted syringe reactors	Agarose100, filled in fritted syringe reactors	Agarose100, filled in fritted syringe reactors	Agarose100, filled in fritted syringe reactors	Agarose100, filled in 96- or 48-well PEC-filter plate
Reducing Agent	PPh_3	DTT (DL-Dithiothreitol)	2-aminoethanol (ETA)	-	DTT (DL-Dithiothreitol)
Blocking Agent	L-Cysteine	L-Cysteine	L-Cysteine	-	L-Cysteine
Buffer salt	Mixture of citric acid-sodium carbonate	Mixture of citric acid-sodium carbonate	Mixture of citric acid-sodium carbonate	-	Mixture of citric acid-sodium carbonate
Accessories					• 96-well TFA collection plate / deep-well plate to collect crude peptides, including 1 top sealing mat [**96x10 µmol Kit only**] • 96- or 48-well peptide collection plate / perforated deep-well plate to collect purified peptides • 1 top sealing mat • 1 bottom sealing mat for filter plate
Documentation	Manual (English)	Manual (English)	Manual (English)	Manual (English)	Manual (English)

11. Developer Kits

11.1 With the PEC-Linker and an adequate amount of Activated Filter Material, the Developer Kit contains the basic components for peptide purification and/or modification. Other chemicals and consumables which are not included in the Kit must be procured separately from the customer.

11.2 The Developer Kit should allow a flexible integration into a customer's existing laboratory infrastructure.

11.3 The Developer Kits are available with PEC-Linker RC and, on written request, with PEC-Linker BL.

11.4 The individual components of the Developer Kits are listed in Table 2.

12. High-Throughput Kits

12.1 The High-Throughput Kits are typically suitable for parallel purification of multiple peptides.

12.2 The High-Throughput Kit contains all individual components that are typically not available in the customer's laboratory to be able to perform a defined amount of peptide purifications in timely manner. Other chemicals and consumables which are not included in the Kit must be procured separately from the customer.

12.3 The High-Throughput Kits are only available with PEC-Linker RC, not with PEC-Linker BL.

12.4 The individual components of the High-Throughput Kits are listed in Table 2. The listed products differ in their size. The High-Throughput Kit 96x10 µmol [180484100] contains an additional deep-well plate and top sealing mat to collect the crude peptides. This is not available for the High-Throughput Kit 48x20 µmol [180484102].

13. Advantages with Belyntic's PEC-Linker

13.1 The use of Belyntic's Kits for the purification of peptides synthesized by SPPS results in numerous benefits, outlined in 13.2 to 13.9.

13.2 The purification technology is orthogonal to chromatography and can therefore be combined with the latter.

13.3 Purification with PEC-Linkers enables parallel purification of peptides in separate fritted syringe reactors.

13.4 The Activated Filter Material can in principle be employed in various containers to allow higher parallelization levels, given that the Activated Filter Material can be retained for washing steps and release of the peptide.

13.5 By using solvents and chaotropic salts of up to 90% in the immobilization buffer, a huge variety of peptides can be dissolved and purified.

13.6 Peptide purification with Catch-and-Release enables the development of routine protocols due to the chemo-selective isolation with the PEC-Linker.

13.7 Modification of the unprotected peptide, bound to the Activated Filter Material, is possible taking advantage of solid phase chemistry.

13.8 If PEC-Linker coupling, immobilization as well as the elution after release is done efficiently, improved yields over low to medium pressure chromatography can be achieved.

13.9 The process is characterized by a low consumption of organic solvents compared to chromatography.

14. Limitations and sources of contamination with Belyntic's PEC-Linker

14.1 The use of Belyntic's Kits for peptide purification can lead to very different results due to the peptides' physicochemical diversity. The outcome is also strongly dependent on the synthesis of the peptide itself as well as on the process factors during use of Belyntic's PEC technology. Currently known limitations and sources of contamination are outlined in 14.3 to 14.10.

14.2 Acetylation **("Capping")** during synthesis is fundamental for peptide purification to ensure the PEC-Linker is coupled solely on the target peptide.

14.3 The PEC-Linker is typically bound to the N-terminus of the peptide. In this case, modifications of the N-terminus are not possible.

14.4 In principle, every compound linked to the PEC-Linker may be contained in the final product. Rephrased: Every compound with a free amine during the step of PEC-Linker coupling will bear the PEC-Linker. Therefore, potential impurities already arise during synthesis. Beside the target peptide, these may be undesired sequences due to e.g. amino acid contamination, incomplete Fmoc deprotection and/or intra- or intermolecular side reactions (e.g. aspartimides, pyroglutamates) if these are present at the time of PEC-Linker coupling.

14.5 Another essential synthesis-related source of contamination may occur when Capping is not (or only incompletely) performed after each amino acid coupling. As a result, the PEC-Linker may bind to truncated or undesired sequences and those will then remain in the final product as by-products.

14.6 The properties of the target peptide may have considerable influence on the purification result. Side reactions cannot be ruled out during the procedure. Solubility is not always guaranteed. Non-natural or modified peptides may particularly be affected. In view of this diversity of peptides, it is often not possible to predict in advance whether a satisfactory purification result can be achieved.

14.7 Further possible peptide impurities may occur during the cleavage of the peptide from the synthesis resin. These are peptide sequences that already carry the PEC-Linker and then react with reactive species (e.g. cleaved protective groups or degradation products of the cleaved synthesis linker). These usually unwanted sequences are not removed and remain in the final product.

14.8 At all stages before the peptide-PEC-Linker-conjugate is bound to the Activated Filter Material, contaminations with aldehydes or ketones in the reaction, precipitation, storage or analysis media can react with the aminooxy of the PEC-Linker. This can reduce the yield and/or distort analysis. Regarding reduced yield, the purity of solvents used for PEC-Linker coupling or the ether used to precipitate the peptide are of specific importance. Regarding analysis, the purity of eluents during chromatography are of specific importance.

14.9 Other systemic impurities are triphenylphosphine oxide (PPh_3O) or other Reducing Agents and their oxidized form, which are produced as a reaction product during the Release step of the PEC-Linker RC. The Manual suggests a treatment to remove this contamination. However, traces may still be present in the final product.

14.10 Further specific limitations of the PEC-Linkers RC and PEC-Linkers BL may be found in 3.5 (a) and 3.5 (b) of this Product Description.

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