Technology Trends of Growth Hormone and Development Strategies for Growtropin

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Introduction

1. General information of Growtropin

Growtropin, a recombinant human growth hormone product released in 1995, is a biological product of Dong-A, for which the revenue is about 60 billion Won through domestic and global sales. The product is currently marketed as a lyophilized, liquid vial and liquid pen cartridge form. The main indication for Growtropin is pediatric growth hormone deficiency (GHD) and Idiopathic Short Stature (ISS).

2. Main subject

1) Trend of development: human growth hormone (hGH)

Recent development trends of hGH have been carried out in three directions (Fig. 1). The first trend is improving the first-generation hGH by upgrading the injection device needed for administration or improving the method of administration for the convenience of patients. The overall flow of this improvement has led to an upgrade of the injection device; however, formulation development for oral and nasal administration is also being studied. The second trend is developing a long-acting second-generation hGH by extending the half-life of the first-generation hGH. The third trend is developing biosimilar products, which have had less impact on the hGH market before now; however, expectations of low-cost products still remain as an opportunity.

Keywords: Growtropin, Human growth hormone (hGH), Biosimilar, Pen device, Long-acting product

Fig. 1. Development trend of human growth hormone (hGH).
hGH in order to reduce the administration frequency for the convenience of patients. The second-generation hGH development using Glycosylation, PEGylation, and Fc-fusion is actively being studied and is expected to be commercially available in the near future. The final trend is developing a biosimilar (similar biological product) product. The concept of the development of “biosimilar” is similar to that of the “generic products” of chemical drugs by supplying expensive biotherapeutics at a lower price for patients to give better treatment opportunities.

2) Upgraded products

The leading development plan of the upgraded product is improving the injection device. The main purpose of developing the injection device is to improve patients’ convenience. The management of accurate administration and administration history are incidental purposes. The development of the injection device for insulin is carried out the most along with hGH. According to Feroz et al., the production of global insulin from 2007–2012 was driven by the cartridge-based pen injector. It has also been reported that an important factor for production growth is the disposable pen in particular. This also appears in recent hGH-related patents. A number of hGH-related patents from global pharmaceutical companies are related to injection devices, and the number of hGH-related patents from Novo Nordisk, a latecomer rhGH manufacturer, is overwhelming (Table 1). Some considerations when developing hGH pen devices are as follows: 1) Ease of operation, 2) Safety, 3) Eased reluctance, and 4) Eased storage conditions. In conclusion, to achieve revenue growth, the development of an easy-to-use, safe pen device should be considered to improve the accessibility of patients. Additionally, Genotropin (Pfizer), Humatrope (Eli Lilly), Nutropin (Genentech), and Norditropin (Novo Nordisk), which are the hGH originator drugs, as well as Omnitrope (Sandoz), a biosimilar product, are mainly sold as pen devices; among these products, Norditropin and Nutropin are supplied as disposable pen products (Table 2). In the case of Norditropin, despite being a latecomer, the market share from the world market in 2014 was 33.4%, making it the best seller for hGH (Fig. 2).

Table 1. hGH-related patents

| Company name          | Product name       | Patents (expiry date) | Patent type | Patent description               |
|-----------------------|--------------------|-----------------------|-------------|----------------------------------|
| NOVO NORDISK          | FlexPro Pen        | US 7686786 (2026-08-03) | Device      | Dial for dose control           |
|                       |                    | US 6899699 (2022-01-02) | Device      | Automatic injection technology   |
|                       |                    | US 6716198 (2021-06-05) | Device      | Device including piston & ampoule |
| NordiFlex Pen         | (NordiLet)         | US 6004297 (2019-01-28) | Device      | Pen device                       |
|                       |                    | US RE41956 (2021-01-21) | Device      | Device for dose control         |
| Norditropin           |                    | US 5849700 (2015-12-15) | Method of use | Liquefied formulation           |
|                       |                    | US 5633352 (2014-05-27) | Process by product | Formulation                   |
| PHARMACIA             | Genotropin         | US 6152897 (2018-11-20) | Composition | Freeze-drying form & disposable syringe |
|                       |                    | US 5435076 (2013-04-16) | Device      | Reconstruction syringe          |
| APPLIED RESEARCH SYSTEMS | Saizen            | US 5898030 (2016-04-27) | Composition | Material                        |
| ELI LILLY             | Humatrope          | US 5612315 (2014-03-18) | Formulation | Oral (not commercialization)     |

Table 2. Device for hGH

| Company              | Norditropin FlexPro | Nutropin AQ NuSpin | Genotropin Pen | HumatroPen | Omnitrope Pen |
|----------------------|---------------------|--------------------|----------------|------------|---------------|
| Needle protection    | √                   | √                  | √              | √          | √             |
| Required mixing      | √                   | √                  |               | √          |               |
| Exchangeable cartridge |                  |                   | √              | √          |               |
| Disposable           | √                   | √                  |               |            |               |
| Maximum dose         | 8 mg                | 7 mg               | 4 mg           | 6 mg       | 5.4 mg        |
| Alarm after dose     | √                   |                    |               |            |               |
due to the following factors: ① Novel delivery device (disposable pen) and ② stable formulation (stable for 3 weeks at room temperature). It can be concluded that the device is having a significant impact on sales. Some examples of the development of the route of administration other than the device upgrade include oral delivery (Hanall BioPharma) and nasal delivery (Critical Pharmaceuticals). 8, 9

3) Second-generation products
The purposes of the development of the second-generation products are to extend the half-life of the biotherapeutics to reduce the dosing frequency for the convenience of patients and to increase patients’ compliance. The major techniques include ① Glycosylation, ② PEGylation, and ③ Fc fusion, and products using these techniques are commercially available (Fig. 3).

(1) Glycosylation
Most of the biotherapeutics are glycoproteins composed of carbohydrate and protein. When the carbohydrate is bound to protein, the body clearance rate is reduced, which may extend the half-life. Amgen’s Aranesp (Erythropoietin), an anemia drug, is a representative product using this principle. In the case of hGH, a study is being held by OPKO and Pfizer by connecting hGH to the carboxyl terminal peptide (CTP), a concentrated carbohydrate binding site, to improve glycosylation 10, 11.

(2) PEGylation
When coupling PEG (polyethylene glycol), a polymer compound, to a protein molecule, the half-life of the protein is extended and the clearance rate and immunogenicity in the blood is reduced. Using this principle, the PEGylation of therapeutic proteins with a short half-life is actively being studied, and Jintrolong, the world’s first PEGylated hGH, has been released by GeneScience in China 12. However, a PEGylated hGH that has been jointly studied by Ambrx and Merck has been halted and should be noted for future research trends.

(3) Fc Fusion
Antibodies have a much longer half-life than any other proteins due to the Fc region present in antibodies. The second-generation biotherapeutics studies are being conducted by combining the antibody Fc region with normal proteins to extend the half-life. In the case of hGH, Genexine, a domestic company, is undertaking a Phase 2 clinical trial in Europe.

4) Biosimilar
The process and documents needed for the approval of biosimilar are relatively simple. It can be approved by proving comparability with formally approved and marketed originator drugs. The comparability testing should include physicochemical, non-clinical, and clinical studies. The advantage of biosimilar is that

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#### hGH market shares in 2014

**Total $3,26 bn**

![hGH market share chart](image)

**Source:** Company annual reports 2014, wisingain 2014

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**Fig. 2. Global hGH market in 2014.**

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#### Technology | Glycosylation | PEGylation | Fc Fusion

| Diagram | Additional carbohydrates | IFN-α | PEG |

| Products | Aranesp® (EPO)/Amgen | Pegasy® (IFN-α)/Roche | Enbrel® (TNF-α)/Amgen |
|----------|-----------------------|-------------|---------------------|
|          | Neulasta® (G-CSF)/Amgen |              | Ocrevus® (CTLA-4)/BMS |
|          | Miricra® (EPO)/Roche   |              |                     |

**Fig. 3. Representative technique for 2nd-generation products.**
the indications of the originator drug can be extrapolated by the comparative clinical phase 1 and phase 3 trials. Since 2006, after Omnitrope (Sandoz), the world’s first biosimilar product, was approved, there have so far been 19 approved biosimilar products sold in Europe (Table 3). Among the biosimilar products, only two products Omnitrope and Somatropin Biopartners (BioPartners), are hGH products, and the product number and market share are relatively low compared with the first-generation biotherapeutics, such as filgrastim and epoetin (Fig. 4). The brand loyalty towards hGH products was the main reason such a matter was analyzed by Visiongain in 2014. For hGH biosimilar market expansion in the future, improvement of the hGH injection device is required.

5) Development strategy for Growtropin
Dong-A is currently in progress to improve the Growtropin pen device and develop the second-generation hGH in order to improve domestic and global sales. The reusable pen device is expected to be changed to an easy-to-use disposable pen device, and extended half-life formulation research is being performed to develop a long-acting formulation. Through this, we expect to provide an opportunity for market expansion by extending the lifecycle of Growtropin.

Conclusion
The improvement of the first-generation hGH is being conducted using various methods worldwide. The research directions can be mainly classified as improved products, long-acting

### Table 3. Approved biosimilar products in the EU (– Jan 2015)

| Reference | Molecule            | Biosimilar       | Manufacturer         | Date marketing approval received |
|-----------|---------------------|------------------|----------------------|----------------------------------|
| Neupogen  | Filgrastim          | Nivestim         | Hospira              | 8 Jun 2010                       |
|           |                     |                  | Sandoz               | 6 Feb 2009                       |
|           |                     |                  | Ratiopharm           | 15 Sep 2008                      |
|           |                     |                  | Teva                 | 15 Sep 2008                      |
|           |                     |                  | CT Aizneimittel      | 15 Sep 2008                      |
|           |                     |                  | Apotex (w/Intas)     | 18 Oct 2013                      |
|           |                     |                  | Accord Healthcare    | 25 Jul 2014 (CHMP positive opinion) |
| Eprex     | Epoetin zeta        | Silapo           | Stada                | 18 Dec 2007                      |
|           |                     |                  | Retacrit             | 18 Dec 2007                      |
|           |                     |                  | Sandoz               | 28 Aug 2007                      |
|           |                     |                  | Hexal                | 28 Aug 2007                      |
| Genotropin| Somatropin          | Omnitrope        | Sandoz               | 12 Apr 2006                      |
| Humatrope | Somatropin          | Somatropin Biopartners | Biopartners       | 5 Aug 2013 (GHD)                 |
| Remicade  | Infliximab          | Inflectra/Remsima | Hospira/Celltrion    | 10 Sep 2013                      |
| Gonal-F   | Follitropin alfa    | Ovaleap          | Teva                 | 27 Sep 2013                      |
|           | Follitropin alfa    | Bernfola          | Finox Biotech        | 27 March 2014                    |
| Lantus    | Insulin glargin     | Abasria (Basaglar, US) | Eli Lilly/BI       | 10 Sep 2014                      |

**Fig. 4.** Biosimilar market shares in 2013–2024.
second-generation products, and biosimilar products. The de-
velopment trends of the improved products are driven towards
improving the injection device to enhance the convenience of
patients, for which, in particular, the introduction of the dispos-
able pen is an important factor. Studies of long-acting second-
generation products aim to extend the half-life of hGH. For each
of the candidates, the clinical trial results are important, and this
is expected to drive the growth of the future hGH market. The
market share of biosimilar products is still not significant, but if a
low-cost product is launched by improving the injection device,
the market share is expected to grow. Dong-A is currently pro-
ceeding with the introduction of the disposable pen device and
development of second-generation products in order to improve
Growtropin.

References

1. Feroz Jameel et al. Quality by Design for Biopharmaceutical
Drug Product Development. Chapter 18. Device and Com-
bination Products for Biopharmaceuticals. Springer. 2015.
2. Matthew Grissinger. Pen Injector Technology Is Not without
'Impending' Risks. Pharmacy and Therapeutics. 2010;35(5):
245-66.
3. Kevin CJ Yuen & Rakesh Amin. Developments in adminis-
tration of growth hormone treatment: focus on Norditrop-
in® Flexpro®. Patient preference and adherence. 2011;5:117-
124.
4. Jakob Lange et al. Usability of devices for self-injection: re-
results of a formative study on a new disposable pen injector.
Med Devices: Evidence and Research. 2014;7:195-203.
5. Dawn Rainer-Hall. Evolution of Growth Hormone Devices:
Matching Devices with Patients, PEDIATRIC NURSING.
2015;41:72-7.
6. https://www.norditropin.com/how-to-take-it/devices-on-
the-market.
7. Visiongain. Biosimilars and follow-on biologics: World in-
dustry and market prospects 2014-2024:212-220.
8. Critical Pharmaceuticals Limited. Absorption of therapeu-
tic agents across mucosal membranes or the skin. 2009.
US8795634.
9. HanAllBiopharma Co., Ltd. Modified growth hormones.
2005. WO2006048777.
10. Prolor Biotech Ltd. Polynucleotides encoding long-acting
growth hormone polypeptides and methods of producing
same. 2009. US8097435.
11. Prolor Biotech Ltd. Long-acting growth hormone and meth-
ods of producing same. 2011. US8450269.
12. Changchun Daxing Pharmaceutical Industry Company
Limited. Medicine containing PEG human growth hormone
conjugate and use thereof. 2008. CN101491681.