JUN 2 2 2000

K994384
1 of 6

510(k) Summary
(As required by 21 CFR 807.92(a))

A.	Submitter Information	Bioject, Inc. 7620 SW Bridgeport Road Portland, Oregon 97224 Phone: 800-683-7221 ext. 424 Fax: 503-624-9002 Email: nancy@bioject.com Contact: Nancy J. Gertlar Manager, QA/RA Date: December 17, 1999
B	Device Information Trade/Proprietary Name:	Clicker™
	Common Name:	Needle Free Injector, Jet Injector
	Classification Name:	Jet Injector, Non-Electrically Powered Fluid Injector
	Predicate Device(s):	• Medi-Jector Needle-Free Bio-Tropin™ Drug Delivery System K960285 • Vitajet K962625
	Device Description:	Clicker™ Needle-Free Self-Injection Device for Personal Use with Saizen® [somatropin (rDNA origin) for injection]. Needle Free Injector, Jet Injector
	Intended Use:	Clicker™ Needle-Free Self-Injection Device for Personal Use with Saizen® [somatropin (rDNA origin) for injection].
C	Comparison of Required Technological Characteristics:	This submission changes the labeling of the Vitajet 3, (Innova) (K962625) to allow the device to be used for needle-free subcutaneous administration of Saizen® [somatropin (rDNAorigin) for injection]. There are no other significant changes to the Vitajet 3 (Innova) in device design or function.

D Summary and Conclusion of Nonclinical and Clinical Tests:

GROWTH HORMONE DELIVERY USING A NEEDLE-FREE JET-INJECTOR

A number of clinical and laboratory studies were completed to prepare for an FDA submission for Saizen® to be used with a needle-free device®. These included laboratory studies designed to address the ability of Saizen® to remain intact after administration through the jet-injector and measurement of any Saizen®, which may adsorb to the plastic component parts. In addition, procedures were developed to measure and identify any microorganisms that may develop after seven daily injections with the same disposable plastic nozzle and vial connector.

LABORATORY STUDIES

The goals of the laboratory studies were to evaluate potential shearing and fragmentation of Saizen® and the interaction of growth hormone with the various plastic device components. In addition, a Bioburden study was performed to evaluate microorganism growth in and on the disposable clear nozzle as well as in the vial itself and on the vial connector. Four protocols were completed to reach the above goals.

SHEAR STRESS TESTING

Clicker™ utilizes a spring to induce a high-pressure injection of growth hormone through the skin. Protocol P-00026-01 was conducted to determine the effect of shear stress on Saizen®. A total of two lots of the 5.0 mg vial Saizen® and one lot of 8.8 mg vial Saizen® were tested. Technical report R-00055-02 summarizes the results. Results were within assay variability for high-pressure liquid chromatography (HPLC) analysis, physical tests and pH. Therefore, shear stress caused by Clicker™ did not physically alter the structure of Saizen®.

CHEMICAL COMPATIBILITY TESTING

CLEAR VIEW NOZZLE STUDY

Clicker™ utilizes a sterile plastic Stem Tip and Clear View Nozzle to perform a high-pressure injection of growth hormone through the skin. Protocol P-00028-01 was performed to assess interaction of growth hormone with the plastic components of the needle-free jet-injector. Two lots of the 5.0 mg vial Saizen® and one lot of 8.8 mg vial Saison® were tested. Technical report R-00056-02 summarizes the results. Results were within assay variability for HPLC analysis, physical tests and pH. Therefore, the Clear View Nozzle and Stem Tip are suitable for use with Saizen®

VIAL CONNECTOR STUDY

Protocol P-00025-01 examined the Vial Connector needed on the vial of growth hormone to facilitate drawing up the material into the injector. The growth hormone

samples were observed at seven and fourteen days for particulates by holding up to the light, checking against black paper and checking against white paper. The samples were also tested for pH and assessed for purity by SE-HPLC. Technical report R-00058-02 summarizes these results. Results demonstrated within- assay variability for HPLC analysis, physical tests and pH. Therefore, the Vial Connector is suitable for use with Saizen®.

BIOBURDEN STUDY

Protocol P-00027-02 investigates the effect of repeated use of Clicker™ on the number and pathogenicity of microorganisms noted on the various component parts. The components (plastic Stem Tip and Clear View Nozzle) can be used for up to seven days, while the reconstituted vial of Saizen® can be used for up to 14 days. This study was conducted to determine the amount and type of microorganism growth on the injector components, in the vial and in the injected drug after 14 days of use.

Multiple drug lots were tested with 12 jet-injectors. Technical report R-00057-01 summarizes the results. The liquid contents injected from the nozzle showed no microorganism growth in any sample, while the nozzle surface itself showed growth in only one sample. The Stem Tip exhibited growth in two samples, but did not show growth on the same, more concentrated filtration samples. One culture grew a non-pathogenic Staphylococcus species and another grew a mold (Aspergillus glaucus) and non-pathogenic bacteria (Bacillus lichenformis). The vial contents exhibited growth on only one sample. This single isolate was a non-pathogenic mold (Aspergillus versicolor). The vial adapter surface showed multiple occurrences of skin contaminants (non- pathogenic Staphylococcus species) only. All recovered isolates were determined not to be Escherichia coli, Pseudomonas aeauginosa, Salmonella or Staphylococcus aureus by screening on selective agar.

In summary, there are no clinically significant microorganisms found within the nozzle or within the Saizen® vial over a period of 14 days. Only minor expected surface contaminants were seen on the outer surface of the Vial Connector, Stem Tip and Clear View nozzle.

CLINICAL STUDIES

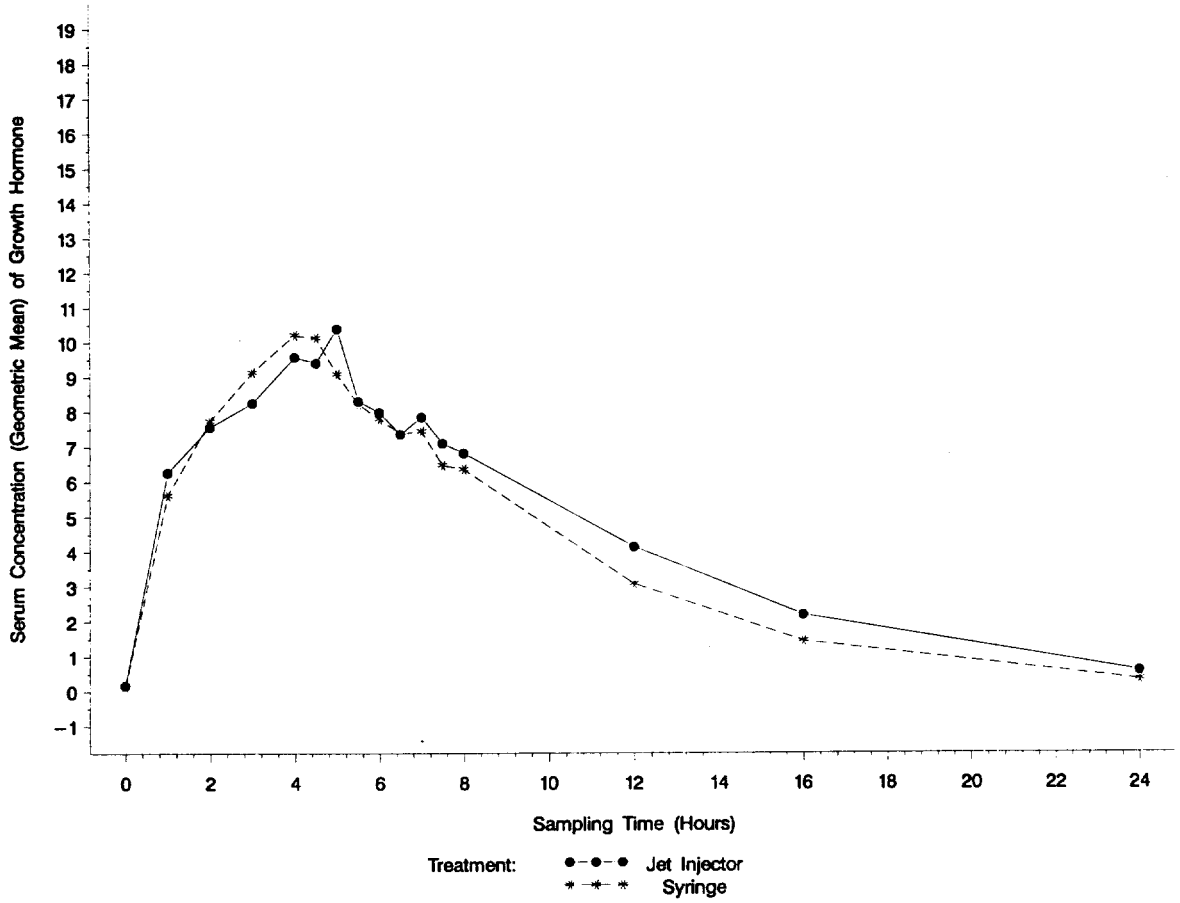
Clinical studies included a randomized crossover pharmacokinetic, pharmacodynamic study comparing a conventional needle injection to Clicker™. A second study evaluated the acceptability of the needle-free device following a single jet-injection compared to needle injection in 29 children (ages 12-18), with Type I diabetes mellitus. The children with diabetes mellitus were taking daily or more frequent insulin needle injections for a period of one to five years. Two separate clinical studies were completed on 21 adults and 29 children.

PHARMACOKINETIC AND PHARNACODYNAMIC CYNAMIC STUDIES IN ADULTS

A randomized, single–dose, two-way crossover relative bioavailability study of Saizen® administered subcutaneously by needle or needle–free device in normal

healthy adult subjects (ages 18- 40 years) was completed to determine bioequivalence between the conventional subcutaneous needle injection of GH and GH administered using a needle-free device. Statistical bioequivalence analyses were based on 21 subjects. In the clinical pharmacokinetic study, the measured GH levels from subjects using the needle injection and the needle-free device were similar during the entire 24 hours of blood monitoring. (Figure 1)

Figure 1



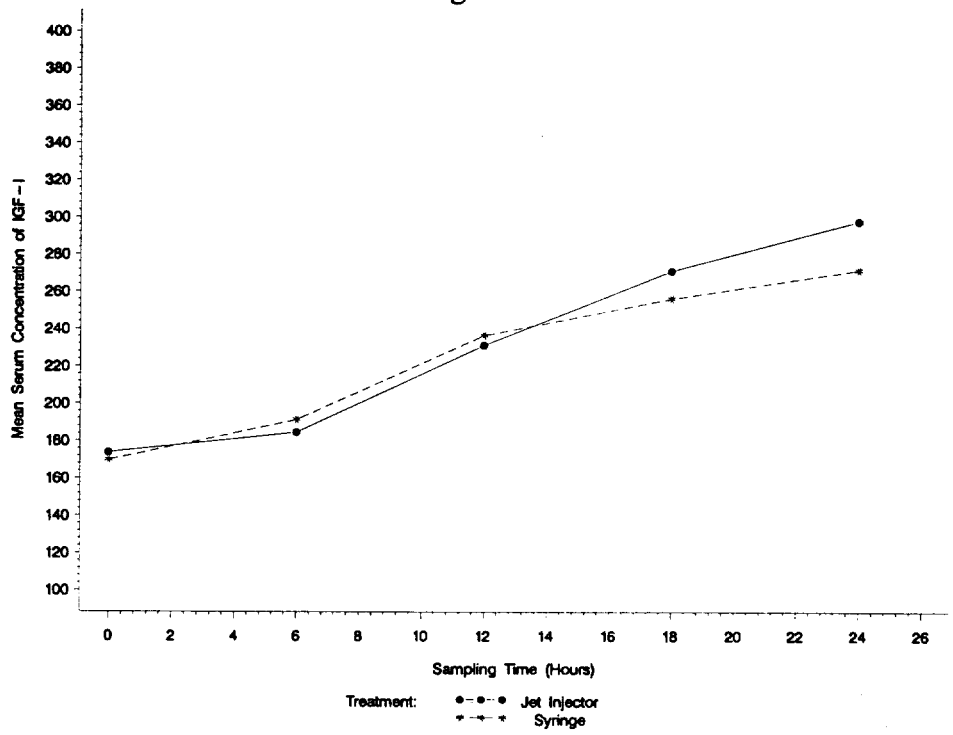
The maximum concentration of GH and the peak time for the maximum GH concentration were also not statistically different. The data for AUC, $AUCt_{last)}$ and C_{max} were log transformed prior to analysis. The data for t_{max} and $t_{1/2}$ were assessed for adherence to assumptions. For $AUC_{t\ last,}$ the 90 % confidence interval for the ratio of test to reference expressed, as a percentage was (0.95, 1.12) falling within the (80%, 125%) interval required for bioequivalence as specified in the protocol. For C_{max} the 90 % confidence interval for the ratio of test to reference expressed as a percentage was (0.81, 1.20), falling within the (80%, 125%) interval required for bioequivalence as specified in the protocol.

For untransformed $t_{max,}$ the p-values associated with the Shapiro-Wilks tests of normality were not statistically significant for intrasubject error (p = 0.428) and

intersubject error (p = 0.857). The test for formulation differences between the reference formulation and the test formulation $t_{max,}$ was not statistically significant (p = 0.523). Period effects were also not statistically significant (p = 0.472).

The serum IGF1 values measured every six hours for 24 hours after injection were very similar when comparing both the needle and needle-free device. (Figure 2) After log transforming the data, the p-values for the Shapiro-Wilks test of normality for both the intrasubject and intersubject error were not significant (p = 0.840 for intrasubject error, p = .0599 for intersubject error).

Figure 2



Analog scales were developed to evaluate drug penetration of the skin, bleeding and bruising immediately after injection, thirty minutes after injection and twenty-four hours after injection. Inspections of these count data suggested that there was no statistically significant difference between both treatments (needle vs. needle- free) with respect to the number of subjects injected and events at various time points (0, 30 minutes and 24 hours after injection).

There were no serious adverse events or deaths in this study and no subjects withdrew prematurely from the study. The mild adverse reactions that were reported did not appear to be device related.

The adult questionnaire (ages 18-40 years) indicated a trend toward less pain with the jet-injector (p = 0.093). However, the response to specific questions relating to "ease of use" (p = 0.017), " convenience" (p = 0.004), "pleasantness" (p = 0.011), " less

apprehension" ($p = 0.0110$ and "overall preference" ($p = 0.053$) showed a highly significant preference for the needle-free jet-injector over the conventional needle injection.

QUESTIONNAIRES IN CHILDREN WITH TYPE I DIABETES MELLITUS

Twenty-nine adolescents with one to five years of insulin dependent diabetes mellitus were asked to compare a single, self-administered needle-free dose of saline with the previous six months of needle injections of insulin. Questionnaires were administered shortly after their needle-free injection. The questionnaires in the group of 29 adolescents with Type I diabetes mellitus (ages 12-18 years) demonstrated highly significant differences relating to both "pain" and "unpleasantness" favoring the needle-free jet-injector over needle injections. The subjects chose the needle as the method that would hurt more by a count of 22 to 7. This confirmed the level of pain data and was again highly significant, $p < 0.01$. The needle-free device was chosen as more pleasant to use by a 22 to 7 ratio ($p < 0.01$). However, in this population, there was no significant difference between the needle-free device and the needle injections in regard to "convenience" or "ease of use". The adolescent group also found that the first needle-free jet-injection made them significantly more nervous than their familiar needle injection.

SUMMARY

In summary, both clinical studies suggest that the needle-free device is easier to use, convenient, more pleasant and generally less painful than conventional needle injection. The adult study demonstrated a clear preference for the needle-free device over needle injection. Measurements of GH and IGF-1 hormone levels demonstrated bioequivalence between needle and needle-free delivery of growth hormone.

The Center for Disease Control in the United States clearly favors the use of needle-free injections to reduce the incidence of Hepatitis B, C, and HIV infection as well as to diminish the pain from needle injection. This new technology is rapidly replacing conventional needle therapy. In recent years, a number of safety features have been devised for the needle and syringe to reduce occupational hazards and associated costs. Needle-free injection is an alternative method that does not require a needle and its wide spread use should reduce the incidence of contagious infections related to needles and at the same time reduce the environmental burden that needle disposal poses on a nation.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUN 22 2000

Ms. Nancy J. Gertlar
Manager, QA/RA
Bioject, Incorporated
7620 SW Bridgeport Road
Portland, Oregon 97224

Re: K994384
Trade Name: Clicker
Regulatory Class: II
Product Code: KZE
Dated: April 11, 2000
Received: April 12, 2000

Dear Ms. Gertlar:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Good Manufacturing Practice for Medical Devices: General (GMP) regulation (21 CFR Part 820) and that, through periodic GMP inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4692. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html".

Sincerely yours,

Timothy A. Ulatowski
Director
Division of Dental, Infection Control,
and General Hospital Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

510(k) Number (if known): new submission

Device Name: Clicker™

Indications for Use:

- This product is indicated for use with Saizen® [somatropin (rDNAorigin) for injection] for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone.

Contraindications:

This product is not recommended for patients:

- Who are visually impaired,
- Who have neuromuscular or arthritic conditions which would make winding the Clicker™ difficult,
- Who are not able to understand and follow the procedure for safe use of the device,
- Who bruise or bleed easily, or are taking anti-coagulant medication (blood thinners), or any other medication or therapy which may contribute to excess bleeding or bruising after injections,
- Who are not willing to fully comply with the procedures of use of the device and with the recommended frequency for replacement of the disposable accessories,
- Where Saizen® [somatropin (rDNAorigin) for injection] is contraindicated for treatment of that patient.

(PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Dental, Infection Control,
and General Hospital Devices
510(k) Number K994384

Prescription Use ✓ OR Over-The-Counter Use ____
(Per 21 CFR 801.109)