SGS DNA Response to [Docket No. 01D-0286] Draft Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays (Published in Federal Register: August 29, 2001)

01 OCT 29 A9:45

Scandinavian Gene Synthesis AB
Jarnvagsgatan 11, 731 30
Koping, Sweden
Tel no.: +46-(0)221-216 40
Fax no.: +46-(0)221-148 99

October 26, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
USA

Re: [Docket No. 01D-0286] Draft Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays (Published in Federal Register: August 29, 2001)

Dear Madam or Sir:

SGS DNA and company are pleased to have the opportunity to provide comments on the Draft Guidance for Industry on Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays.

We applaud the FDA and Center for Biologics Evaluation and Research for developing the Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays Guidance and recognize the effort by CBER to produce such a comprehensive document.

There are some issues upon which we wish to comment. We hope that these comments will result in revisions that will make the guidance more encompassing. We would encourage the FDA to utilize a forum for industry inputs prior to issuing draft guidance's.

To facilitate FDA review, our attachments are divided into three parts: (1) An Introduction to SGS DNA, (2) A Brief Overview of the Genetic Testing Industry, and (3) Comments on the "Draft Guidance for Industry on Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays".

Please feel free to contact me at 310.467.2986 or Jonas Lundqvist at +46-(0)221-216 40 for clarification of any comments or concerns.

Thank you for your time,

Bluegrass Biggs, Ph.D.
Regulatory Affairs, Consultant

01D-0286 C4

Address
Scandinavian Gene Synthesis AB
Box 91
S-731 22 Köping
SWEDEN

E-mail address
info@sgsdna.com
Internet
http://www.sgsdna.com

Telefax
+46 (0)221-148 99
Telephone
+46 (0)221-216 40, adm.
+46 (0)221-288 10, lab.

Org. No
556378-5046
VAT No
SE556378-504601

SGS DNA Response to [Docket No. 01D-0286] Draft Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays (Published in Federal Register: August 29, 2001)

INTRODUCTION: SCANDINAVIAN GENE SYNTHESIS AB (SGS DNA), A MANUFACTURER OF HIGH QUALITY OLIGONUCLEOTIDES.

We would like to describe briefly our background and position in the scientific community.

SGS DNA has manufactured high quality synthetic oligonucleotides since 1990. The founder, Sune Kvist, Ph.D., gained extensive experience of DNA synthesis from prominent medical and molecular biology research institutes such as the European Molecular Biology Laboratory (EMBL, Heidelberg), the Swiss Institute for Cancer Research (Lausanne), and the Ludwig Institute for Cancer Research at the Karolinska Institute (Stockholm). The scope of SGS DNA has always been the manufacture of synthetic DNA and RNA, and derivatives thereof.

SGS DNA's expertise is in the manufacture and purification of high purity oligonucleotides. Although molecular biological methods used in genetic testing may work with primers and probes of low purity, the high level of purity that SGS DNA provides is essential when it comes to diagnostics, where "may work" is not acceptable. SGS DNA utilizes several proprietary methods for the manufacture, purification and analysis of synthetic oligonucleotides to achieve the highest possible levels of purity.

SGS DNA's customers are scientists, researchers, hospitals, laboratories, major pharmaceutical and diagnostic companies around the world, which all have realised the importance of high quality oligonucleotides. Since 1995 SGS DNA has provided synthetic oligonucleotides to market leading manufacturers of diagnostic kits. SGS DNA manufactures synthetic oligonucleotides according to customer specifications and requirements (sequence, modifications, batch size, purity).

As a manufacturer of high quality oligonucleotides SGS DNA follows the Quality System Regulation and are registered at the FDA (FDA Registration No. 9276027) in order to provide the US market with Class I Analyte Specific Reagents (ASR). Oligonucleotides (including ASR's) are manufactured according to customer specifications. Customers requiring ASR's have extensive quality requirements for their oligonucleotides, such as dedicated HPLC Columns, Processing in Laminar Flow Hoods, and Effective Change Over Protocols. These methods ensure the customer receives the highest quality oligonucleotides.

Today SGS DNA is proud to be the supplier of synthetic oligonucleotides to more than ten diagnostic kit manufacturers and laboratories, including companies performing HIV and HCV In-Vitro testing under FDA Licensure in the United States.

Address
Scandinavian Gene Synthesis AB
Box 91
S-731 22 Köping
SWEDEN

E-mail address
info@sgsdna.com
Internet
http://www.sgsdna.com

Telefax
+46 (0)221-148 99
Telephone
+46 (0)221-216 40, adm.
+46 (0)221-288 10, lab.

Org. No
556378-5046
VAT No
SE556378-504601

SGS DNA Response to [Docket No. 01D-0286] Draft Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays (Published in Federal Register: August 29, 2001)

A BRIEF OVERVIEW OF THE "GENETIC TESTING INDUSTRY" FROM THE PERSPECTIVE OF SGS DNA

The scenario outlined below is an example of the typical development of a "genetic test", from research to final use. The focus is kept on steps relevant to oligonucleotide manufactures.

Company "X", a manufacturer of diagnostic kits, decides to launch a new kit or method on the market in order to detect or diagnose disease "Y". The research department at "X" searches databases for and determines suitable nucleotide sequences to be used as primers and probes to detect "Y". The oligonucleotides are designed, manufactured and tested "in house". Based on molecular biological testing the research department will select a number of nucleotide sequences that are relevant for the detection or diagnosis of "Y". The following steps are to design a diagnostic kit or method that fulfils all relevant quality requirements.

Based on the determined nucleotide sequences, "X" will require primers and probes that fulfill applicable quality requirements on a routine basis. Company "X" neither have the capability, nor the necessary expertise to manufacture synthetic oligonucleotides of the quality required for a diagnostic kit or method. Company "W", a manufacturer of high-quality oligonucleotides, has the expertise and the knowledge to manufacture these synthetic oligonucleotides.

It might seem unusual that "W" manufactures oligonucleotides of higher quality than "X", who designed the sequences, even if "W" has not manufactured that sequence previously. The explanation is, in contrast to the conventional pharmaceutical industry, the design and manufacture of synthetic oligonucleotides constitute two completely separate processes. The answer to this difference lies in the complexity and the simplicity of DNA.

DNA is complex when considering the number of permutations that a random nucleotide sequence can possess. The number of permutations for a 20-mer (oligonucleotide with 20 nucleotides) are 4^{20} or one *thousand billion*, where 4 is the number of possible nucleotides at each position and 20 is the length of the oligonucleotide. The number of permutations is further increased when considering every possible length from a 10-mer to a 40-mer, and if we include possible modifications and derivatives, the end result is immense. This variability is the key to the specificity of the oligonucleotide as an Analyte Specific Reagent. The variability also displays the importance of correct design of the oligonucleotide sequence; sequences that have been chosen wisely will have the utmost specificity.

The simplicity of DNA lies in the fact that the basic chemistry in manufacturing an oligonucleotide is consistent, independent of sequence. As a result, sequence variability is a negligible factor in the manufacture of oligonucleotides.

Simplicity also plays a role during purification of oligonucleotides, and purity is essential when using oligonucleotides for diagnostic purposes. Chemical and physical properties (hydrophobicity, size, net charge) of DNA are utilised during purification. Oligonucleotides can then be grouped according to similar chemical and physical properties, resulting in the use of a limited number of purification methods to purify oligonucleotides of different sequences. This enables "W" to purify an oligonucleotide with a previously qualified/validated method, and not have to develop then validate a "new" purification method for every unique oligonucleotide.

After successful production, purification, and delivery, of the ordered oligonucleotide from "W", "X" is able to begin testing the newly developed kit or test to detect or diagnose "Y".

To conclude, companies involved in the genetic testing industry work together in developing methods and techniques to benefit the health care industry. Companies such as SGS DNA specialize in the manufacture and purification of oligonucleotides, while other companies specialize in the development of kits and tests that utilize oligonucleotides to detect or diagnose disease. Working together, specialized companies can produce higher quality, more reliable and more efficient products.

Address
Scandinavian Gene Synthesis AB
Box 91
S-731 22 Köping
SWEDEN

E-mail address
info@sgsdna.com
Internet
http://www.sgsdna.com

Telefax
+46 (0)221-148 99
Telephone
+46 (0)221-216 40, adm.
+46 (0)221-288 10, lab.

Org. No
556378-5046
VAT No
SE556378-504601

SGS DNA Response to [Docket No. 01D-0286] Draft Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays (Published in Federal Register: August 29, 2001)

COMMENTS:

ANALYTE SPECIFIC REAGENTS

Page 2, Last Paragraph, "We consider commercially distributed ASRs used in genotyping systems to detect HIV mutations to be class III devices requiring premarket approval"

Our interpretation of the current draft guidance language is that ASR synthetic oligonucleotides supplied to diagnostic "kit" manufactures and diagnostic testing facilities performing In Vitro HIV assays would be classified as Class III devices requiring premarket approval. This would require that SGS DNA, solely without any assistance from the final user, shall provide evidence, by extensive pre-clinical and clinical testing, that the primer(s) we distribute can be used to detect, in this case, HIV. Such evidence should also include HOW the primer can be used to detect HIV. That would require that SGS DNA: names, specifies and distributes all reagents; defines procedures for sampling; defines procedures for how to perform the test; establishes limits of detection for the test and more. These specifications must be thoroughly tested, examined, documented and proven by scientific evidence.

We feel the responsibility for fulfilling these requirements is held by the company manufacturing a "kit" or performing diagnostic testing. SGS DNA makes no claims or market for use of synthetic oligonucleotides.

We recommend the distinction be made or clarification added to differentiate between the suppliers of "ingredients" that do not market or make claims for use and the end users that use these "ingredients" to make claims of use and market.

We recommend explanation/clarification of the regulatory differences pertaining to manufactures that produce crucial components (oligonucleotides) and supply them to manufactures of FDA approved "kits" as an "ingredient" but do not produce the "kits" themselves, be added.

We recommend differentiation between supplying an ASR to a "kit" producer and supplying an ASR to a FDA licensed laboratory that performs diagnostic testing, but does not use a "kit", be explained.

PRIMERS AND PROBES:

Page 10 Section 8, Reagent Characterisation, Reference 4 "Guidance In the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Nucleic Acid Sequences of Human Immunodeficiecy Virus Types 1 and 2".

"If synthetic oligonucleotides are used as primers and probes, details of the manufacture and purification should be provided. In addition, the following information should also be included:

4. **The yield and composition for the first 3 lots (at a minimum) by absorbance and DNA fingerprinting, restriction endonuclease mapping or nucleotide sequence analysis;**
5. **A description of the chemical nature of the modification, for modified oligonucleotides and procedure(s) to insure lot to lot consistency of ligand content;**
6. **Nucleotide sequence analysis to establish the fidelity of the procedure for oligonucleotide synthesis;**
7. **The purity of the final product should be analysed by an appropriate state-of-the art analytical technique (e.g., reverse phase high performance liquid chromatography, electrophoresis or ion exchange HPLC), that has been validated according to ICH guidelines;**

Address	E-mail address	Telefax	Org. No
Scandinavian Gene Synthesis AB	info@sgsdna.com	+46 (0)221-148 99	556378-5046
Box 91	Internet	Telephone	VAT No
S-731 22 Köping	http://www.sgsdna.com	+46 (0)221-216 40, adm.	SE556378-504601
SWEDEN		+46 (0)221-288 10, lab.	

8. **Potency of primers and probes. This may be addressed by dilutional analysis comparing lot-to-lot consistency in functional efficiency or other methodology appropriate to the technology under development.**

The analyses listed in 6-8 should be conducted on each lot of oligonucleotides manufactured as a routine part of new product development and characterisation. If a high degree of consistency is demonstrated over time the sponsor may request a reduction in the frequency of required monitoring."

Item 4:

Increased clarification is required of the quality testing requirements for synthetic single stranded DNA (primers) distributed to companies performing In-Vitro HIV testing. The methods referenced in "Guidance In the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Nucleic Acid Sequences of Human Immunodeficiecy Virus Types 1 and 2" are not applicable to single stranded, short ("20 bases) DNA. Expanded below.

a) "DNA fingerprinting" also known as "DNA typing", is a technique that is most commonly used when comparing two samples of heterogeneous double stranded genetic material. With this technique a sample is amplified by PCR (double stranded DNA) using other primers, digest the amplified sample with restriction enzymes and separate by gel electrophoresis (difficult to achieve single base resolution). The resulting gel is then compared against a gel with the other sample, or a reference sample.

b) Restriction endonuclease mapping is a technique that neither can be used on single stranded, short DNA.

c) Nucleotide sequence analyses will neither work since the essential PCR-reaction will not work due to reasons described above under item a).

d) Nucleotide sequence analysis with Mass Spectrometry (MS) is possible, however MS for nucleotide sequencing is a novel technique.

Item 8:

Item number eight states that the functionality of each separate batch shall be tested for its intended purposes. This can only be done by the final user, since only they have full access to the intended application.

Final Paragraph

The final paragraph contains the phrases "new product development" and "consistency over time". We suggest clarification be added to include situations where primer/probes are not manufactured for extended time periods or manufactured in single batches where long production history is not available.

APPRECIATIONS:

We would like to extend our thanks and appreciation to the reviewer(s) for taking the time to review and consider SGS DNA's comments to the draft document [Docket No. 01D-0286] Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays (Published in Federal Register: August 29, 2001).

Address
Scandinavian Gene Synthesis AB
Box 91
S-731 22 Köping
SWEDEN

E-mail address
info@sgsdna.com
Internet
http://www.sgsdna.com

Telefax
+46 (0)221-148 99
Telephone
+46 (0)221-216 40, adm.
+46 (0)221-288 10, lab.

Org. No
556378-5046
VAT No
SE556378-504601

FedEx Express **USA Airbill** FedEx Tracking Number **8284 1644 6236**

Form ID No. **0200** **Recipient's Copy**

1 From

Date 10.26.01

Sender's Name Thomas Biggs Phone 310 467 1486

Company Commercial Finance Corp

Address 523 South Lake Ave Suite #6 Dept./Floor/Suite/Room

City Pasadena State CA ZIP 91101

2 Your Internal Billing Reference

3 To

Recipient's Name Rockets Management Branch Phone

Company Federal Drug Administration (HFA-305)

Address 5630 Fishers Lane, Rm 1061

To "HOLD" at FedEx location, print FedEx address. We cannot deliver to P.O. boxes or P.O. ZIP codes.

Dept./Floor/Suite/Room

City Rockville State MD ZIP 20852

8284 1644 6236

4a Express Package Service — *Packages up to 150 lbs.* Delivery commitment may be later in some areas.

- [x] FedEx Priority Overnight — Next business morning
- [ ] FedEx Standard Overnight — Next business afternoon
- [ ] FedEx First Overnight — Earliest next business morning delivery to select locations
- [ ] FedEx 2Day — Second business day
- [ ] FedEx Express Saver — Third business day
- [ ] **NEW** FedEx Extra Hours — Later drop-off with next business afternoon delivery for select locations

FedEx Envelope rate not available. Minimum charge: One-pound rate

4b Express Freight Service — *Packages over 150 lbs.* Delivery commitment may be later in some areas.

- [ ] FedEx 1Day Freight* — Next business day
- [ ] FedEx 2Day Freight — Second business day
- [ ] FedEx 3Day Freight — Third business day

* Call for Confirmation: * Declared value limit $500

5 Packaging

- [x] FedEx Envelope*
- [ ] FedEx Pak* — Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
- [ ] Other Pkg. — Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling — Include FedEx address in Section 3.

- [ ] **SATURDAY Delivery** — Available only for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
- [ ] **SUNDAY Delivery** — Available only for FedEx Priority Overnight to select ZIP codes
- [ ] **HOLD Weekday** at FedEx Location — Not available with FedEx First Overnight
- [ ] **HOLD Saturday** at FedEx Location — Available only for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.

- [x] No
- [ ] Yes — As per attached Shipper's Declaration
- [ ] Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg
- [ ] Cargo Aircraft Only

Dangerous Goods (incl. Dry Ice) cannot be shipped in FedEx packaging or with FedEx Extra Hours service.

7 Payment *Bill to:* Enter FedEx Acct. No. or Credit Card No. below. Obtain Recip. Acct. No.

- [x] Sender — Acct. No. in Section 1 will be billed.
- [ ] Recipient
- [ ] Third Party
- [ ] Credit Card
- [ ] Cash/Check

Total Packages	Total Weight	Total Declared Value†	Total Charges
		$ .00	Credit Card Auth.

†Our liability is limited to $100 unless you declare a higher value. See back for details.

8 Release Signature *Sign to authorize delivery without obtaining signature.*

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

Questions? Visit our Web site at fedex.com or call 1-800-Go-FedEx® (800)463-3339.

Rev. Date 12/00 • Part #155915 • ©1994–2000 FedEx • PRINTED IN U.S.A. GBFE 3/01

404