

**Chapter 1 : Contents - Cell Culture - ALPF Medical Research**

*Fleck, R. and Fuller, B. () Cell Preservation, in Medicines from Animal Cell Culture (eds G. Stacey and J. Davis), John Wiley & Sons, Ltd, Chichester, UK. doi: /ch21 Division of Cell Biology and Imaging, National Institute for Biological Standards and Control, South Mimms.*

Examples are given below. There is now a specific product for this purpose – Neurocell PD cell therapy. The market for cell therapy is huge. Sheets of keratinocyte are produced for burns patients e. Other products are OrCell, which stimulates repair and a regeneration of tissue, and CCS composite cultured skin, which is a dermal and epidermal layer supported in a bovine type I porous collagen matrix. To avoid rejection, active cells are encapsulated in a porous membrane or fibre e. A wide range of potential cell therapies Gage, is listed in Table 1. These techniques give rise to a new technological challenge – that of scale-down of bioreactors. For implantation small bioreactors supporting in excess of cells in a small, semipermeable unit that will keep cells viable and active for long periods of time are needed. The future is expected to be dominated by stem cell therapy, i. Over clinical products are under investigation or in trial but are beset by many problems, including development of safe and efficient gene delivery systems Clayton b; Chapter 9. The principal targets are Anderson Even when successful, treatment may still be ineffective in many diseases because the offending gene is still present e. A problem is that a single gene deletion or malfunction may need several replacement genes to effect repair of the malfunctioning gene. Gene therapy techniques are: The main research effort is currently on engineering viruses. The era of modern medicines has achieved a great deal but we are still currently in this period because there is so much more to be achieved, particularly in overcoming the basic problems in gene therapy. At some stage the critical technical breakthroughs will be achieved that will see a dramatic range of diseases being treated by these novel technologies. The landmarks have been: Product range Target diseases Vaccines: Against this list of landmarks, the cell culture process itself has shown remarkable progress. In multiple flasks, followed by roller bottles were used and this developed into 10<sup>20</sup> 1 unit processes based on stirred or airlift bioreactors with innovative adaptations such as spin filters for perfusion. It is interesting to reflect that after 45 years of trying every means possible to scale-up, a current requirement is for scale-down for implantable bioreactors. Products have been highlighted that have had a particular significance in the development of animal cell technology. These are by no means the only products produced with animal cells and a full list is given in Table 1. The subject is still evolving fast and is no longer the province of just chemical engineers, but now includes a range of disciplines from the biochemist and geneticist through the various engineers to medical practitioners. Also the cell is now becoming the principal product rather than just being a vehicle or factory for producing proteins. Academic Press, London; Vol 5: Academic Press, London; Vol 4: Gage FH Nature Supplement ; Kubicek MT Cancer Res. Gold M A Conspiracy of cells. IRL Press, Oxford; – Oxford University Press, Oxford; 19 – Laboratory Procedures in Biotechnology. Academic Press, London; Vol 6: Kluwer Academic Publishers, Dordrecht. Marcel Dekker, New York; Vol. Academic Press, London; Vol. Initially his main concern was making the water fit and palatable to drink. In The Deipnosophists dating from BC, Athenaeus of Naucratis describes how the Egyptians purified jars of river water by a combination of exposure to sunlight and air, straining and allowing to settle overnight. Similar techniques are seen in engravings in Egyptian tombs dating from the fifteenth century BC Purchas However, it was in the nineteenth and twentieth centuries that drinking-water purification technologies developed on a large scale, for example with the introduction of compulsory filtration of drinking water in London in , and the addition of chlorine to control bacteria levels in water in the UK in Scott Distillation has long been the method of purifying water for scientific use. A still was standard equipment for alchemists in the Middle Ages Saunders It was not until the twentieth century that it was displaced as the major water purification process following the invention of a whole battery of alternative technologies, such as ion-exchange softening in Gans , cation and anion exchange in Adams , and reverse osmosis in the s Loeb ;

Schultz These and other technologies have been developed and refined to meet the ever more stringent demands for highly purified water of the microelectronics and pharmaceutical industries see, for example, ASTM 99 and ultra-trace analytical techniques such as ICP-MS and gradient HPLC. Purified water is a key component in cell culture work and related preparative and analytical activities. The water purity is critical. This water can be provided by a variety of means and the approach chosen is often a function of the other activities on-site. The purity specified and technologies used are based on a combination of the technical requirements of the work and the selection of a suitable standard specification that corresponds with these requirements. This chapter will provide some background information on impurities present in water and their origins, the standards to be met and the means to achieve the required purity. Potable water is sourced from a combination of surface water, river water and underground aquifer. Impurities originally present can be divided into dissolved ionic matter, organic compounds, particulates, colloids, and a range of bacteria and other life forms. Dissolved salts are leached into the water from rocks or soil – calcium, sodium, bicarbonate, chloride and sulphate are the most common ions found. Organic compounds in the feed-water are both naturally occurring and man-made. The former are mainly a complex mixture of fulvic and humic acids and tannins derived from the decomposition of leaves and grasses. Industrial, agricultural and domestic wastes contribute detergents, solvents and oils along with fertilizers, herbicides and pesticides. As the water is treated to make it suitable for domestic or industrial use, many of the impurities are removed, among them heavy metals and pesticides, but others are introduced, for example plasticizers from plastic pipes and tanks. Other compounds are produced by reactions with the chlorine or ozone used to control bacterial levels. The main alternatives to potable water as a water source are boreholes that take water directly from an aquifer. The cost savings advantage of this approach can be seriously offset by the need for extensive extra water treatment to bring the water to a sufficient standard for purification. Dissolved iron and carbon dioxide can be particularly problematic in such waters. Where the purified water is to be used for pharmacopoeia applications there is a further requirement that the source water is of an equivalent purity to potable water USP ; EP Depending on local sources the impurities in mains water will vary widely. Typical ranges are shown in Table 2. In addition, levels of ionic contaminants, especially multivalent ions and heavy metals, and organic contaminants must be kept low. For ancillary operations, such as initial rinsing of equipment and some media preparation, less tight specifications are acceptable see Finter et al. The potential adverse effects of endotoxins on cell culture have been widely reported see Case Gould Dawson produced an interesting review, highlighting the wide range of effects and great variation in sensitivity of even parent and daughter cell lines. A series of papers describing the interactions of endotoxins with cells are included in Levin et al. Endotoxins are well known to have deleterious effects on in-vitro fertilization, see for example Fukuda et al. Weiss and Goldwasser observed that the biological effects attributed to erythropoietin were, at least in part, due to the use of material contaminated with bacterial endotoxin. However, standardized measurements of bacterial endotoxin use the limulus amoebocyte lysate assay Novitsky , USP that determines endotoxin levels in international units for which the acceptable maximum limit for water for injection WFI is 0. However, even this standardized test for endotoxin will not detect the non-classified endotoxins of Gram-positive organisms. These are detected only by the use of human peripheral blood leucocytes Gaines Das et al. Pseudomonas species are the bacteria most widely found in purified water. As described in Whitehead , salts present can form deposits that can act as centres for bacterial growth. Dissolved organic compounds, also act as a source of nutrients for bacteria. Organic compounds present in the water can also cause a variety of problems with trace HPLC and GC analyses including poor detection limits and reproducibility, and contamination of separation media and detectors. Examples of the sensitivity of analyses to trace contaminants are given by Anantharaman et al. The organizations and relevant water grades are summarized in Table 2. Of these, the pharmacopoeial standards are the ones most widely applied to cell culture production activities. Many countries produce and apply their own pharmacopoeial standards. For the different grades of purified water these pharmacopoeia set broadly similar standards with the main differences relating to restrictions on methods of production and testing. In

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practice, the key standards are those set down by the US and European pharmacopoeias USP ; EP ; see web site addresses at the end of the chapter. This grade is identical in terms of purity Table 2. These specifications are summarized in Tables 2. Mains water tends to be produced locally and contains a wide variation in impurities that have to be removed before the water is fit for purpose. As shown in Table 2. The maintenance of low bacterial levels within a water system is a particular challenge and needs to be considered at each stage of the system design. Water purification will normally consist of several pre-treatment steps, the choice of which is largely governed by the nature of the local feedwater, main purification in one or more stages and final treatment to achieve and maintain the required water purity. Water for Injection Highly Purified Water.

## Chapter 2 : Research Publications

21 Cell Preservation (R Fleck and B Fuller). *PROPERTIES OF CELL PRODUCTS*. 22 Product Characterization from Gene to Therapeutic Product (K Baker, S Flatman and J Birch).

## Chapter 3 : Norma S Kenyon, Ph.D. " Research Output " University of Miami's Research Profiles

*Provides comprehensive descriptions of methods for cell culture and nutrition as well as the technologies for the preservation and characterisation of both the cells and the derived products Describes the preparation of stem cells and others for use in cell-based therapies - an area of burgeoning.*

## Chapter 4 : Advances in Biopreservation: 1st Edition (Hardback) - Routledge

*While methods for the cryopreservation of hematopoietic stem cells are well established, new sources of progenitor cells, such as umbilical cord blood, fetal tissue, and ex vivo expanded.*

## Chapter 5 : Medicines from Animal Cell Culture : Glyn N. Stacey :

*PROCESSING AND PRESERVATION OF CELLS AND PRODUCTS R Fleck and B Fuller. PROPERTIES OF CELL PRODUCTS 28 Cell Culture in Tissue Engineering*

## Chapter 6 : Medicines from Animal Cell Culture : John M. Davis :

*Medicines from Animal Cell Culture focuses on the use of animal cell culture, which has been used to produce human and veterinary vaccines, interferon, monoclonal antibodies and genetically engineered products such as tPA and erythropoietin. It also addresses the recent dramatic expansion in cell-based therapies, including the use of live cells for tissue regeneration and the culture of.*

## Chapter 7 : Medicines from Animal Cell Culture - Glyn N Stacey, John M Davis - Bok () | Bokus

*Medicines from Animal Cell Culture focuses on the use of animal cell culture, which has been used to produce human and veterinary vaccines, interferon, monoclonal antibodies and genetically.*

## Chapter 8 : 21st Century Medecine Publications

*PROCESSING AND PRESERVATION OF CELLS AND PRODUCTS R Fleck and B Fuller PROPERTIES OF CELL PRODUCTS 28 Cell Culture in Tissue Engineering*

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## Chapter 9 : Medicines from Animal Cell Culture - PDF Free Download

*For osmotic excursion (dehydration) of a mammalian cell through the addition of glycerol (for this example a murine oocyte), there was a large initial shrinkage as water flowed out of the cell.*