Paper 23

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Good Radiation Practices in Industry and Research

View from the pharmaceuticals industry

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Introduction

For many years, the pharmaceutical industry has been one of the UK's most successful industrial sectors. In 1995, total pharmaceutical sales were £11893 million (7% of the world total pharmaceutical sales), 5 of the world's top selling drugs were discovered in the UK and the trade surplus of £2133 million was second only to the oil industry. In the same year, the industry employed 75000 people, of which 20000 people worked in research and development spending £1902 million which represented 25% of the total for all UK industrial research (ref 2). Excluding the production of radiopharmaceuticals, which is undertaken by only a small number of specialist companies, the major use of radiation in the pharmaceutical industry is in its research and development (R&D) laboratories.

There was relatively little inter-company communication on radiation safety issues until 1994 when the Pharmaceutical Industry Radiation Safety Discussion Group (PIRSDG) was founded. By 1998 this comprised a total of ca 25 organisations involved in biomedical research and included most of the largest pharmaceutical companies in the UK (see Table).

Table: PIRSDG membership (largest pharmaceutical company members)

Name of organisation		
Astra Charnwood	Novartis	Sanofi
Glaxo Wellcome	Organon	SmithKline Beecham
Eli Lilley	Pfizer	Zeneca
Merck Sharpe & Dohme	Roche	

The Association of the British Pharmaceutical Industry (ABPI) is the trade association for the industry in the UK and although the PIRSDG does not have formal links with the Association, there is close liaison where appropriate. Overall, the PIRSDG represents organisations with ca 3000 radiation workers on ca 25 authorised sites. Last year I undertook a survey of the way that the membership manages its radiation safety programmes. Data from this survey will be used to illustrate the methods by which the UK pharmaceutical industry optimises its use of radiation and keeps radiation exposures to the public and its work force as low as reasonably achievable, economic and social factors being taken into account (ALARA) (ref 3).

Sources of radiation exposure in pharmaceutical R&D

The R&D work undertaken in the pharmaceutical industry mainly takes the form of biomedical research using relatively low levels of radioactivity. This work is similar to that carried out in hospitals and universities and, like them, the pharmaceutical industry is a 'small user' of radioactivity compared to the nuclear sector. New technologies have been introduced over the past few years which have significantly changed the way that R&D is now carried out. Advances in genetics have given rise to a vast increase in our knowledge of the human genome and the correct interpretation of this data has led to a huge increase in the number of identified potential protein targets. In addition, the new technique of combinatorial chemistry can now produce thousands of compounds which when coupled to the availability of robots has led to a large increase in the scale of screening for potential new drugs.

The main potential sources of radiation exposure in pharmaceutical R&D are:

unsealed radioactive materials used as markers in biotechnology, pharmacology and drug metabolism studies
X-ray sources, such as diffraction units and veterinary sets
large sealed sources in cell irradiators
small sealed sources, usually in testing instruments (eg liquid scintillation counters, gas chromatographs)

It should be noted that some studies include low level radiation doses to human volunteers during the development phase of new drugs. In particular, in bioavailability studies by oral or iv dosing with low levels of tritium or carbon-14 labelled drugs or possibly positron emission tomography (PET) studies using short lived radionuclides such as carbon-11 or fluorine-18. Overall, these represent a relatively minor source of exposure, which is optimised by experimental design. As both the clinical and radiation safety aspects of these studies are carefully managed in compliance with national legislation and EU Directives and exposure is well documented and minimised, I will not consider them further here but discuss the other potential sources of exposure.

Unsealed radioactive materials

Unsealed radioactive materials are widely used in many aspects of pharmaceutical R&D and as such represent the most likely potential source of radiation exposure. They are used as markers in a variety of reagents and drugs for both in vitro and in vivo pharmacological and bioavailability experiments. The reagents and drugs are often purchased from external suppliers but may be produced in-house by radiochemists from simpler radiolabelled precursors. Despite the increasing availability of sensitive non-radioactive techniques such as fluorescence, radioactive methods retain their popularity as they only require relatively cheap, simple and well-established technology to produce good quality results. In particular, the increase in the use of high throughput screening has actually led to a rise in the use of radioactivity. The radionuclides commonly used are listed below:

soft beta emitters: eg tritium, carbon-14, phosphorus-33, sulphur-35, calcium-45
hard beta emitters: eg phosphorus-32, rubidium-86
gamma emitters: eg iodine-125, chromium-51, rubidium-86

It should be noted that the recent increase in genetics research has increased the use of phosphorus and sulphur radionuclides. However, much work previously undertaken with the hard beta emitter, phosphorus-32, now uses the soft beta emitter, phosphorus-33 with the subsequent lowering of external radiation hazard. This particular switch of radionuclides is very important as phosphorus-32 is probably the largest single contributor of radiation dose in the industry and the switch to the more expensive phosphorus-33 is one of the best recent examples of optimisation.

Generally, low levels of radioactivity (<37 MBq, 1mCi) are used in each experiment, although the large number of individual radiation workers and types of work on particular sites may require site authorisations for the holding and disposal of multi GBq amounts. In addition, some sites undertake radiosyntheses and therefore may use much higher levels of tritium, carbon-14 and iodine-125. The recent application of modern tritium gas handling technology to the radiolabelling of drugs now involves the use of TBq amounts on a few sites.
In general, the main potential source of radiation exposure from this work is the ingestion of radioactivity due to poor working techniques and a lack of contamination control. External radiation is normally only significant for relatively few radionuclides in use (eg phosphorus-32 and rubidium-86).

Sealed sources and X-rays

Small sealed sources such as those in testing instruments are normally securely housed and contain relatively low levels of radioactivity. Providing that the sources are well controlled and correctly disposed of they are unlikely to give rise to significant radiation doses. Some member's sites have cell irradiators, which may contain sealed sources containing up to 100 TBq (2700 Ci) of radionuclides such as caesium-137. These represent a major potential source of radiation dose. However, their hazard is well recognised and they are housed in highly shielded containment and the subject of strict work instructions, monitoring regimes, risk assessments and contingency plans. Consequently, under these circumstances they should not normally represent a significant hazard.
X-ray producing equipment is widely used, normally in the form of diffraction equipment for crystal structure elucidation or veterinary sets. In the pharmaceutical industry, the use of X-radiation represents the major potential source for acute radiation, particularly to the fingers. The use of X-ray equipment appears to be increasing but fortunately most of the equipment in use is relatively modern and provides good interlocked shielding. Although the potential for radiation exposure may be minimised by the use of interlocked total exclusion zones, some procedures still require access to the X-ray beam. For X-ray diffraction this is normally during beam alignment and for veterinary sets this is normally during fluoroscopy procedures. However, the potential for exposure is minimised by restricting access to well trained staff working under the terms of written systems of work using personal and area monitoring where appropriate.

Factors contributing to optimisation

The following are considered the main factors that contribute to ensuring that radiation exposure of the public and workers is optimised:

experimental design
facility design
radiation safety organisation
instruction and training
work practices
dosimetry
source and waste management
inspection and audit

I will deal with each of these in turn.

Experimental design

A good experimental design is essential to optimise radiation dose. All members have their own in-house procedures for designing experiments. At SmithKline Beecham (SB) Pharmaceuticals R&D, experimental design will be agreed by the experimenter(s), their supervisor (if appropriate) and the local Radiation Protection Supervisor (RPS). If necessary, the Radiation Protection Adviser (RPA) may be involved in the process. A system of generic work authorisations is in place for each work area and these are subject to regular review. A risk assessment will be undertaken before commencing the experiment and the potential radiation dose to the experimenter(s) and other persons estimated and steps taken to minimise it. There are many standard well established types of experiment that are undertaken in pharmaceuticals R&D and generic hazard assessments/contingency plans are in place for all reasonably foreseeable accidents, or occurrences likely to lead to unplanned radiation exposure. Work will only take place in correctly designated areas and all persons involved will be appropriately trained and provided with appropriate personal protective equipment and dosimetry. The experiments will be designed to minimise the use of radiation and/or unsealed radioactive materials and, the amount and type waste arising from the experiment will be optimised. Appropriate containment and/or shielding will be agreed and contact time with radiation sources minimised. Where necessary, engineering controls (eg fume cupboard) will be used. All equipment used, including radiation monitors, will be in good working order. The experiment must comply with local rules and/or written systems of work which, if necessary, will be amended.

Facility design

The pharmaceutical industry relies more heavily than almost all other sectors on the innovative quality of its research. This requirement, coupled with the continuing relatively high profitability of the industry has given rise to high levels of investment in its R&D facilities and consequently a good quality of facilities for the handling of radiation. For example, hundreds of millions of pounds have been invested over the last five years in UK R&D facilities by Astra Charnwood at Loughborough, SB at Harlow and Glaxo Wellcome at Stevenage. The provision of these state of the art facilities significantly enhances the ability of the organisations to optimise their use of radiation, particularly with respect to the use of unsealed sources. There is general agreement in the industry on what constitutes good laboratory standards and recently two useful guideline documents have been produced (ref 6). The use of high quality non-absorbent work surfaces and flooring is fundamental, as is the wide spread use of high quality aerodynamic fume cupboards and biological containment cabinets. Most work is undertaken at 'work stations' using trays and appropriate shielding (eg acrylic sheet for phosphorus-32). A more recent building innovation is the introduction of a system of service corridors to ensure that 'dirty' items/equipment do not enter ‘clean’ writing up/office areas which are strictly segregated from the radioactive work areas. The use of see-though walls between laboratories and their adjacent writing up/office areas is a useful safety feature. In addition, it has led to a significant improvement in staff compliance with rules on the use of personal protective equipment (eg laboratory coats and safety spectacles) in laboratories where there is 'nowhere to hide'. The modern need for high throughput biological screening of candidate compounds has led to a vast increase in the use of robotic systems. These are an important optimisation enhancement as they allow the throughput of vast numbers of radioactive assays without the presence of scientists. This significantly lowers the potential for radiation dose providing that radioactive reagents are initially loaded and unloaded under highly controlled conditions.

The IRR85 require the use of controlled and supervised areas for work that could give rise to doses that are likely to exceed 3/10 and 1/10 respectively of a dose limit. These areas are normally defined in the industry in terms of the amounts of unsealed radioactivity being handled which have the potential for contamination and ingestion. Often this definition is relatively conservative and is in terms of Annual Limit on Intake (ALI) of radionuclides. For example the use of >3 ALI could require the use of a supervised area and >10 ALI a controlled

area. However, most radioactive work in the industry uses <3 ALI and represents an even lower radiation dose risk. These low level areas are not defined in the IRR85 but member companies use their own terminology such as 'registered' or 'tracer areas'. These areas have radioactive warning signs and are subject to local rules. The survey of the industry revealed that each site averages 54 radioactive work areas, of which 9 are supervised and 6 are controlled. Half of all controlled areas have a temporary status and, following monitoring and decontamination, revert to a lower category at the end of a particular use. The flexibility in area designation, which should result from the non-prescriptive, goal setting approach of the proposed IRRrev, is welcomed by most members.

Radiation safety organisation

The PIRSDG contains both large and small UK biomedical research organisations. However, the vast majority of radioactive work takes place in pharmaceutical R&D establishments, which are subsidiaries of large multinational companies with well-established line management structures. There are often dedicated occupational safety and environment affairs departments at corporate and local level to advise and assist management to meet their corporate and legal radiation safety obligations. The most important pieces of legislation which allow the UK to comply with the requirements of the 1980 Euratom Basic Safety Standards (BSS) (ref 4) are the Ionising Radiations Regulations 1985 (IRR85) and the Radioactive Substances Act 1993 (RSA93). All member companies have set up radiation safety organisations to meet the requirements of this legislation. For most members, the radiation safety organisations have been in place for many years and have achieved a high degree of acceptance by both workers and management.

Although the pharmaceutical industry would appear to be very successful, it is under intense commercial pressure largely due to the drive by governments around the world to reduce their burgeoning healthcare expenditure. R&D costs have also risen dramatically and it has now been estimated that it costs up to £300 million and takes 10-12 years to develop a new drug. This has led to major changes in the UK industry with mergers (eg formation of SB in 1989 and Glaxo Wellcome in 1995), demergers (eg Zeneca from ICI) and take-overs (eg Fisons by Astra and the pharmaceutical arm of Boots by BASF) being commonplace as companies attempt to gain the commercial advantages that accrue from larger R&D departments and rationalised sales forces. These organisational changes have been felt in R&D where staff transfers, departmental reorganisations, new site/building occupation and old site/building closure/remediation continue to provide a major challenge to maintenance of sound radiation safety management.

At a departmental level, the role of Radiation Protection Supervisor (RPS) as required by the IRR85 is crucial in optimisation. This person is usually an experienced scientist appointed to provide local radiation safety supervision on part time basis. The number of duties and responsibilities of these Supervisors varies between companies but on average, there is 1 RPS per 14 radiation workers. The RPS needs to be sufficiently senior to command respect but still be practically involved day-to-day in the work areas. Obtaining the correct balance is a major challenge. Most companies appoint a Radiation Safety Officer (RSO) or equivalent to co-ordinate the activity of the RPSs, oversee site wide activities such as waste disposal and record keeping and provide a contact point with the regulators. This person is normally a senior experienced scientist who in most instances also combines this role with other duties. Virtually all companies make use of an appointed 'qualified expert' in the form of a Radiation Protection Adviser (RPA) as defined in the IRR85. This individual will advise management on optimisation and other radiation safety issues, in particular compliance with their legal responsibilities. Some companies combine the role of RPA with that of RSO but the majority employ external consultants, with over 70% making use of the National Radiological Protection Board (NRPB). It is interesting to note that unlike much of Europe, 'qualified experts' in the UK do not require formal qualification/certification. The new BSS (ref 5) as enacted in the revised Ionising Radiations Regulations (IRRrev) will enhance the role of the RPA and require formal certification. PIRSDG members also hope that the role of corporate RPAs will be clarified.

Training and instruction

The training of radiation workers and RPSs in good working practices is regarded as fundamental to optimising doses to radiation workers. The crucial role of the RPS in optimisation is recognised both as supervisor of radioactive work and in the cascading down of training and good practices to new radiation users. Only scientists with sufficient direct experience are normally appointed as RPSs. However, newly appointed RPSs often have inadequate knowledge of topics such as the legislation, hazards and risk assessment, dosimetry, monitoring techniques and accident and emergency procedures. They therefore normally require additional training, which can normally be adequately covered in a two-day course. The turnover of RPSs within an organisation is usually too small to warrant the setting up of in-house courses and therefore use must be made of external courses. Last year PIRSDG concluded that most external courses in the UK were inadequate to meet their needs due to one or more of the following reasons:

infrequency
inappropriate duration and costs
poor teaching methods
too general syllabus

For this reason PIRSDG decided to commission their own specific two day RPS training course, clearly specifying teaching methods which minimised formal lecturing and maximised an interactive approach using group exercises and practical work. In addition, the syllabus was specifically designed to meet the needs of RPSs using unsealed sources in biomedical R&D. The trainees are sent copies of the IRR85 and the associated Approved Code of Practice (ACoP) together with a questionnaire to ensure that the documents are read before the start of the course. A short examination is held at the end of the course and, although there is not a pass level, the results are sent to the RSO and line manager of the participants to review. The courses are held on various R&D sites and the number of trainees is limited to 12 with no more than 3 from any one organisation. This is to ensure that the trainees to see other R&D facilities and to maximise interaction between trainees from different organisations. A commercial course provider was selected after a tender exercise and to date five courses have been held which have trained 56 RPSs from 11 member organisations.

While RPSs may be expected to provide the initial training to new radiation users and their work supervisors provide 'on the job' training/supervision, the main training vehicle used by most companies is an in-house one day training course covering the fundamentals of radiation safety. Most new radiation workers are inexperienced graduates or placement students. Over 80% of companies make use of external trainers for these courses and also refresher training where appropriate. It is essential that all this training be recorded, particularly to confirm to the regulators that all radiation workers are adequately trained.

The provision of good, clear and concise working instructions is an essential component of good radiation practices. All PIRSDG members provide these and usually call them 'local rules' as defined by the IRR85. The size and complexity of these local rules varies greatly between members as they attempt the difficult balance of simplicity and ease of use with the need to be sufficiently comprehensive. Keeping written instructions up to date is recognised as a major challenge and many members are now taking advantage of the proliferation of electronic communication systems to transfer local rules to electronic databases. This has the major advantage of allowing rapid and easy updating but it must be recognised that electronic systems must be sufficiently widely available within organisations to ensure that all radiation users have good access. In 1997, half of the members used paper only systems and half used a mixture of paper and electronic. The average revision period for local rules was 1.5 years. To date, the regulatory authorities appear to have been slow to recognise the power and importance of electronic communication systems in modern R&D based organisations and still appear to think in terms of paper only communication.

Work practices

Good work practices are essential to minimise any radiation dose.

For unsealed sources, initial risk assessment is used to minimise the amount of radioactivity used or even identify non-radioactive alternatives. No member sites are permitted by the authorities to use unsealed alpha emitting radionuclides. Much of the work can be undertaken with soft beta emitting radionuclides that do not present an external radiation hazard. Sophisticated acrylic shielding equipment and, if necessary, forceps are used to minimise radiation dose from hard beta emitters and lead impregnated versions are used for soft gamma emitters (eg iodine-125) with the occasional need to use lead sheet/bricks for harder gamma emitters. However, most precautions are designed to minimise the contamination hazard by working over trays at designated workstations. Fume cupboards are used for potentially volatile materials and biological cabinets for biohazardous materials. The wide availability of relatively cheap contamination monitors allows for contamination monitoring both during work activity and routinely in the work areas. Tritium continues to be problematic due to the lack of reliable monitoring

methods other than 'wipe tests'. Some spillages of unsealed sources may occur during experiments. These will normally be of a minor nature and radiation exposure should be minimal and below limits that require reporting to the regulators. Risk assessments and contingency plans should allow for these occurrences. However, in the light of the proposed IRRrev it is risk assessment and contingency plans that may require more attention in future, especially with respect to incident rehearsal.

As described previously, X-ray diffraction units and veterinary X-ray sets are widely used in pharmaceutical R&D. They will normally be operated using total exclusion controlled areas. Robust written systems of work are used to ensure that radiation doses are avoided during the potentially most hazardous operations such as beam alignment (diffraction) and fluoroscopy (veterinary).

Dosimetry

In 1997, members of PIRSDG had only 4 classified (category A) workers out of a total radiation work force of 3000. The classification of workers is felt to be an unnecessary bureaucratic burden and written systems of work are used to alleviate the need for classification. Workers in the industry are not expected to receive any measurable occupation radiation dose due both to the type of work undertaken and to the safety systems in place. This has been confirmed by the extensive of personal dosimetry for users of hard beta, gamma and X-rays. Despite these very low radiation doses, all members restrict the radiation work of pregnant female workers. There is however, little consistency in approach and restrictions may vary from just preventing their entry to X-ray controlled areas to full removal from any radioactive work.

Over 80% of members use thermoluminescent dosimeters (TLDs) as personal dosimeters and most maintain a wear period of one month for both body and extremity. These dosimeters are all provided by third parties. Electronic dosimeters are not used. The only other methods of personal dosimetry used are urine monitoring high level users of tritium, carbon-14 and sulphur-35 and thyroid monitoring for iodine-125 users. The major problem with the use of personal dosimeters remains the relatively high number of false positives which all require investigation.

Source and waste management

All radioactive source and waste management is subject to the RSA93 (and the IRR85) and all member sites are registered to hold unsealed (and occasionally sealed) radioactive sources and authorised to accumulate and dispose of radioactive waste by the Environment Agency (EA) or, where appropriate, the Scottish Environmental Protection Agency (SEPA).

Records must be kept of all radioactive holdings and disposals and annual returns are sent to the EA/ SEPA. The record keeping of the thousands of radioactive stock items and disposals represents a major organisational challenge to members, who use a mixture of electronic and paper record systems. The main weakness of paper systems is they do not work in real time and are usually only collated at the end of each month. In addition, they are unable to cope with the complexity of half-life decay calculations and therefore are at best only estimates for short-lived radionuclides. By 1997, two thirds of members used in-house electronic systems and the recent availability of commercial electronic systems should increase the proportion using these methods. It is interesting to note that, to date no members using electronic systems have completely abandoned the use of paper methods.

All permitted radioactive disposals are the subject of dose assessment to critical groups and are normally subject to a dose constraint of 0.3 mSv/year (ref 7). Unlike many other European countries, the government does not offer a disposal service and producers are expected to develop their own waste strategies (refs 7 and 8). Consequently, radioactive disposal is extensively undertaken by the private sector, often making use of incineration technology. All members are permitted to dispose of limited amounts of aqueous radioactive waste to the public sewers. Liquid scintillation counting (LSC) is used extensively in the industry and this generates large volumes of water miscible low level scintillation solvent waste. Despite the claims by the manufacturers' that this is biodegradable, its disposal into the public sewers is not permitted by the water utilities. Gaseous radioactivity is disposed of by 42% of members via their fume cupboards. Nearly all members make use of the allowance to send Very Low Level Radioactive Waste (VLLW) to landfill. In order to maximise the dispersion of this waste, the landfill site used must be one that has not been designated for radioactive disposal. Members do not use any shallow land repositories. Incineration has been used for many years in the UK as a major radioactive disposal route and in the past, most members used their own on-site incinerators for the disposal radioactive solid and scintillation solvent waste. The recent requirement for increased pollution abatement measures has led to the closure of many of these incinerators. The large capital outlay required to replace old plant has now resulted in only one third of members possessing their own on-site incinerators and increased use being made of third party commercial operators. Those with new incineration facilities have been requested by the EA to undertake radionuclide partitioning studies to confirm that the disposal of ash and spent abatement solids may be disposed of as VLLW

(ref 9). Over 90% of members use third party incineration contractors, often for the disposal of contaminated organic (non-scintillation) solvent waste.

The disposal of waste containing short-lived radionuclides by decay storage is becoming increasingly popular and most members now use this route. This use of this particular 'disposal route' could be considered as the most important method used by the industry to optimise radiation dose to the public. Whilst the EA/SEPA take a practical and pragmatic approach to radioactive waste disposal PIRSDG members are disappointed by a lack of flexibility in their authorisations (ref 10). The EA Inspectors also often exhibit a lack of consistency but this should be improved by the work of the EA Small Users Liaison Group on which the PIRSDG has representation. A lack of coherent national policy on the disposal of water miscible scintillation fluids is also regretted. In addition, the high cost of sealed source disposal as Intermediate Level Radioactive Waste remains a concern. PIRSDG members are concerned that commercial pressures and action by environmental pressure groups will lead to a significant reduction in the flexibility and capacity of waste disposal routes in the UK. They hope that future discussion on these matters in both the UK and Europe will remain objective and decisions will only be taken following balanced and scientific risk assessment.

Some members are also involved in site decommissioning prior to the revoking of registrations and authorisations. At present there is no formal guidance provided by the EA and individual strategies must be agreed with local EA inspectors. It is hoped that this will be remedied in the near future.

Inspection and audits

All PIRSDG members are subject to periodic inspection by the regulatory authorities. Inspection by specialist inspectors from the Health and Safety Executive (HSE) is relatively infrequent with the average inspection interval being 6 years. However, inspection by the EA is much more frequent and 50% of members are inspected at least once every 18 months. Reorganisations within the EA have often resulted in the Inspectors being relatively inexperienced in radiation matters. The EA has acknowledged this (ref 8) and intends to address the situation. Regular audit and feedback is an essential component in optimisation and most members conduct their own internal audits of their radiation safety programmes, often using consultant RPAs. At SB Pharmaceuticals R&D, we have recently introduced a system of bi-monthly self audit by RPSs of their areas of responsibility. This self-audit and other local radiation management systems will then in turn be the subject of a radiation management audit by the RPA. These audits will use a scoring system and results will be fed back to management.

Conclusion

For many years, pharmaceutical R&D has applied the principle of optimisation of radiation doses to both their workforce and the public. Fortunately, this has been aided by the fact that pharmaceutical R&D can be undertaken using relatively low levels of radionuclides of low radiotoxicity. This has been further assisted by the availability of sufficient resources to maintain high quality radiation safety organisations, facilities and training regimes. For these reasons, occupational radiation doses have been very low. Future reorganisations within the industry coupled with changes in R&D methodologies are likely to continue to offer a challenge to the management of radiation safety in the industry. Over the next two years well established radiation safety procedures will need to be amended in a timely manner if they are to meet the requirements of the revised IRR and RSA.

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The author is Radiation Protection Adviser to SmithKline Beecham Pharmaceuticals. The views expressed are those of the author and do not necessarily represent those of SmithKline Beecham Pharmaceuticals or the members of PIRSDG.

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