BIOMEDICAL RESEARCH PRODUCTS DELETED DUE TO RADIOACTIVE WASTE ISSUES

Introduction

The Council on Radionuclides and Radiopharmaceuticals (CORAR)[1] members and their customers in the biomedical research community generate radioactive wastes including low-level-radioactive-waste (LLRW) and mixed waste. Difficulties in treating and/or disposing certain radwaste forms have caused the biomedical research community to restrict or eliminate research that generates these wastes. CORAR members who supply radiochemicals for the research community have had to delete certain products for similar reasons causing further restrictions on biomedical research.

Radiochemical Manufacturing

CORAR companies routinely manufacture commonly used radiochemicals and place them in stock. Customers from the research community can order these products from a catalog and typically receive them within a couple of days. These catalog products are consequently readily available. They can be batch processed by the manufacturer and the production scale results in them being inexpensive and therefore affordable to the research community.

These same radiochemicals can also be available as special orders where the customer specifies size, concentration and/or packaging, etc., for their particular need. Special orders are usually more expensive due to the extra processing and handling costs.

[1] CORAR is a North American trade association that includes members who are the major manufacturers and distributors of radiopharmaceuticals, radioactive sources and research radiochemicals used for therapeutic and diagnostic medical applications and for environmental and biomedical research and quality controls.

Radiochemicals can also be ordered from a manufacturer as a custom product. These are products that are individually processed for a customer where the process could be complex and may require research and development to build the required radiochemical. Consequently custom products are usually much more expensive than catalog products and may take weeks or months to manufacture.

Deletion of Catalog Products Due to Radwaste Issues

Since 1994, there have been a series of difficulties concerning the radwastes that are generated when radiochemicals are manufactured and used. Certain mixed waste forms have been very expensive to treat to provide a form that is acceptable for disposal. Another difficulty has been the high cost and unreliable access for disposal of LLRW.

Many States require that licensed manufacturers or users of radioactive materials must maintain a waste minimization program to reduce the quantity or the hazardous characteristics of radwaste. For certain radiochemicals the only practical way to achieve this requirement is to eliminate the product. Waste minimization and waste costs have caused manufacturers to delete many catalog products since 1994. If a researcher needs one of these deleted catalog products they either have to order it as a custom product or manufacture it themselves. These alternatives can be very unsatisfactory because it may be difficult to provide the product when the researcher needs it, larger quantities of waste are likely to be generated and increased processing and handling all result in increased cost. For example, a catalog product that typically costs three or four hundred dollars may cost thousands, even ten thousand dollars when manufactured as a

custom order. Often poor availability and high cost will make it unfeasible to order and the research must be abandoned.

Deleted Catalog Products

Table 1 is a partial list of over 100 catalog products deleted since 1994 out of about 1500 products previously offered by manufacturers. Most of these products were deleted to avoid the generation of mixed waste during manufacture. Other deletions were due to the need to avoid the generation of LLRW that was either too expensive to treat and/or dispose or there was no access for disposal. Table 2 is another partial list of over 200 additional deleted catalog products. These products were deleted for a variety of reasons which included radwaste difficulties.

Products Deleted to Avoid the Generation of Mixed Waste

Catalog products were deleted to avoid the generation of mixed waste because this waste form is often difficult and costly to treat for disposal. Since 2001, the Environmental Protection Agency's (EPA) Conditional Exemption Rule (1), when adopted by a State, allows radioactive material licensees in such State to treat mixed waste according to license conditions and State regulatory requirements. This is the preferred strategy for processing the higher concentration mixed wastes that are generated by manufacturers. However, treatment of certain mixed wastes can still be expensive. A common and particularly problematic group of mixed wastes are those with compounds containing fluorine or chlorine. These reactive elements often compromise catalysts that we need to treat the waste and may damage and require replacement of expensive processing equipment.

Licensed vendors are permitted to treat mixed waste with costs that vary considerably according to the properties of the waste. Some mixed wastes forms are prohibitively costly to treat and must be placed in storage until a viable treatment technology is available. Storing these mixed wastes can be problematic, for some manufacturers, because they typically have volatility, corrosion and flammability properties that must be controlled.

Manufacturers commonly use a sequence of chemical reactions to make a family of catalog products. If a processing sequence generated unacceptable waste, it is sometimes possible to avoid this by creating a different sequence. However, the alternative sequence may not be suitable for making all the products that were previously manufactured, resulting in further deletions from the catalog.

Although radwastes generated by end-users are usually lower quantity and lower concentration than those generated by the manufacturers, they can experience similar difficulties with mixed waste. This causes researchers to avoid using those products that generate mixed waste. This can lead to a drop in demand causing the manufacturer to delete a catalog product when demand is too low for it to be practical and/or cost effective to manufacture. Consequently researchers may only be able to use an alternative catalog product that may not exactly suit their needs or purchase a custom order that may be prohibitively expensive.

To summarize, numerous catalog products have been deleted because the costs of mixed wastes generated during manufacture or use of the product are too high.

Products Deleted Due to High Cost and Lack of Access for LLRW Disposal

Manufacturers have also deleted catalog products because of the high cost of, or lack of access for disposal of associated LLRW. Most manufacturers in the U.S. are located in States that are not members of a compact with a viable LLRW disposal site. These manufacturers used to send their Class B, C and Class A sealed source and biological radwastes to the Barnwell, S.C. LLRW disposal site. Since this site closed access to radwaste generators in out-of-compact States on July 1, 2008, these wastes must be placed in interim storage until a viable disposal option is available. Manufacturers do not know when another LLRW site will be available. We expect that to create a new site will take ten to fifteen or more years. The potential need to store LLRW at the generator's site for fifteen or more years raises several concerns requiring contingencies. We do not know the characteristics of a future LLRW site. The technology for processing and packaging radwaste is continuously developing. We are consequently unlikely to be able to accurately predict what waste forms will be acceptable for disposal in ten to fifteen years time.

Normal practice is to promptly treat radwaste, place it in final package ready for transportation and disposal, and send it to the disposal site as soon as a consolidated shipment is achieved. Some of this LLRW must be treated to improve its stability and reduce its leachability. Usually liquid wastes are converted to concrete or plastic forms. However, manufacturers have to consider that current treatments that are acceptable at today's disposal sites may not meet future disposal criteria. It might be too difficult or expensive to reprocess solidified radwaste. Manufacturers may have to store some of their LLRW in liquid or other

non-disposable form until the final disposal criteria are known. While this can be done safely, it is more costly to manage and is not the optimal procedure. Also, even if reprocessing is not necessary, we have an ongoing need to monitor LLRW accumulating in interim storage to ensure packaging integrity, airborne emissions and radiation levels are continuously controlled to meet stringent safety and security requirements.

Manufacturers currently have sufficient qualified space for interim storage for a few years. Also, most manufacturers have means to increase storage space. However, if interim storage is extended to fifteen years or longer, some manufacturers would need to establish new licensed storage facilities which might be both costly and locally unacceptable. Licensees are generally opposed to storing radwaste on site. Although historically, interim storage has proven to be safe and secure, the licensee may have to consider that the local public might have a different perception that must be addressed.

To summarize, the loss of access for disposal of certain classes of LLRW incurs extra occupational radiation exposure, and management, facility and disposal costs that are likely to increase as interim storage time increases. Licensees are required to reserve funds to pay for the ultimate treatment and disposal of radwaste in interim storage. Such financial assurance must anticipate potential cost increases. Alternatively, manufacturers can partially avoid these costs by minimizing the generation of LLRW that must be kept in interim storage. This has been done by deleting certain catalog products that generate excessive waste.

Historically, manufacturers generated Greater-Than-Class C (GTCC) LLRW that is very difficult and expensive to dispose in the U.S. To avoid this cost those precursor processes that generate GTCC were discontinued in the U.S. and these precursor materials are now purchased from Europe, which adds further cost to the manufacturing process.

Another concern is that the costs of disposal of radwaste at accessible LLRW sites vary considerably and are mostly excessively high due to various surcharges that are imposed. Consequently difficult access for LLRW disposal and the high cost of disposal have led to numerous catalog products, listed in Table 1, being deleted.

Other Reasons for Deleting Catalog Products

CORAR has information on over 200 additional catalog products that were deleted since 1994. These are listed in Table 2. They were deleted for various combinations of multiple reasons. At this time we have not yet determined the primary reason for deletion. Similar to the products listed in Table 1, products in Table 2 were deleted due to mixed waste, loss of access to LLRW disposal and the high cost of disposal. Also, some of these products were deleted because the research community stopped buying them because they had similar concerns about treatment and disposal.

Research institutions typically have less qualified radwaste storage space than manufacturers. Because of this, there have been numerous restrictions and administrative prohibitions on using long-lived radionuclides that are needed for biomedical research. During the past 20 years, researchers have been increasingly using alternative research methods with

non-radioactive chemical tracers. The research community needs to have access to a variety of techniques to use in their research. However, a concern is that we are foregoing radiotracer methods that provide better precision, are easier to use and should be less costly. Also many non-radioactive tracer methods use hazardous chemicals where controls on handling and disposal are not as effective as the controls on radioactive material uses.

To summarize, the radiochemical manufacturing industry used to supply about 1500 catalog products prior to 1994. Since then over 100 catalog products were deleted due to the high cost of treating mixed waste and the lack of access and high cost for disposal of LLRW. In addition, over 200 catalog products were deleted for multiple reasons including radwaste issues.

Biomedical Research Potentially Jeopardized by Deleted Catalog Products

To understand the consequences of LLRW difficulties on biomedical research, we shall now review deleted products in Table 1 and explain what research may be jeopardized when these products are difficult to obtain or use.

Starting near the beginning of Table 1, there is a group of ^{14}C- labeled amino acids including aspartic acid, histidine, isoleucine, threonine, tyrosine and valine. These are used mostly to study metabolism and metabolic deficiencies. They are also used by researchers to make other radiochemicals. This is actually done by feeding these amino acids to organisms that create other radiochemicals that can then be used further in molecular biology and other research.

The ^{14}C-labeled fatty acids; stearic acid, oleic acid, arachidonyl CoA, myristic acid, eicosatrienoic acid, eicosapentaenoic acid and docosahexaenoic acid are used to document changes in the metabolism of these fatty acids in mouse/human models of metabolic disease.

^{14}C-labeled pyrene and ^{3}H-labeled benzopyrene are used in environmental fossil fuel pollution studies.

The following examples from Table 1 are all ^{3}H-labeled radiochemicals:

- The two hydroxyl eicosatetraenoic acids are prostaglandins used for testing receptor centers.
- Retinoic acid is used for neurochemical binding studies on neuron receptors.
- Cholesterol, testosterone and dehydro epiandrosterone are steroids used to study steroid receptors.
- Dinitrofluorobenzene is used in photochemical experiments in cells.
- Benzopyrene, again, and phorbo-myristate-acetate are used to test the mechanisms of tumor formation in cancer research.
- Phencyclidine, ethylketocyclazocine and amino clonidine are ligands which are used to study neuroreceptors.
- Propylbenzilylcholine mustard HCl, tetrophenylphosphonium bromide and imipramine hydrochloride are drug-like ligands also used to study neuroreceptors.
- Two enkephalin radiochemicals are peptides used for studying the effects of endorphins in humans.
- Zolpidem is a drug used to study relaxing and sleep induction.

- The ligands telenzepine, CGS 19755 and S-(-)-BAY K8644 are also used to study receptors and the last one used for cardiovascular receptors.
- Dextromethorphan is an opiate used in opiate receptor studies. 9-CIS Retinoic acid and Retinol all rans are used to study and potentially treat skin cancer.

Table 2 is another list of deleted catalog products. There were multiple reasons for deleting these products including radwaste difficulties. Again we find that these products have important beneficial uses for society that may be not currently available unless they can be once again manufactured as a catalog product. In Table 2:

- Three deleted ^{3}H-labeled radiochemicals, androst-4-ene-3, 17-dione, dihydrotestosterone and testosterone are used for studies of the androgen steroid receptor to improve knowledge and prevention of prostate cancer.
- Other ^{3}H-labeled radiochemicals include estradiol, estrone and hydroxyprogesterone are used to study the estrogen receptor to understand and prevent breast cancer. Tamoxifen is used to better understand the biological behavior of this drug which is used to treat breast cancer.
- Hydroxy eicosatetraenoic acids and prostaglandin-E1 are prostaglandins used in cancer research to study receptors' complex signaling pathways that might promote tumor growth.
- Morphine and bremazocine are analgesics used to study the control of pain in cancer patients.

- Clozapine, haloperidol, prazosin, SKF10,047,QNB and DOB are ^{3}H-labeled radiochemicals used to study neurochemical receptors of the central nervous system and cardiovascular system.

These lists of deleted products can be used by the research community to identify planned research that was delayed, restricted or canceled due to radwaste difficulties. This information would be useful to share with regulators, legislators and other stakeholders. It should serve to demonstrate the benefits to society that could be recovered and justify the need to provide reliable and cost effective LLRW disposal for the radwaste generated during manufacture and use.

Other LLRW Concerns in the Biomedical Community

The focus of this paper is on radiochemicals that are used in biomedical research. However, it should be recognized that medical therapy and diagnosis and biomedical research use of radiopharmaceuticals and sealed sources are also compromised by LLRW disposal difficulties. For example, ^{90}Y is extensively used in cancer therapy clinical trials. It is manufactured mostly in the U.S. from ^{90}Sr. The ^{90}Sr waste generated is mostly Class B LLRW that has no disposal pathway and is being accumulated in interim storage. Similarly, disused ^{90}Sr eye applicators are being placed in interim storage in numerous hospitals due to lack of access for disposal. Disused sealed sources in most States containing ^{60}Co and ^{137}Cs used in blood irradiators and for medical instrument quality control also lack access for disposal.

A major national concern is the increasing unreliability of aging foreign reactors to supply ^{99}Mo, the most commonly used radiopharmaceutical in nuclear medicine. Covidien, Babcock and Wilcox and the Missouri University Research Reactor (MURR) have plans to

develop a reliable domestic supply but may not have the ability to dispose of the moderate quantities of LLRW that would be generated, and MURR lacks qualified space to place LLRW in interim storage.

The Need for Out-of-Compact Access to the Andrews County, Texas LLRW Disposal Site

A critical concern of the biomedical community is that lack of access for disposal of LLRW leads to increased cost and this and the artificially high costs of disposal currently available decreases funds available for biomedical research and healthcare. There is a critical need to provide reliable, cost effective LLRW disposal. An obvious solution to this problem is to allow the research community and their suppliers in out-of-compact States to have access for disposal of LLRW at the Andrews County, Texas LLRW disposal site. The world class Texas cancer research facilities, including Texas MD Anderson Cancer Center, Houston, University of Texas Southwestern, Dallas and University of Texas Health Science Center, San Antonio, will soon be able to dispose their radwaste in Andrews County. However, it is also a benefit to these institutions if their out-of –State radioactive materials suppliers also have access for LLRW disposal.

The Texas Compact Commission must be applauded for their leadership in establishing the first new LLRW disposal site for commercial radwaste under the compact system. It is of critical concern to licensees that this facility is successful. Opening access for out-of-compact radwaste from the research community and their suppliers should make a significant contribution towards this site achieving financial viability. To ensure that Class B and C radwaste disposal options are reliable, cost-effective and accessible, it is essential that Federal and State regulatory agencies maintain and establish conducive policies and regulations. Regulatory agencies and

policy makers should determine and avoid any unintended consequences that could effectively strand Class B and C radwaste indefinitely.

CORAR therefore requests that the Andrews County LLRW disposal site be opened for access to radwaste generators in out-of-compact States and believes that this will be of benefit to our community and Texas licensees, who we supply, the financial viability of the site and the healthcare of society we all serve.

REFERENCES

1. U.S. Environmental Protection Agency, 40 CFR Part 266 Subpart N – Conditional Exemption for Low-Level Mixed Waste Storage, Treatment, Transportation and Disposal. Federal Register, May 16, 2001, Volume 66, Number 95.