



ARCHAEA: UNDERESTIMATED DOMAIN IN PHARMACEUTICAL QUALITY CONTROL

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ABSTRACT

Quality control monitoring of microbiological attribute of the pharmaceutical environment - including pharmaceutical water and compressed gases- and products is an essential prerequisite to judge the goodness of the manufacturing environment and safe release of the pharmaceutical article into the market, respectively. While most of the quality control tests mainly focus on detection and/or enumeration of both bacteria and fungi, Archaea were not considered on regular testing despite the fact that they are widely distributed in nature and found in human body. Conventional culture techniques in laboratories are not suitable for most members of Archaea. The ever-growing number of patients with a defective immune system - accompanied by increasing list of objectionable microbes - highlights the potential risk that may emerge from underestimating other non-culturable microorganisms on traditional microbiological media even if it has not shown any signs of pathogenesis till now. The pharmaceutical technology should overcome this barrier to guard against any possible outbreaks provisionally that may emerge from creeping microbes undetected to the body of patients in addition to the possible spoiling of pharmaceutical products, especially those with significant water activity.

Keywords: Quality control, Archaea, Non-culturable, Pharmaceutical products, Water activity

INTRODUCTION

The earth aged more than 4.5 billion years [1, 2] & the earliest form of life may have been emerged from 4.1 years as evidence of biotic life has been discovered recently in 2015 at western Australia [3, 4]. Microorganisms from Archaeal lineage may be the oldest form of life that existed on earth [5]. Figure 1 shows the evolution of the three domains (Bacteria, Archaea and Eukarya) from common ancestral life source [6]. However, there are many differences that exist between the three domains. Among which is the diversity that exists in Threonyl-tRNA synthetase (ThrRS) - as an integral part in the protein synthesis quality control - between both bacteria and eukaryotes on one hand and Archaea on the other hand. Most Archaeal ThrRS lacks the editing domain that is present in the other two domains [7].

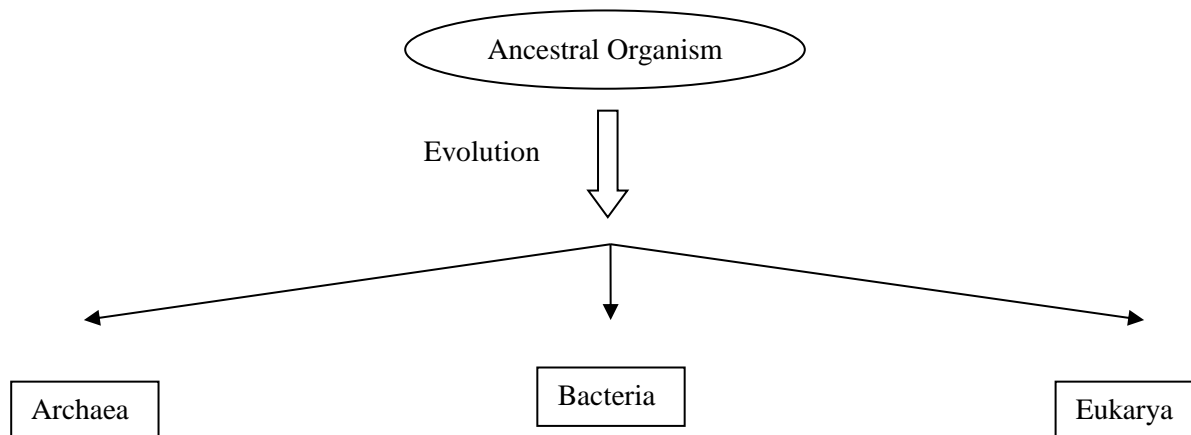


Figure 1. Simple diagram of the evolution of life on earth [6]

Archaea were assumed to be extremophiles that live in extreme environmental conditions at the beginning. However, after that they have been found at different wide range of habitat including oceans, marchland, soil, oral cavity, human colon and skin [8]. Accordingly, an overview of the possible provisional impact of this domain in the pharmaceutical field will be discussed in the next section.

EXPOSURE OF PHARMACEUTICAL INDUSTRY TO ARCHAEA

Monitoring of microbiological quality of both pharmaceutical products and manufacturing area including utilities of compressed gases and water is critical aspect to judge the safe release of manufactured articles into medical market. Most of microbiological quality control (QC) tests and environmental monitoring (EM) programs focus on different types of bacteria and fungi (yeasts and molds). These routine monitoring regimes aim to enumerate, detect and/or identify microbial entities in pharmaceutical manufacturing areas and product matrix [9]. However, human body and the surrounding environment harbor diverse types of other microorganisms that belong to domain Archaea. It includes different well identified genera such as *Thermoproteus*, *Thermococcus*, *Methanococcus*, *Methanosarcina*, *Methanopyrus* and *Thermoplasma* [10]. The comparison between the three domains (Eukarya, Archaea and bacteria are shown in Table 1 [11, 12].

Most of these microorganisms require techniques that are different from those methods which depend on ordinary culture media which are used in conventional microbiology laboratory [13]. Moreover, many of Archaeal species can survive harsh environmental conditions (physical and chemical) that surpass that of bacteria due to unique enzyme system [14]. Thus this domain may survive different hostile manufacturing conditions. Although there is not any strong proof that links Archaea with any type of human pathogenesis, yet the ubiquitous nature of this domain is expected to represent challenge



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for controlling the microbiological quality in clean rooms and sterile manufacturing. Many medicinal and pharmaceutical articles are dedicated for ill-population with many procedures of administration involving invasive processes that penetrate natural body barriers. The risk may be intensified when considering increasing number of patients with defective immune system or under treatment with immunosuppressive medication. Food and drug administration (FDA) continuously updates the list of objectionable microbes. Most of them are not covered in the official guidelines such as pharmacopeia [10]. The testing for each will be laborious, time consuming and expensive. Accordingly, each firm must justify testing of specific groups of microorganisms by intelligent approach using risk assessment.

Table 1. Comparison between the three domains that constitute universal phylogenetic tree that is believed to stem from common ancestral organism [11, 12]

Comparison	Eukarya	Archaea	Bacteria
1. Mean of reproduction	Asexual and sexual	Asexual - horizontal gene transfer	
2. Method of metabolism	Cellular respiration and photosynthesis	Diverse	
3. Presence of membrane bound organelles and nucleus	+	-	
4. Genomic structure	Many linear chromosomes	Circular chromosomes	
5. Transcription and translation	Similar		Unique
6. Composition of the cell membrane	Various structure (ester-linked lipid)	Pseudopeptidoglycan (ether-linked lipid)	Peptidoglycan (ester-linked lipid)

Archaea has the ability to form biofilm - like bacteria - and hence may influence the quality of water used for pharmaceutical purposes [15]. This effect may extend to damaging effect on water stations. The consequences are severe financial loss with possible adverse microbiological quality on manufactured products. Product with significant water activity such as liquid oral products and topical creams are normally prone to spoilage by virtue of high water content that is available for microbial survival metabolism. The source of contamination may originate from manufacturing facility and/or final consumer of the product. Preservatives are added as a safeguard for this reason against microbial proliferation and spoilage of the product. The effect of these chemicals and its interaction with Archaea are poorly studied with limited data [16]. The practical problem to include archaea in regular QC test at present is influenced by the current limitations of the conventional microbiological media that are widely used in the routine monitoring in pharmaceutical industry. Many archaeal species cannot be grown on culture media but the new expensive molecular technologies are able to detect them. Microbiological culture media are already suffer from several limitations such as underestimation of



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the actual population present in the sample in addition to the inability to detect those microbes that enter into the state of viable-but-not-culturable (VBNC) [17].

CONCLUSION

Monitoring of bioburden is important to justify safe pharmaceutical release. However, the current conventional techniques suffer from limitations in sensitivity, especially when considering domain Archaea. Some of the new and innovative techniques may be useful for detection and/or enumeration of Archaea. The assumption of the all Archaea members are non-pathogenic could be an overestimation because till now limited reports have been addressed about their interaction with human and other mammalian bodies. Accordingly, careful control in the ecological distribution of Archaea is needed to avoid any source of microbial outbreak in the future through pharmaceutical articles. The passion of researchers - to make best use for microorganisms from domain Archaea in different biotechnological and industrial applications - should not obscure them from extensive evaluation of its interaction with human and animals and the possible emergence of risk from contamination with these “ancient” microbes. The effect of Archaea in the pharmaceutical field should be extensively subjected to scientific studies to assess their possible risk on this vital industry.

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