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Regulatory implications for the use of pharmaceutical markers to improve the detection of human growth hormone

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Introduction

Human growth hormone (hGH) is a 191 amino acid protein that is synthesized and secreted by the pituitary gland. The hormone has been used to enhance athletic performance, along with anabolic steroids. International sports competitions such as the Olympic Games routinely test all competitors for performance-enhancing drugs and a number of professional sports leagues do as well. Difficulties in developing a simple rapid test for exogenous administered hGH have led to the consideration of modification of the protein or the addition an inert marker to hGH preparations to improve detection. Such approaches are unlikely to be successful as manufacturers would have to carry out new clinical trials and relicense their products. In addition, some modifications may reduce the efficacy of the preparations or raise new safety considerations.

Human growth hormone stimulates cell growth and reproduction in humans. In 1960 the National Pituitary Agency was established at the National Institutes of Health to collect and process hGH from cadaver pituitary glands for the treatment of growth hormone deficiency in children. Enough hGH was processed to treat on average 1600 patients per year. Unfortunately several cases of Creutzfeld-Jakob disease emerged in individuals treated with pituitary-derived hGH.[1] Distribution of pituitary-derived hGH was suspended.

The emergence of recombinant DNA technology in the mid-1970s made it possible to produce large amounts of human proteins via simple fermentation technology. Human growth hormone was one of the initial proteins targeted for cloning.[2] In 1979, workers at the biotechnology company Genetech and researchers at the University of California at San Francisco reported the cloning and expression of hGH in the bacterium *E. coli*.

The pharmaceutical use of proteins from recombinant DNA technology is regulated by the Food and Drug Administration (FDA). At the outset, the majority of the products were regulated under the biologics provisions of the Public Health Service Act.[3] Hormones, however, are exempted from regulation as biologics and are instead regulated as drugs.[4] Following scale up of the manufacturing process, Genentech submitted a New Drug Application (NDA) to the Food and Drug Administration for a recombinant version of hGH. Methionyl-hGH (recombinant proteins produced in *E. coli* had an extra methionine on the amino terminus of the protein) or somatrem was approved by the FDA for the treatment of pituitary dwarfism in 1985. Shortly thereafter, a similar version of hGH manufactured by Eli Lilly was also approved.

The presence of an extra methionine on somatrem raised concerns about possible immunogenicity of the pharmaceutical preparation. While antibodies were observed, they proved not to be neutralizing and growth was observed in all but one of the patients observed as compared with patients treated with pituitary-derived hGH.[5] This also proved to be a short-lived issue as technology evolved to remove the methionine and pharmaceutical hGH now had the identical amino acid sequence as the pituitary-derived version. In 1993, the FDA approved the first versions of somatropin and the early methionyl-hGH preparations were withdrawn from the US market.

Human Growth Hormone Uses and Pharmacology

According to the FDA Orange Book,[6] there are nine manufacturers of hGH (Table 1). The existence of a listing in the Orange Book does not imply the respective company is marketing the drug in the US. Human growth hormone has been approved for the treatments of pituitary dwarfism and short stature in children, growth failure because of chronic renal insufficiency, adult growth hormone deficiency, idiopathic short stature and Turner syndrome.[7] EMD Serono has a separate branded version of hGH, Serostim, which is approved for wasting related to acquired immunodeficiency syndrome (AIDS). That company is the only one to have conducted clinical trials for this indication.

With the exception of a long-acting paediatric formulation, all of the licensed hGH preparations are identical and administered subcutaneously (SC) on a daily basis. Mean terminal half life of hGH (administered SC) varies according to manufacturers' reported clinical pharmacology data and is in the range from two to seven hours depending on formulation (taken from clinical pharmacology studies performed by each licensed manufacturer of hGH as reported on their FDA-approved drug levels per reference 7). Clearance from the body is rapid based on studies of hGH administered intravenously, where the half life is 15 to 20 minutes (depending on formulation) indicating that SC absorption is slow and rate limiting. The long-acting paediatric version contains hGH embedded in polylactide-coglycolide (PLG) microspheres (Nutropin Depot, manufactured by Genentech). This can be administered once or twice a month and results in a longer

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Table 1. FDA licensed manufacturers of human growth hormone

Company	Trade name
Cangene	Accretropin
EMD Serono	Serostim
EMD Serono	Saizen
Ferring	Tev-Tropin
Genentech	Nutropin
LG Life	Valtopin
Lilly	Humatrope
Novo-Nordisk	Norditropin
Pharmacia & Upjohn (now Pfizer)	Genotropin
Sandoz	Omnitrope

half life in the body. While still a licensed product, the company is no longer actively marketing it.

There is currently no regulatory pathway for the approval of a generic formulation of hGH that is analogous to how low molecular weight chemically derived drugs are approved.[8] The FDA has required full clinical trials from each manufacturer to demonstrate that the hGH preparations are safe and effective when prescribed according to the approved drug label.

Potential Alterations to Hgh to Allow Drug Testing Detection

The numerous reports of the use of hGH to enhance sports performance have led to questions about whether current pharmaceutical preparations could be modified to enhance detection using current testing regimes (blood or urine analysis). There are three possible approaches to accomplishing this:

- alter the amino acid sequence of the protein while preserving the biological activity, creating a potentially new epitope that could be used in an immunoassay (in fact this was the situation with the early version of hGH that had the extra methionine);
- covalently attach a marker to the protein that would be measurable; or
- add a traceable additive to the formulation that could be easily detected by a biological or chemical assay.

The additive would have to be carefully chosen so that it could be positively correlated with administration of hGH. Moreover, the impact of the additive on human health would need to be evaluated. Even trace amounts of an inert chemical might need to be subject to carcinogenicity testing in addition to some type of short-term acute toxicity testing. These testing protocols would have to be negotiated with the FDA. It is likely that studies on organ and tissue distribution would need to be conducted. The half life of the marker in the body would also need to be measured. This would be extremely important in terms of the usefulness of a marker in the testing for performance enhancing drugs. If the half life were too short the marker might not be useful.

Each of the three approaches has significant regulatory consequences. Any change in the primary structure of the protein will result in a new drug substance and require the submission of an NDA with clinical trials to demonstrate safety and efficacy. A new formulation containing a marker might also trigger clinical trials depending on whether it is likely to interfere with the activity of the drug. One could not exclude the possibility of new pharmacology and toxicology studies on a new version of hGH based on discussions with the FDA.

Recently the FDA has been releasing summaries of statistical evaluations for new drugs to its Internet site. A recently licensed hGH manufacturer studied two principal indications: pituitary dwarfism and Turner syndrome. This included six months of initial treatment followed by 30 months of long-term assessment.[9]

A fundamental difficulty in addressing any of the above approaches is the need for a common solution across all manufacturers. It is not clear whether FDA has any legal authority to impose any of the solutions mentioned above. Furthermore, other manufacturers of hGH not licensed in the US could still manufacture hGH that would not have the traceability solution, leading to an underground market for unmodified hGH. Given the clinical and other testing requirements, the minimal time to implement any of the solutions is on the order of four to six years (potentially longer if safety or efficacy issues arise during testing). The cost of multiple companies carrying out the required clinical trials is not trivial given that the drug has a very limited target patient population in order to deter abuse by a relatively small number of elite athletes.

The likelihood of developing a traceable formulation of hGH through modification of the protein or by adding an inert substance is extremely remote. Although hGH represents a challenge to sports drug testing, a concerted effort to improve on current tests is more practical and likely to be accomplished sooner than efforts modifying the drug structure or formulation.

References

[1] G. Kolata, *Science* **1986**, *234*, 22.
[2] *Commercial Biotechnology: An International Analysis*, US Congress, Office of Technology Assessment, Washington DC, January **1984**, OTA-BA-218. The report is archived at: www.princeton.edu/~ota/ns20/topic_f.html (accessed 16 November 2009) and there is an extensive chapter on the use of the technology for the production of pharmaceuticals including hGH.
[3] Public Health Service Act § 351 provides the legislative authority for the regulation of biological products and this is distinct from the Federal Food Drug and Cosmetic Act that gives FDA the authority to regulate drugs. Despite these two differing regulatory authorities, FDA uses the same standard for therapeutic and safety evaluation.
[4] *21 Code of Federal Regulations Part 600.3(h)(5)(ii)*. Hormones such as hGH require the submission and evaluation of a New Drug Application (NDA) that contains all of the clinical trial and manufacturing data.
[5] S. L. Kaplan, L. E. Underwood, G. P. August, J. J. Bell, S. L. Blethen, R. M. Blizzard, D. R. Brown, T. P. Foley, R. L. Hintz, N. J. Hopwood, *Lancet* **1986**, *8483*, 697, www.ncbi.nlm.nih.gov/pubmed/2870221, accessed 16 November 2009.
[6] The Orange Book contains listings of all approved drugs by brand and generic name and is searchable at: www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm, accessed 16 November **2009**.
[7] Full prescribing information for any of the growth hormone preparations can be found at the National Library of Medicine's DailyMed web site at: http://dailymed.nlm.nih.gov/dailymed/about.cfm, accessed 16 November **2009**, Labels are searchable by brand and generic name (for example, somatropin).
[8] *Federal Food Drug and Cosmetic Act, § 505(j)* gives FDA the authority to approve a generic drug based on bioequivalence provided the innovator drug is newly off patent. There has been considerable debate about how to handle biological products whose characterization and manufacturing processes are not amenable to routine characterization as used for small molecules.
[9] *Statistical Review and Evaluation of Accretropin; NDA #21-538/N000*; accessed at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm072824.pdf, accessed 16 November **2009**.