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Discontinuity in the Unitage for HuIFN α -N1 (Human Lymphoblastoid IFN)

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**The Second International Standard For Lymphoblastoid
Interferon- α , 95/568
Second Evaluation studies in Japan in 2002**

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Mochida Pharmaceutical Co., Ltd.
Otsuka Pharmaceutical Co., Ltd.
Sumitomo Pharmaceuticals Co., Ltd.**

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The Second International Standard For Lymphoblastoid Interferon- α , 951568 Second Evaluation studies in Japan in 2002

Introduction

In our previous study, four Japanese companies assayed J-501, National Standard For Lymphoblastoid Interferon-a (the assigned **unitage** is 6500IU/ampoule against Ga23-901-532), against the Second International Standard For Lymphoblastoid Interferon-a, 951568.

Four companies have been using J-501 for a long time since their Interferon products were launched in Japan.

In the study, Sumitomo obtained the lowest average figure, **4,680IU/ampoule** (72% of the assigned **unitage**, 6,500IU/ampoule). Hayashibara obtained the highest average figure, **5,455IU/ampoule** (83.9% of the assigned **unitage**) but still apparently lower than the assigned **unitage**, 6,500IU/ampoule.

Otsuka and Mochida obtained the average figures, **5,000 IU/ampoule** (76.9% of the assigned **unitage**) and **5,070 IU/ampoule** (78.0% of the assigned **unitage**) respectively. The average of the four companies results was **5051IU/ampoule** (77.7% of the assigned **unitage**).

The result indicates that the assigned **unitage** of 95/568, **38,000IU/ampoule**, is too low and this **unitage** can not be accepted in Japan.

Similar findings were observed for the first International Standard, Ga23-901-532 when we assayed Ga23-901-532 against 951568.

To confirm the reproducibility of these findings, using more ampoules of these standards, the second evaluation studies were conducted by the same four Japanese companies who participated in the first studies with the consultation of National Institute of Infectious Diseases.

Materials and methods:

Standards

Three ampoules of Ga23-901-532 (25,000IU/ampoule) were obtained from National Institute of Allergy and Infectious Diseases (NIAID), and one ampoule was sent to Mochida, Otsuka and Sumitomo. Three ampoules of 95/ 568 (38,000IU/ampoule) were obtained from WHO, and one ampoule was sent to Mochida, Otsuka and Sumitomo.

Six ampoules of J-501 (6,500IU/ampoule) were obtained from National Institute of Infectious Diseases (NIID, former Japanese NIH) and two ampoules were sent to Mochida, Otsuka and Sumitomo.

These ampoules were reconstituted by 1mL purified water, diluted by 10% FCS containing Eagle-MEM and frozen at Mochida, Otsuka and Sumitomo. The first diluted standard solutions of 95/568, J-501 and Ga23-901-532 contained interferon 760IU/mL, 260IU/mL and 500IU/mL respectively.

These solutions prepared at one company were sent to the other three companies with dry ice, for example, the solutions prepared at Sumitomo were sent to Mochida, Otsuka and Hayashibara.

The four companies individually prepared the second diluted standard solutions which contained interferon about 30IU/mL and froze these solutions until bioassay was conducted.

Bioassay

All four companies used FL cell-Sindbis virus bioassay system which was established by NIID.

Both FL cell and Sindbis virus were provided to the each company from NIID separately, cultured by each company and used for bioassay. Each company conducted 3 or 4 independent assays and each assay gave 4 or 6 data.

Results

The assay results from each company were summarized in table 1 and 2.

The assay results of 95/568 against J-501 show that the **unitages** of 95/568 against J-501 from all four companies are much higher than the labeled **unitage**, 38,000IU/ampoule. Sumitomo gives the highest figure, **52,500±2216/ampoule** and Hayashibara gives the lowest figure, **46,765±1024IU/ampoule** but still higher than its assigned **unitage**, 38,000IU/ampoule. Similar finding was observed on the assay results of 95/568 against Ga23-901-532. Sumitomo gives the highest figure **42,156±1403IU/ampoule**, and Hayashibara gives the lowest figure, **38,606±757IU/ampoule**.

Discussion

In our previous study, we found that the **unitage** of 95/568 against J-501 was higher than the WHO assigned **unitage** 38,000 IU/ampoule, and all four companies gave higher figures of 95/568 than its assigned **unitage**. We also found that Hayashibara gave the lowest figure, **45,280IU/ampoule** and Sumitomo gave the highest figure, **52,778IU/ampoule**. In addition we also found that the **unitage** of 95/568 against Ga23-901-532 was higher than the WHO assigned **unitage**. All four companies gave higher figures than its assigned **unitage**, and Sumitomo gave the highest figure, 118%.

In this second study, we confirmed that these findings are reproducible.

The reason of this higher figure is that **38,000IU/ampoule** was assigned based on the assay results from V₃ monkey kidney cells and Semliki Forest Virus assay system conducted by Glaxo Wellcome. In general, different assay systems give different assay results even on the same sample although the same standard is used.

Two studies strongly indicate that the assigned **unitage** of the 951568, **38,00IU/ampoule**, is not acceptable in Japan considering the consistency of the **unitage** of the natural interferon- α products in Japan,

In order to maintain the continuity of the **unitage** for this type of interferon, two ways could be discussed. One is to carry out further collaborative assay studies in which the four Japanese companies would take part, and so derive a new value for 951568, which would maintain continuity of the **unitage** with the 1st International Standard. The other way is to reinstate the 1st International Standard, Ga23-901-532, as an easier and more reliable way of solving the **unitage** problem than to try to derive a new and acceptable potency to be assigned to the 2nd International Standard.

Reference

The Second International Standard For Lymphoblastoid Interferon-0,951568
Evaluation studies in Japan in 2001

Table I Assay result of 951568 against J-501

ALL DATA POOLED

Company	95/568		
	n	Titre (IU/ampoule)±S.D.	% of label
HAYASHIBARA	162	46,765 ± 1024	123.1
OTSUKA	162	50,561 ± 1545	133.1
MOCHIDA	162	53,022 ± 1709	139.5
SUMITOMO	144	52,500 ± 2216	138.2
AVERAGE		50,712	133.5

1ST DILUTION PREPARED BY MOCHIDA

Company	95/568		
	n	Titer (IU/ampoule)±S.D.	% of label
HAYASHIBARA	18	46,573 ± 3230	123
OTSUKA	18	51,625 ± 3270	136
MOCHIDA	18	53,600 ± 5070	141
SUMITOMO	16	52,500 ± 2068	138

1ST DILUTION PREPARED BY OTSUKA

Company	951568		
	n	Titer (IU/ampoule)±S.D.	% of label
HAYASHIBARA	18	46,684 ± 3475	123
OTSUKA	18	49,042 ± 2490	129
MOCHIDA	18	53,000 ± 3900	139
SUMITOMO	16	50,100 ± 1651	132

1ST DILUTION PREPARED BY SUMITOMO

Company	95/568		
	n	Titre (IU/ampoule)±S.D.	% of label
HAYASHIBARA	18	46,796 ± 3599	123
OTSUKA	18	49,831 ± 2810	131
MOCHIDA	18	51,300 ± 2650	135
SUMITOMO	16	52,500 ± 1500	138

**Table 2 Assay result of 95/568 Against Ga23-901-532
ALL DATA POOLED**

Company	95/568		
	n	Titer (IU/ampoule)±S.D.	% of label
HAYASHIBARA	162	38,606±757	101.6
OTSUKA	162	41,114±980	108.2
MOCHIDA	162	42,011±997	110.6
SUMITOMO	144	42,156±1403	110.9
AVERAGE		40,972	107.8

1ST DILUTION PREPARED BY MOCHIDA

Company	95/568		
	n	Titer (IU/ampoule)±S.D.	% of label
HAYASHIBARA	18	38,576±1598	102
OTSUKA	18	40,836±2841	107
MOCHIDA	18	41,700±2920	110
SUMITOMO	16	44,700±2114	118

1ST DILUTION PREPARED BY OTSUKA

Company	95/568		
	n	Titer (IU/ampoule)±S.D.	% of label
HAYASHIBARA	18	38,862±1566	102
OTSUKA	18	40,886±1939	108
MOCHIDA	18	43,000±2440	113
SUMITOMO	16	41,700±1753	110

1ST DILUTION PREPARED BY SUMITOMO

Company	95/568		
	n	Titer (IU/ampoule)±S.D.	% of label
HAYASHIBARA	18	38,885±3427	102
OTSUKA	18	40,736±1885	107
MOCHIDA	18	40,500±2700	107
SUMITOMO	16	40,700±2809	107

[Reference]

Assay results from our previous study “The Second International Standard For Lymphoblastoid Interferon- α , 95/568 Evaluation studies in Japan in 2001” page 12.

Table 6 Calculated unitage of 95/568 both against Ga23-901-532 and J-501

COMPANY	against Ga23-901-532		95/568 against J-501	
	n	IU/AMPOULE	n	IU/AMPOULE
HAYASHIBARA	18	40,329	18	45,280
OTSUKA	18	42,930	18	49,400
MOCHIDA	18	43,578	18	48,718
SUMITOMO	16	47,619	16	52,778
		% OF LABEL		% OF LABEL
		106		119
		112		130
		114		128
		118		139

These data were calculated from the date reported in table 5.
All data of 95/568 were much higher than the assigned figure, 38,000IU/ampoule.

**Meeting of the Standards Committee of the
International Society of Interferon and Cytokine Research
Sunday, 6 October 2002
Torino, Italy**

Attendees

Guido Antonelli*, Ronald Bordens*, Norman Finter*, Kenji Harada, Wendy Jones*, Yoshimi Kawade, Masayoshi Kohase*, Aida Prync*, Shingou Sakurai, Louis Westreich, and Sidney Grossberg* (Chairman)

Dr. Grossberg opened the meeting at 1415 hours and asked the attendees to introduce themselves and state their affiliations. Drs. Ron Bordens and Lou Westreich agreed to take the minutes of the meeting. Additional copies of the agenda and its attachments were distributed to those who had not received them.

1. Old Business

At its last meeting in Cleveland (7 October 2001) the Committee had agreed to forward to the World Health Organization (WHO) its recommendation to establish **as** a common unit for expressing neutralizing antibody potency the Ten-fold Reduction Unit (TRU), to be presented possibly at the next meeting of the WHO Informal Consultation on Standards for Cytokines, Growth Factors, and Endocrinological Substances. However, no meeting of that consultation group has been held. It was recently announced that Dr. Elwyn Griffith, Head of the Biologics Division at WHO, had retired 30 September 2002, and no replacement has been named. It was suggested that the recommendation could be sent to the WHO Expert Committee on Biological Standardization (ECBS) but the annual meeting, usually scheduled in October, has been deferred, possibly until spring 2003. It was agreed that the Committee recommendation regarding neutralization **unitage** be prepared so that it can be brought to ECBS at its next meeting, the time of which was to be determined.

2. Approval of Minutes

The minutes of the previous Committee meeting on 7 October 2001 in Cleveland, Ohio were approved as distributed.

3. Update on the Interferon-beta International Collaborative Study

The circumstances of the current WHO interferon-beta international collaborative study were briefly reviewed, as summarized by Dr. Tony Meager of NIBSC in last year's Standards Committee meeting minutes. In the first phase study, 17 laboratories had assayed six different IFN-beta preparations, including current WHO International Standards (I.S.) and new candidate I.S. preparations. This study was stopped in 1999 because of concerns about the stability of reconstituted preparations. The second phase study was begun when it was shown that formulation with human serum albumin and bovine casein resolved the instability problems. The second study included four new candidate IFN-beta standard preparations prepared at NIBSC

along with the two existing I.S. as well as the Japanese national standard for IFN-beta and a reference preparation from the first phase, for a total of ten samples. The data from the 16 participating laboratories had been received by NIBSC for analysis by the end of August 2002 and included antiviral assays from 12 laboratories, antiproliferative assays from four laboratories, and reporter gene assays from three laboratories. Wendy Jones noted that the reporter gene assay does not give the same relative results from one preparation to another as the antiviral assay. Dr. Prync felt that it was very important to have the analyses undertaken according to types of assays as well as by other parameters, for which there was general agreement. Dr. Grossberg indicated that Dr. Meager had generously agreed to send to him the raw data from the second phase study for statistical analysis, primarily of dose-response curve slopes. Dr. Meager had informed Dr. Grossberg that the data from the participating laboratories on the 10 IFN-beta preparations in this second phase study had indeed been received by NIBSC, but the analysis of the data has been assigned a relatively low priority for processing and therefore would be delayed for an undetermined period. There was considerable discussion about the urgent need by the pharmaceutical industry to have the results analyzed and shared by the participating laboratories with appropriate prior consultation so that the ECBS could be provided at its next meeting a consensus report with data analysis and recommendations regarding IFN-beta standardization.

The question was raised during discussion whether ECBS can receive input from international scientific societies, and Dr. Grossberg commented that when he was an *ad hoc* member of ECBS, the advice from an international hematological society presented to ECBS was well received, seriously considered, and formed the basis for a recommendation. Ron Bordens suggested that financial support to NIBSC from industry might advance the proposed analysis of data to a much earlier completion time, a suggestion which was favored by the Committee.

It was moved, seconded, and unanimously approved that the ISICR Standards Committee petition the NIBSC to process the data and produce a report for distribution and review by the study participants at the earliest possible time, preferably by 31 December 2002.

4. Issues concerning the International Standards for Human Lymphoblastoid Interferon

Dr. Norman Finter had detailed in a document, circulated with the agenda to the members of the Committee, concerning the problem of discontinuity in the **unitage** for human lymphoblastoid interferon (HuIFN-alphaN1). Dr. Finter reported that this type of interferon is now only made by four companies in Japan, namely, Hayashibara, Mochida, Otsuka, and Sumitomo. These companies have for several years issued their products for clinical use in containers labeled with their interferon content in International Units (I.U.) as standardized against the 1st I.S. for **HuIFN-alphaN1**, labeled **Ga23-901-532**. For reasons that regrettably have not been recorded (see below), the ECBS withdrew this standard in 1999 and replaced it with a 2nd I.S., code 951568, with an assigned potency of **38,000 I.U. per ampoule**. This value was derived from analysis of the data obtained for the 1st I.S. and 951568 in a very large international assay study in 1997 and two adjunct studies, including one by the International Federation of Pharmaceutical Manufacturers in which **Wellcome** participated as a major producer; **Wellcome**

no longer produces IFN- α N1. Unfortunately, the four Japanese manufacturers of lymphoblastoid interferon have found in two collaborative studies a discrepancy of approximately 30% between the units defined by the 1st and 2nd I.S.

The Committee discussed two ways in which continuity in the **unitage** for this type of interferon could be maintained either: (1) by carrying out further collaborative assay studies in which the four Japanese companies would take part, and so derive a new value for 951568, which would maintain continuity of the **unitage** with the 1st I.S., and which could then be recommended to the ECBS to be assigned to the 2nd I.S., or (2) by recommending that the ECBS should withdraw 95/568 and reinstate the 1st I.S., Ga23-901-532.

In a letter Dr. Tony Meager (unfortunately unable to attend this meeting) had previously given possible reasons for the withdrawal of the 1st I.S. He had suggested that the interferon batch used to make the 2nd I.S. was purer than that used for the 1st I.S. Dr. Finter had been ultimately responsible for the production of both batches at Wellcome Laboratories and explained that they were produced identically, and due to technical analytical advances, the second batch had been better characterized in terms of **subtype** composition. Dr. Meager also felt that the 3% moisture content in containers of the 1st I.S. suggested possible long-term instability, but Dr. Grossberg reported that long-term stability studies which were ongoing had shown no loss of activity and testing had predicted a very long storage life. At the current rate of usage, the > 2000 containers held by the NIAID, NIH, Bethesda, USA would suffice for more than 15 years. In response to a question posed by Dr. Bordens as to when Ga23-901-532 was calibrated, it was noted that the NIH Reference Reagent #30 was undated, but it was subsequently determined that WHO had approved its **unitage** of 25,000 I.U. in 1983 (WHO Technical Report Series 725:28-64, 1985). Dr. Meager had favoured recalibration of 95/568 because there was no precedent for the ECBS reinstating an I.S. once withdrawn.

After additional discussion, the Committee unanimously agreed that to reinstate the 1st I.S., Ga23-901-532 was both an easier and more reliable way of solving the **unitage** problem than to try to derive a new and acceptable potency to be assigned to the 2nd I.S. They agreed that the Chairman should pass a recommendation to this effect to the ECBS for consideration at their next meeting.

5. New Cytokine Standards

Dr. Meager provided *in absentia* the following update on new cytokine standards. Presently, NIBSC is concentrating its efforts on developing reference materials for IL-17 and IL-18, and is planning to develop reference materials for TNF-related, apoptosis-inducing ligand (TRAIL), B-lymphocyte stimulator (BlyS) and some pegylated cytokines, e.g. pegylated IFN- α 2, and possibly soluble cytokine receptors.

6. Participation in Committee Proceedings

Dr. Kohase announced that he will be retiring soon from his position in Japan. Dr. Harada expressed the need for involvement of Japanese company representatives in the Committee. Dr. Grossberg explained that membership on the Committee was limited by ISICR rules but that

attendance and participation in its meetings has always been open to Society members and welcomed by the Committee.

There being no further business, the meeting was adjourned at 1600 hours.

Respectfully submitted,
Louis Westreich
Ron Bordens
Sidney Grossberg

Summary

The five commercial manufacturers of human lymphoblastoid interferon (HuIFN-a N1) preparations have for many years issued containers for clinical use with their interferon content labeled in International Units (I.U.), as standardized against the 1st. International Standard (I.S.) for HuIFN-a N1, reference code Ga23-901-532. No problems arising from the use of this I.S. have reported, and there are still ample stocks. For reasons which are not recorded, this I.S. was replaced in 1999 by a 2nd I.S. reference code 951568, which was calibrated against the 1st I.S. in a large international collaborative assay study, and from the results assigned a potency of 38,000 I.U. per container. One of the manufacturers, Wellcome, is now part of Glaxo, Smith, Kline and no longer makes lymphoblastoid interferon; the remaining 4 companies, all in Japan, find a consistent and unacceptable 30% discrepancy when their products are calibrated against this 2nd I.S. instead of the 1st I.S.

This problem could be resolved by re-calibrating the 2nd I.S., or by reinstating the 1st I.S.

Background information

In 1981, a batch of lymphoblastoid interferon made by the **Wellcome** laboratories in England was dispensed into numerous containers, freeze-dried and coded Ga23-901-532. From the results obtained in an international collaborative assay study involving 8 laboratories (see WHO Techn. Rept. ser. 725, 1985), the WHO Expert Committee on Biological Standardization (ECBS) accepted this preparation as the 1st I.S. for HuIFNa-N1, and assigned a potency of 25,000 International Units (IU) per container. **Wellcome** calibrated its in-house reference standard against this I.S. so that containers of **Wellferon**, the only lymphoblastoid interferon then being used in several countries, were labeled with their content in I.U.

In 1995, the question was raised whether the 1st I.S. for human leucocyte interferon, 69119, might serve as a common reference standard for all IFN-alpha products, as would be possible if the interferon dose - response curves for all had the same slope. The ECBS asked for more data to resolve this point, and at its next meeting, the WHO Informal Consultation on the Standardization of Cytokines agreed to provide relevant data. Accordingly, the U.K. National Institute for Biological Standards and Control (NIBSC) organized a large international collaborative assay study of 17 IFN alpha standards, which included both Ga23-901-532 and another preparation, 951568, prepared by NIBSC as a potential standard preparation. A total of 97 laboratories took part, each receiving only 5-10 coded preparations; unfortunately, **Wellcome** which had a critical interest in lymphoblastoid IFN was not assigned both lymphoblastoid preparations to test in parallel. By then, four pharmaceutical companies in Japan, Hayashibara, Sumitomo, Mochida and Otsuka were also issuing human lymphoblastoid IFN preparations for clinical use, but only Hayashibara and Sumitomo participated in this study. Also, at its meeting in Baltimore in 1995, the ISICR Standards Committee arranged a smaller adjunct study in which laboratories in several countries with particular expertise assayed nine interferon standards with the particular aim of obtaining good data for the slopes of their dose-response curves. This study included Ga23-901-532, but not preparation 951568.

All the data from NIBSC study and the adjunct study were analyzed at NIBSC, and the results were presented in a lengthy report to a meeting of the WHO Informal Consultation on the Standardization of Cytokines held 15-16 May 1997 at NIBSC (full report available from NIBSC). Among its recommendations, the 5th states that Ga23-901-532 should be retained as the I.S. for human lymphoblastoid IFN-alpha with an unchanged assigned potency of 25,000 I.U. per container, so that there would be continuity of unitage.

Because the potency values recommended in this report for some interferon I.S. preparations would have caused difficulties for certain manufacturers, representatives of the International Federation of Pharmaceutical Manufacturers (IFPMA) arranged with NIBSC for another limited collaborative study, to be carried out in the laboratories of 10 manufacturers of commercially available IFN-alpha preparations. None of the Japanese manufacturers took part in this study. The results of this study and re-evaluations of the earlier data were reported to the WHO Consultation on Cytokine Standards held at NIBSC 28-29 July 1999. In the draft Minutes of that meeting [no final minute were issued], the ECBS was recommended to establish 8 new I.S. for various HuIFN-a subtypes and mixtures, and to withdraw the corresponding current I.S. preparations. In particular, preparation 95/568 was to be established as the second I.S. for human lymphoblastoid interferon, with an assigned potency of 38,000 I.U. per container, and the first I.S., Ga23-901-532, was to be withdrawn. No reasons for this particular recommendation are minuted and at least 4 of those participating in the meeting do not recollect that the matter was discussed. A further analysis of data, including those subsequently submitted by Wellcome as part of the IFPMA study, confirmed the value of 38,000 I.U. per container to be assigned to preparation 951568. Accordingly, the ECBS established 951568 as the second I.S. for lymphoblastoid interferon with this potency, and withdrew the 1st I.S.

Since that time, the Wellcome laboratories have become part of Glaxo Smith Kline, and Wellferon is no longer made. Four Japanese pharmaceutical companies, Sumitomo, Hayashibara, Mochida and Otsuka are now the only manufacturers of interferons derived from human lymphoblastoid cells. These companies have from the start assayed their interferon batches in parallel with the Japanese National standard J-501, which has been rigorously correlated with Ga23-901-532, and so issued their products in containers labeled with their content in I.U. When the 2nd I.S., 951568, was introduced, the Japanese manufacturers tested this against J-501 in a collaborative assay study. The potency values obtained ranged from 45,300 to 52,800 units per container: the mean value was 49,000 units per container which is 129% of the assigned value of 38,000. Dr Kohase in the Japanese National Control laboratory has organized a further collaborative study, now in progress, but it seems unlikely that the results will be significantly different. *In consequence, if these companies issue a container for clinical use which would be labeled with a content of 3 million I.U., as standardized against Ga23-501 932, it would instead be shown with a content of 2.3 million I.U., if standardized against 95/568. This would cause great confusion to doctors who are accustomed to administering doses of 3 million I.U. to their patients. The alternative of increasing the amount dispensed to provide 3 million I.U. per container in terms of 95/568 would involve an unacceptable 30% increase in the dose per patient.*

Ways in which the problem could be solved

There seem to be two ways of solving this problem.

1. To assign a new value for the potency of 951568 that would maintain the **unitage** used by the 4 Japanese companies.

To meet WHO requirements, this would require a new collaborative assay exercise, involving laboratories in several countries, including Japan. There would be no great reason to expect that a value greatly different from the previous 38,000 would be obtained, except that this value was much influenced by the very numerous assays is no longer relevant, and if now the 4 Japanese laboratories were similarly to carry out numerous assays of 951568, a new value acceptable to them might be obtained. This could be recommended to the ECBS for their consideration and hopefully approval. However this would be a lengthy, laborious and expensive process.

2. To withdraw 951568 and return to the use of the 1st. I.S. for lymphoblastoid interferon, Ga23-501 932.

This course is greatly favoured by the 4 Japanese manufacturers. It would very simply overcome all their problems, and their material issued for clinical use would be labelled exactly as at present, thus avoiding any confusion for clinicians and patients. It is important to note that although the participants of the 5th WHO Consultation on Cytokine Standards in 1999 agreed that this 1st I.S. should be withdrawn and replaced by 951568, the reasons for doing this are not recorded in the Draft Minutes, and seem not to be known now. The repositories at NIBSC and at the U.S. NIAID, NIH, Bethesda between them hold more than 2000 containers of Ga23-901-532, sufficient at the present very low rate of issue to last for very many years to come, and stability tests predict a life at -70 C of hundreds of years. There seem therefore no reasons why this 1st standard should not be reinstated, and a recommendation to this effect could be sent to the ECBS for consideration at their next meeting, thus hopefully soon resolving the problem in Japan.

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