IAA

Institute of Accelerator Analysis Ltd.

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URL: http://www.iaa-ams.co.jp

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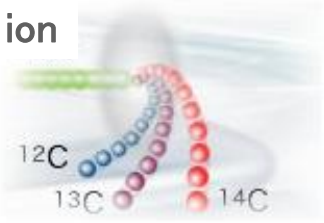
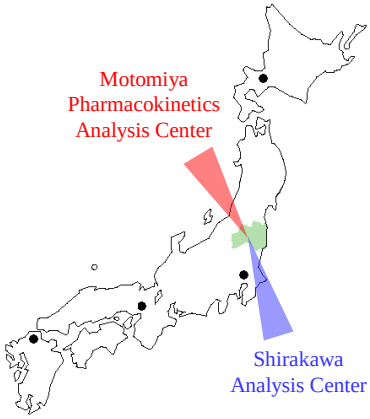


History of IAA

1999 March: Establishment of Institute of Accelerator Analysis Ltd. (IAA)
2000 April: Initiation of radiocarbon dating by beta-ray counting methods;
Start of marketing for radiocarbon dating by AMS
November: Completion of the Shirakawa Analysis Center (IAA-SAC)
December: Installment of AMS unit (Pelletron 9SDH-2) in IAA-SAC
2001 February: Initiation of radiocarbon dating with AMS in IAA-SAC
May: Start of dating by AMS analysis at IAA-SAC
August: Start of service of dating by beta ray counting method at IAA-SAC
July: Start of marketing for 14C-labeled drug analysis of biological samples by AMS
2004 March: Agency agreement with Daiichi Pure Chemicals Co. Ltd. in pharmacokinetic studies
August: Start of construction of Motomiya Pharmacokinetics Analysis Center (IAA-MPAC)
2005 January: Installation of AMS unit (Pelletron 1.5SDH-1) in IAA-MPAC
February: Completion of IAA-MPAC
March: Start of AMS analysis for pharmacokinetic studies with AMS in conformity with GLP at IAA-MPAC
May: Completion ceremony for IAA-MPAC
July: Agency agreement with Fuji Biomedix Co. Ltd. in pharmacokinetic Studies



Message from CEO

Takao Mutsui
President and CEO

I am pleased to present to the global scientific community, the dedicated commitment and professionalism of my staff at the Institute of Accelerator Analysis Ltd. (IAA) – providing state-of-the-art Accelerator Mass Spectrometry (AMS) technological research and analysis services.

Accelerator Mass Spectrometry (AMS) measures the three carbon isotopes (^{14}C, ^{13}C and ^{12}C) for archaeological and geological dating and biomedical research. Since AMS directly measures the amount of ^{14}C contained in samples, the sensitivity of AMS is over 1,000 times higher than the conventional beta ray counting methods, and thus, AMS allows high precision dating of precious samples in very small quantity.

In recent years, AMS has attracted growing attention from various fields, including archaeology, anthropology, conservation of cultural property, geology, space and earth sciences, new drug development, environmental science, and pure science. IAA is committed to serving demands in a broad range of fields.

An area of particular interest for IAA is the application of AMS to pharmokinetic testing. AMS is capable of measuring the ^{14}C-labeled drug concentration at very low levels of radioactivity in biological samples, such as plasma, urine, feces, tissue/organ, and HPLC eluate etc. Compared to conventional radiometric methods, AMS makes it possible to reduce the amount of radioactive dose to human volunteers for pharmacokinetic studies on new drug trials to 1/1,000 or even less.

The precision assessment of AMS offers several advantages in terms of the safety of examinees as well as that of the researchers who are handling ^{14}C, the disposal of radioactive waste, and the potential environmental impact.

In February 2005, IAA opened the Motomiya Pharmacokinetics Analysis Center in Motomiya City (Fukushima Prefecture, Japan). We plan to extend our research and analysis services to such fields as in-vitro studies (early screening stage) of new drug development and drug concentration measurement in biological samples.

With AMS, we believe that IAA can make a significant contribution to society. We make constant efforts to provide analytical services that meet your expectations, working together with business and research communities.

IAA keeps strict scientific control over the data we measure. The continuity of this data is a scientific property that is ultimately shared by all human beings. This knowledge will become a legacy for future generations.

The IAA provides precise scientific data. Accelerator Mass Spectrometry belongs to the state-of-art technology, a field that is still in the process of development. In order to maximize the advantage of this technology most effectively, the staff members of IAA believe in humanism and in creativity. Also, our team is endowed with an awareness of the value of their work to your research and our staff enjoys autonomy in fulfilling their professional duties.

Science is a founding pillar of today's advanced society. We believe that IAA's engagement in scientific service can contribute to the development of scientific market, by materializing the ideals herein. In the process, we believe that our precision and professionalism will gain the trust and appreciation of society, as our work will help lead you to exacting results.

Applications of AMS Analysis to Clinical Trials

<< Development Process >>

Screening

Pre-clinical Test

Clinical Test

Phase 1

Phase 2

Phase 3

Approval

Animal Study

Analytical processes can be established in advance and confirmed under the assumption that human samples will be analyzed by AMS.

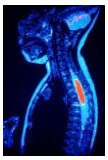
Microdosing Study

Low radioactivity of 200nCi (7.4kBq) is required for a microdosing study analyzed by AMS. At this level, a human study is allowed to be conducted in Japan.
The human samples collected in a microdosing study can be handled at non-radiation controlled area.

・Pharmacokinetics
Time courses of drug concentration in plasma can be obtained from the total radioactivity analyzed by AMS

・Mass balance
The excretion rate is analyzed by measuring urine and feces

・Metabolite profile
Metabolite profiles in plasma, urine and feces are analyzed to calculate AUCs of each metabolite
AMS can quantify all metabolites containing human specific metabolites and unknown ones without the calibration curves



・PET-AMS
Combination of PET and AMS will be useful approach to accelerate drug development
More effective information can be provided from drug distribution imaged by PET as well as metabolite profiles by AMS

Tracer Hot Phase 1 Study

Cassette dose of ^{14}C-labeled drug and unlabeled one can enhance the efficiency of clinical study.

・Samples obtained from cassette dose of ^{14}C-labeled drug and unlabeled one provide the drug information on the drug concentration in plasma, its mass balance and metabolite profiles within one clinical protocol

・Bioavailability (BA) is also calculated by administration of unlabeled and ^{14}C-labeled drugs in different routes (*p.o.* and *i.v.*)

・Cassette dose can reduce the time and cost because a protocol of hot study is unnecessary
Volunteers' load can be also reduced so that the frequency of administration is decreased

・AMS can analyze human samples obtained from a conventional hot study using the radioactivity of 50~100μCi (1.8~3.7kBq)

Accuracy Control of AMS Analysis at IAA

AMS studies must be performed according to the "Standards for Reliability of Application", Article 43 of the Enforcement Regulations of Pharmaceutical Affairs Law issued by the Ministry of Health and Welfare (MHLW) of Japan.

- Establishment of a sample preparation process (full validation)
- Sample preparation based on SOPs
- Contamination check by using process control samples
- On-line measurement of carbon content in sample
- High-quality standards for AMS measurement prepared by ourselves
- Management of AMS measurement condition and stability with standards
- Cross-check of sample preparation processes and AMS measurement in two facilities;
  Motomiya Center (0.6MV AMS for bioanalysis) v.s. Shirakawa Center (3MV AMS for dating)

Analytical Process

Pre-discussion & Protocol

Protocol is issued after a sufficient discussion with the sponsor.

Partial Validation & Sample Preparation

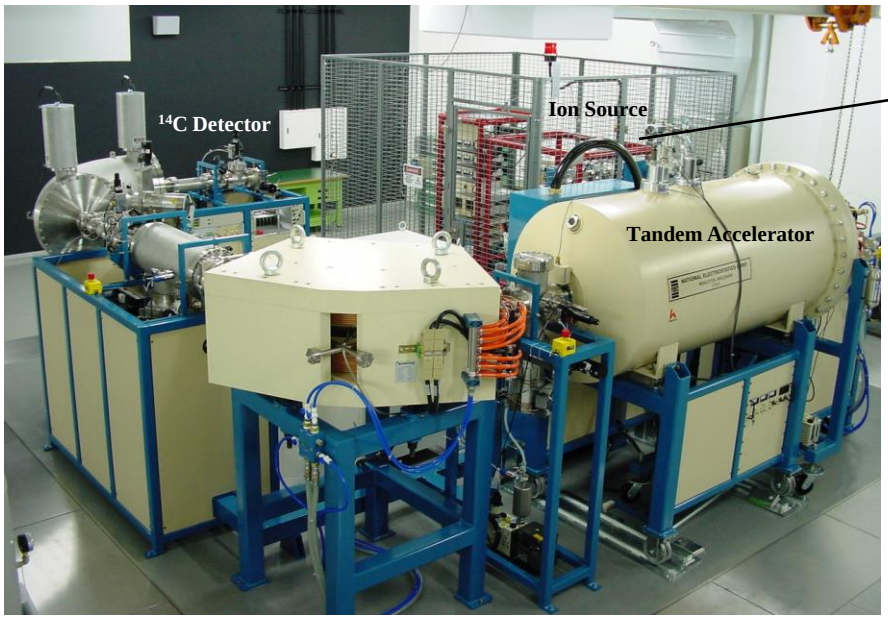
Full Validation has been already carried out. Depending on the characteristics of test compound, a partial validation will be performed before analysis. Especially, we examine whether sample preparations such as dilution, extraction, collection and combustion are appropriate. All samples are transferred into graphite through serial oxidation and reduction reactions.

AMS Measurement

A maximum of 133 samples including standard and process control samples are measured in the same lot. The validity of AMS measurement is judged upon the basis that both the standard samples and process control samples meet the acceptance criteria.

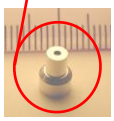
Final Report

A final report is submitted after a full discussion with the sponsor based on the results of a draft final report.



1.5SDH-1 Pelletron Accelerator Based AMS System (0.6MV)

Cathode Wheel



Aluminum Cathode (graphite)