3G5 exam 2023/24 Crib

Q1

(a) The procedure involves an incision in the patient's groin and then a guidewire is inserted through the aorta (largest artery leaving the heart) to the arteries surrounding the heart. A catheter is then inserted along the guidewire. Once the catheter is in place, a small amount of contrast material (dye) is injected through the catheter and is photographed with an X-ray [*tentative answer*] as it moves through the heart's chambers, valves, and major vessels to find the blocked vessel. The doctor will move the catheter into the point of narrowing in the vessel. The catheter (known as a balloon angioplasty catheter) contains a deflated balloon at its tip. The balloon is inflated to open and widen the blocked vessel, compressing the plaque against the wall and restoring blood flow. The balloon is withdrawn after deflating.

The main criterion in deciding on the placement of a stent is the outcome of balloon angioplasty. If the vessel collapses after balloon angioplasty, then the surgeon will place a stent.

(b) Stents can be divided into two main groups on the basis of the method of expansion. *Balloon expandable stents* arrive premounted on a balloon anglioplasty catheter. While mounted the stent is moved into place and the balloon is inflated to expand the stent to the desired diameter. *Self-expanding stents* come premounted or sheathed. Once deployed to the treatment area, the sheath is pulled back, allowing the stent to expand to its predetermined diameter.

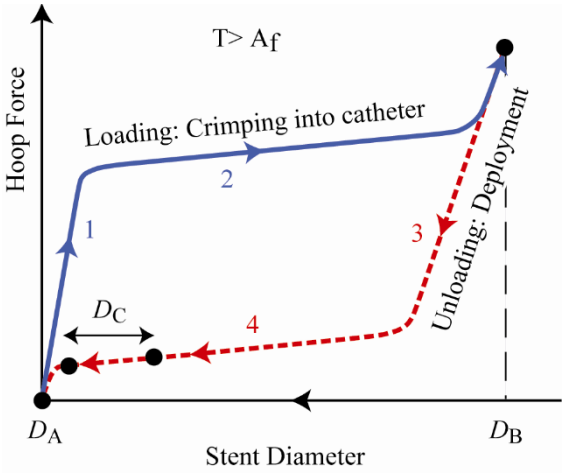
Balloon expandable stents expand by *plastic deformation* by an angioplasty balloon while self-expanding ones use the "*superelasticity*" or the "*shape memory*" effect.

High flexibility, i.e. low axial beam stiffness is required during delivery of a stent to allow the stent to curve around corners and hence reduce injury to the vessel wall. This is achieved by having strut members at high orientation angles with respect to the horizontal at all positions along the length of the stent.

(c) Both superelasticity ("pseudo-elasticity") and shape memory involve martensitic transformations. Martensitic transformations occur by means of a phase change from a "parent" phase (austenite) to a "martensitic" phase. In superelasticity martentisitic transformations are stimulated by imposed mechanical stress whereas in shape memory they are stimulated by changes in temperature.
The conditions that must be satisfied for the two effects are: For superelasticity, the material needs to be in the parent phase (austenite) (i.e. $T > A_f$). In shape memory, the material is in the martensitic phase (i.e. $T < M_f$). Also, shape memory involves the concept of training.

The superelastic effect takes place when the material is in the parent phase (austenite) (i.e. $T > A_f$) The stent in the parent phase (austenite) with an original diameter D_A (higher than the relaxed diameter of the vessel) is collapsed to a small diameter D_B and constrained by a sheath. Initially, there is conventional elastic straining (Regime 1), which is then followed by a superelastic plateau whereby the austenite transforms to martensite (Regime 2). The crimped stent is then inserted into a catheter. Once delivered into the desired location, the sheath is pulled back. Initially the stent gets elastically unloaded (Regime 3) followed then by reversal of the phase transformation (Regime 4). The stent is trying to recover its original shape but is constrained from full recovery to D_A by

the lumen walls. The stent exerts an outward force on the vessel (trying to expand to its relaxed diameter) and, conversely, the vessel exerts a constrictive force on the stent. A suitable equilibrium diameter is then established with a value intermediate between these two (D_C).



The obvious choice for a cardiovascular stent is to utilise the superelastic effect as it does not rely on changes in temperature. In superelastic stents, the stimulus for the transformation is provided by crimping the stent onto a catheter whereas in shape memory stents, a change in temperature is required for the deformed stent to recover its original shape. The latter requires that the stent is kept in the martensitic phase (low temperature phase, eg in cold saline) and, once in the desired location, retraction of the sheath allows the stent to expand and warm up to body temperature and recover its shape.

(d) The early complication of stenting involves thrombosis that occurs within a few days of the procedure. This complication is largely overcome by treating patients with anti-platelet agents such as aspirin. The major long-term complication of stenting is vessel renarrowing (restenosis), known as "Neointimal Hyperplasia", which occurs within 6 months or so in 30% of patients who are stented. This is attributed to post-implant injury (roughly analogous to a scar forming over an injury) and a foreign body response. The following four treatments are used to stenting complications.

1. Electropolishing is commonly carried out, in order to smoothen the stent metal surfaces and hence reduce the danger of injury to the vessel wall.
2. Passivation to improve the corrosion resistance of the metal surfaces and inhibit any inflammatory reactions.
3. To reduce the danger of neointimal hyperplasia, approaches included degradable and non-degradable polymeric coatings.
4. Drug eluting coatings. In drug-eluting stents, drugs are embedded in a polymer matrix that is coated onto the stent. The drug is released into the vessel by diffusion and/or polymer degradation over varying periods of time that can be engineered by the specifics of the polymer-drug system.

[<u>Examiner's comment</u>: This was a question on cardiovascular stent. The question was answered well by most candidates and a good score was achieved.]

Q2

(a) (i) A basic answer will give a clear indication that the student understands what is meant by classification of a medical device and will indicate a valid challenge. A strong answer will show an excellent understanding of that challenge. Only one challenge is requested.
One challenge will be deciding if this indeed falls under medical device regulations or in fact needs to be dealt with under medicines regulations. As it is a new device the firm will not have been through this before and will need to decide based on the regulations and maybe through advice from a Competent Authority if following European Regulations. This is because insulin is clearly a medicine, a single use syringe would be considered a device if that was the mode of delivery. A disposable device with integrated insulin is considered to fall under medicine regulations, while the re-usable devices would fall under the medical devices regulations. It would not be expected that a student could give this level of detail but they would note that there is uncertainty depending on the delivery method.
Another example challenge is dealing with two separate devices. The firm will need to be very clear what is the potential hazard to the patient and then classify both devices (watch and implant) to that level. All challenges noted will be considered, such as the long time that may be needed to identify the classification, or the cost of going through a professional service if the expertise is not already within the firm, etc.
(ii) This needs the student to provide other challenges beyond just device classification. Also, the question refers to the device described at the beginning and so while a basic answer will give general challenges accurately, a strong answer will make sure these relate back to this particular device.
These may include:
The integration of machine learning means that the rules around regulations are still under development, which may either delay approval or mean they will change again in the near future.
The fact this is a long-term implantable device delivering essential medicines means it is likely going to be a Class III medical device and so there will need to be a very detailed report prepared for the approval including information from clinical trials. These trials will also be very expensive for the firm.
There will need to be biocompatibility studies that relate to long term implantation of the device, following all the required international standards. This is to ensure any degradation or leachants over time are fully understood.
Identifying a sterilisation technique may be challenging if the medicine is integrated into the implantable, because sterilisation may impact the function of the active ingredient. Alternatively, a sterile/aseptic manufacturing setup will be required.

(b) A basic answer will give a clear understanding of 2-3 challenges or a very brief overview of 4 challenges. A strong answer will show a very good understanding of any four challenges. This is not a topic that was expressly tackled in the class and so is expecting the students to draw upon their knowledge from across the lectures and apply it to this situation.
One challenge will be sterilisation. Medical devices, such as equipment used in a surgical theatre, or gowns, may be re-usable with decontamination and sterilisation. Hospitals will likely have some sterilisation technique in-house (often steam sterilisation / autoclaves). It is very unlikely that hospitals will have a suite of sterilisation techniques available. If the original manufacturer selected a particular technique, then it may have been due to cost or to

ensure it did not effect the function of the device. This means they may not have a sterilisation technique available that is suitable for the device.
A second challenge linked to sterilisation is how the hospital will know that they have not changed the product, its biocompatibility, its mechanical properties etc. after sterilisation. This means if may not be suitable for devices if this could lead to a risk for a patient.
A third challenge linked to sterilisation is the overall cost due to energy required and capital expenditure may cancel out any savings on devices.

Another challenge is that many devices (eg syringe bodies, catheters) are noted as single use devices. If the hospital decides to decontaminate and re-use these devices, they will take on the responsibility of the manufacturer in terms of safety, port-market surveillance, etc. this challenge could be broken down into further challenges relating to manufacturing of devices, such as ensuring there is a unique identification code now included on the device so they can trace its remanufacture, needing to get approval, etc.
There may be bioethical challenges raised, thinking about if informed consent is needed when moving to a re-used medical device with a patient.

(c) (i) A very strong answer will indicate a clear understanding of bioburden and sterility assurance level as the initial level of contamination and the target level of sterility (likely 10^{-6}). It will explain how tests will need to be carried out at multiple exposure times, at each point measuring the level of contamination. It may be noted that these could be plotted in a log-linear graph or simply noted they will be used with the bioburden to extrapolate to the sterility assurance level. A graph may be used to explain this too. There may also be comments such as using a most resistant organism for these tests, or including other tests to ensure in the future parametric release can be obtained. A basic answer will just note that tests over time will be used to extrapolate to the sterility assurance level and allow the time to be calculated.
(ii) This is a very brief question to just examine the basic understanding of sterilisation techniques. Only very brief answers are needed. For example:

- in steam sterilisation the temperature and pressure will need to be measured
- in radiation sterilisation then the dose will need to be measured, i.e. 25 kGy
- in ethylene oxide sterilisation, there are a range of parameters, such as relative humidity, concentration of ethylene oxide, pressure, temperature, etc.

the answer requires 4 process parameters and they do not need to be from 4 different techniques. The answers above are the most likely to be drawn upon. A very strong answer will show a good understanding of which parameters are linked to which sterilisation techniques.

[<u>Examiner's comments</u>: This was a popular question on regulatory standard and sterilization of medical devices. Nearly all candidates were able to provide comprehensive answers and thus a high average score was achieved.]

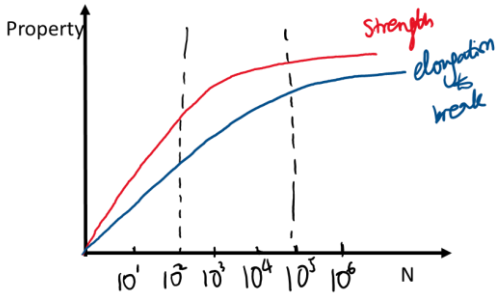
Q3

(a)(i) Heart valve flap is in direct contact with blood and is subjected to blood flow (shear stress and impacts). Thus, the biomaterial biocompatibility consideration should be blood-

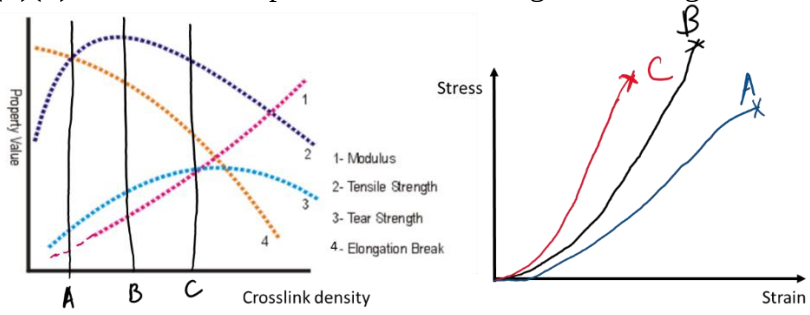
compatible, thrombo-resistant, biochemical stability, mechanically durable (fatigue, toughness, impact resistant), and having smooth surface which is preferably erosion resistant. For a permanent implant, the properties should remain for over a number of years. Pyrolite® Carbon is strong and mechanically durable (durability over 20 years), but does not have the thrombo-resistant property, thus the patient will need to undergo life-long anticoagulation treatment. Cell-free biological tissues have blood compatibility but comparatively poorer mechanical durability, and will need to be replaced after about 8 years.

(a)(ii) The biocompatibility and material selection is dependent on the site of the suture implantation. Nylon (or polyamide) suture is suited for superficial tissues with low regeneration ability like suture. A biodegradable/ hydrolysable system (e.g. PLGA) would release degraded products which cause inflammation in the cornea which cannot be regenerated. Thus a non-biodegradable, non-hydrolysable polymer with adequate tensile property and good surface finishing is needed. For suture used for internal organs having regeneration ability, the PLGA suture offers the advantage of biodegradability in situ without needing to have a second surgery.

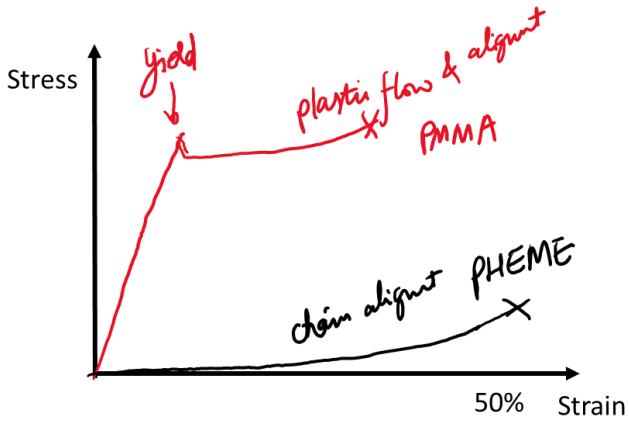
(b)(i) This will be dependent on which regime the degree of polymerization lies.



(b)(ii) This will be dependent on which regime the original crosslinking lies.



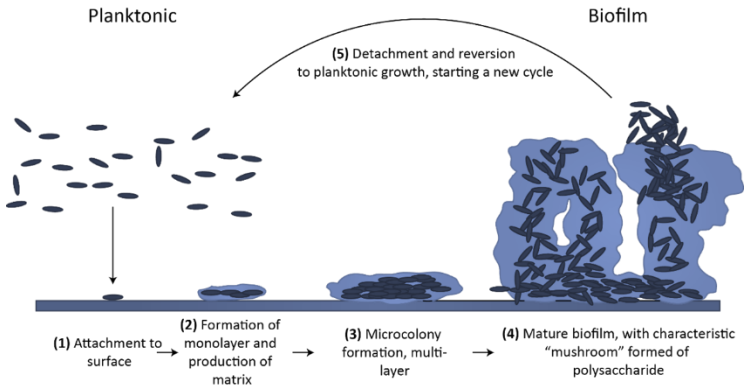
(b)(iii) PMMA has orders of magnitude higher yield stress than the failure stress of hydrogel (PMMA sigma_f~ MPa, while PMMA sigma_f~kPa), hence expected hardness and wear-resistance of PMMA will be better. On the other hand, hydrogel has orders of magnitude lower modulus than PMMA (PMMA E ~GPa, while pHEMA hydrogel E~MPa), which could offer more wear comfort. PMMA can be worn month-long. pHEMA hydrogel does not offer sufficient wear-resistant as reusable lenses.



[Examiner's comment: This question required the students to draw their knowledge across different lectures.]

Q4

(a)(i)



(a)(ii) B. Fracture fixation devices

(a) (iii) A. Complement proteins; C. Leukocytes

(b)(i) Existing heart valve systems have drawbacks in that the structure is conserved. Especially for child recipient, the child will grow which means that a structurally-conserved valve will need to be replaced every few years until the child is in their adulthood. Tissue engineered heart valve could be of regenerative (i.e. grow with the patient), in addition to be immunocompatible, tailored to patient needs, and readily available.

(b)(ii) The examples of tissue engineering to date have largely focused on tissues where there is little vascular supply. To make the leap to more complicated solid organ structures, integration with the local vascular supply has to be considered. Strategies for inducing vascularization in engineered tissues include inclusion within the construct the delivery ofgrowth factors such as Vascular Endothelial Growth Factor (VEGF) and basic Fibroblast Growth Factor (bFGF) as recombinant proteins or gene vectors. Alternatively, Endothelial Progenitor Cell (EPC)-mobilizing cytokines such as Granulocyte-Colony Stimulating Factor

(G-CSF) could be included. Another strategy is to include in the tissue engineered scaffold progenitor cells such as Endothelial Progenitor Cells and Mesenchymal Stem Cells which will kick-start the formation of blood vessels. A biomaterials approach could use bioactive Poly Ethylene Glycol or other hydrogels that sequester and display endogenous growth factors to encourage angiogenesis. It is of course likely that a combination of all of the above approaches will provide the optimal conditions for vascularisation of an implanted construct.
Another strategy is to use large blood vessels at a site in the patient, the AV shunt loop model, to directly facilitate angiogenesis in an implant. An artery and vein are connected either by an autologous vein or synthetic substitute to form the vascular loop. Inserted into a chamber and implanted into a vascularized site of the recipient, angiogenesis is then induced in vivo. The vascularized construct can then be moved to a target site if required.
Another approach is to create large blood vessels in the lab using tissue engineering approaches. Microtissue building blocks composed of human artery-derived fibroblasts (HAFs) coated after 2 days with human umbilical vein endothelial cells can be combined in a custom built bioreactor that assembles the building block in a hollow tube that experiences medium recirculation via a pulsatile flow. After extended periods in culture (>14 days) the resulting tissue construct displays the cellular organisation and protein marker distribution that replicates a blood vessel and has the potential to be used clinically.
To integrate vasculature within a tissue construct, angiogenesis can be induced during a period of in vitro culture prior to implantation. For example, endothelial cells can be cultured on myoblast sheets where given the appropriate culture conditions will for an endothelial tubular network. Using thermopolymer responsive plates the minitissue sheets can be released and combined to create a more complex tissue network with the potential to be implanted to address a clinical need.
The first approach uses the angiogenic potential of the body to vascularize a construct (which may include angiogenic growth factors, cells or both) whilst the other two approaches use periods of in vitro culture to induce the formation of vascular structures. The building of large blood vessels using tissue building blocks results in the formation of structure with potential to repair individual arteries or veins. Whilst the final approach uses a coculture model to establish small blood vessels within a complementary tissue structure which upon implantation would require the patients vasculature to integrate it.

(c) Cellulose is useful in wound addressing applications due to its ability to trigger blood clotting. The complications of extracting cellulose from bacteria culture is that any residual bacteria could cause infection to the wound/ skin. Various sterilization process can be potentially used to kill the bacteria; but care needs to be taken not to degrade or denature the cellulose molecular structure.

[Examiner's comment: This was a question on the biological aspects of biomaterials. The question was answered well by most candidates and a good score was achieved.]