Crib

Q1

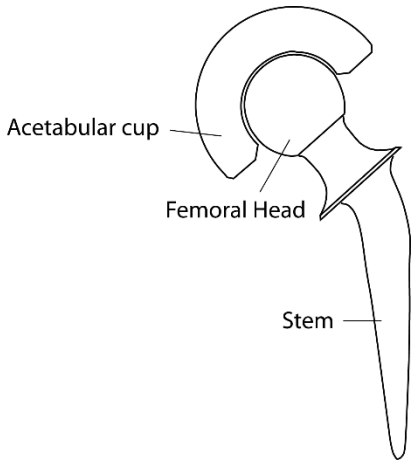
(a) Bone is composed of collagen fibrils (non-mineral) and calcium phosphate (mineral (ceramic)). At the nanoscale level, bone is a composite of 30% (dry weight) collagen fibrils surrounded by 70% calcium phosphate. At the micron scale, the collagen fibres are arranged either as a block of randomly oriented woven fibrils (woven bone) or wrapped into densely packed, concentric lamellar structures known as osteons (lamellar bone). Osteons are cylindrical structures whose long axis lies along the long axis of the bone.

At the millimeter scale, there two types of bone: (i) Cortical bone, which is dense (5-10% porosity) and comes as tightly packed lamellar or woven bone. Lamellar bone can be found in adult humans and woven bone in situations of large growth (e.g. in children). (ii) Trabecular bone comes as a highly porous solid (50-90% porosity). It consists of a network of trabeculae. Cortical bone (compact) is found in the shaft of long bones and forms the outer shell around cancellous bone at the ends of bones.

(b) Bone is an active material, it responds to stresses and strains. Examples include bone loss in bed-ridden patients or in astronauts during extended exposure to micro-gravity. Also, bone loss is observed around prostheses due to stress shielding. (Prostheses are typically stiffer than the surrounding bone, inhibiting the bone from being strained, resulting in bone loss around the implant.)

This behaviour can be explained in the context of Wolff's law proposed in 1892. The law states that bones that are not loaded sufficiently will lose mass (remodelling), whereas bones that are loaded in a greater level than previously will add bone (modelling).

(c) A total hip prosthesis comprises an acetabular component (cup) and a femoral component (stem+head) – see schematic below. The stem of the hip prosthesis would be inserted into the femoral cavity and secured either using bone cement or a porous coating. The cup would be placed into the acetabulum of the pelvis.



The femoral head is commonly made of metals such as Ti-6Al-4V, 316L or Co-Cr alloys. They are chosen because of their mechanical properties (respectable strain tolerance, strength and toughness). Femoral heads can also be made of Al_2O_3 and ZrO_2. Femoral heads need to have a low coefficient of friction and high wear resistance. An advantage of using a ceramic instead of metal for the femoral head is that it is harder and can be made smoother and more wear resistant. Hence they produce little wear debris (articulating with either an alumina or ultra-high molecular weight

polyethylene (UHMWPE) acetabular cup) as compared with metal heads (articulating either with metal or UHMWPE acetabular cup). However, ceramics are brittle.

(d) There are two types of implants fixation. Those involving the use of bone cement known as cemented and the cementless ones. In the latter, bone-implant attachment is achieved via bone-in-growth into a rough/porous surface.

Cemented prostheses -Eldery patients
Advantages
Cemented implants are generally used for older patients, since the implant can be load-bearing within hours of the operation. Extended rest can lead to secondary problems such as bedsores.
Disadvantages
Poor cement mixing can lead to poor mechanical properties
Implant repositioning while the cement is curing
Cement cures through an exothermic reaction, potentially damaging surrounding tissue
Cement deteriorates through fatigue and biological processes – production of wear debris which can cause osteolysis (bone loss)
There are two interfaces to contend with (bone-cement and cement-implant)

Cementless prostheses – Younger patients
Advantages
Cementless implants are normally used in younger patients, since bone requires time to bond to the coated implants. Better bone fixation to implant (direct fixation). Better long-term lifetime performance.
Disadvantages
Requires more surgeon skill for implant placement
Bond with bone takes time to develop - immobilisation may be required for 5-10 weeks post operation.
Additional risks depend on the details of the porous /rough surfaces (e.g. debonding of coatings)

(e)) Porous coatings are used in the proximal region of the stem to encourage bone in-growth and improve fixation. Titanium or hydroxyapatite can be thermally sprayed onto the stem; beads of cobalt-chromium or titanium can be sintered on to the stem; steel or titanium wire or fibre meshes can be sintered onto the stem. Thermally-sprayed coatings encourage bone on-growth whereas the bead-sintered coatings and wire/fibre meshes promote bone in-growth.

Q2

Part (a)
(i) A basic answer will give a very brief and cursory explanation of each concept and note the role of the manufacturer in general terms only.
A good answer will give a clear explanation of each concept and give a very brief indication about the role of the manufacturer in each case.
An excellent answer will give a detailed explanation of each concept, show a very good understanding of what the concept means, and also give three clear descriptions about the role of the manufacturer.

Key points where it would be important to show a good level of understanding (precise phrasing is not important):
Classification: This was the concept discussed in most detail and so will be the one where a greater level of understanding is expected. Devices are classified in a graduated system based on the device risks and the vulnerability of the human body to the use of the device. The higher the risk, the more likely the product can do harm. This is a graduated system of control. Excellent answers would convey this clearly and it may be through examples. This helps patients through clear communication about the level of risk. It helps manufacturers control costs while ensuring correct controls are in place and it guides regulatory bodies, such as Notified Bodies, to focus their efforts on higher risk-level products.
The manufacturer self-assesses the classification using rules set in place by the regulation, and documents this in their submission of a conformity assessment.

Monitoring of devices and adverse events in-use: The directives require that devices are subject to post-market surveillance. This is continuous monitoring of device performance and taking corrective action when needed. It is defined in the international standard for the design and manufacture of medical devices. This keeps track of adverse events suffered by users of the device, malfunctioning devices, deterioration of devices, or any additional aspects that may lead to the need to recall a device or take action. They have to be recorded and evaluated.
The manufacturer is responsible for carrying out this post-market surveillance and taking action when needed, which is part of their accreditation under ISO 13485. The Competent Authority records and evaluates such events reported by the Manufacturer and investigates when needed.

Clinical data requirements: Clinical data is needed to show the safety and performance of the device. It needs to be representative of the lifecycle of the device and is updated throughout the product lifetime. This may be a wide range of different data sets and it is anticipated that an excellent answer will note something about one example and give an indication about the range of data. This may be biocompatibility, where there will be literature studies, animal studies and even clinical trials carried out. An excellent answer will link the level of data required to the classification. The role of the manufacturer is very clear in that they need to generate and document the data required as guided by ISO13485.

(ii) A basic answer will describe one change, a good answer will note two changes very briefly, a strong answer will show a good understanding of two changes.
Examples include:
Classification - A classification of in-vitro diagnostics was introduced in the new regulations, again with a level of seriousness to the user increasing in the classifications A to D.
Monitoring of devices and adverse events in-use - Improvements to traceability include the introduction of a mandatory ‘Unique Device Identifier’ (‘UDI’). This is a series of numbers that enables the tracing of the manufacturer, device and the unit of device production, to ensure recalls can be carried out when necessary.
Under either this concept or regarding clinical data, there is an acceptable point around each manufacturer needing to employ a qualified person with 5 years regulatory experience to be responsible for the conformity of batches to be released, maintenance for the technical documentation and declaration of conformity plus vigilance reporting.
Other changes are of course acceptable, but the above are the most likely examples.

(iii) A basic answer will note very briefly a concept correctly and give very little detail as to the reason, i.e. something very generic regarding safety. A good answer will note a concept correctly and explain more clearly why this change would be beneficial. A strong answer will give a very clear description of the area where regulations could be further developed, along with suggestions

about how this may be achieved, and clearly explain the problem that exists now and how a change would help.

This is a very open question and can draw upon many aspects from across 3G5. Some examples include:

At the moment, the EU and US have two separate systems for regulatory approval but are the two largest markets. It is very expensive and also slow for medical device manufacturers to go through and maintain two sets of regulatory approvals. Further harmonisation of regulations across the EU and US to allow for a single process of regulatory approval would be a development that benefits companies and users.

There may be comments about the need to ensure clinical trials for a greater number of products under European Regulations, more similar to the US approach. This would likely cite examples of devices that were approved under the EU rules without trial but were recalled due to additional findings when undergoing trials in the US system. This would benefit patient safety, while compromising speed to market.

Additional areas may include aspects of:
- updating regulations rapidly and in advance of new technologies coming to market to reduce the time to patients, with examples drawn from tissue engineering startups
- including sustainability requirements or further re-use details within regulations to reduce the number of single use disposable plastics.

Part (b)
(i) A basic answer will give two brief headline answers that correctly highlight areas where researchers need to consider. A good answer will give brief description of each consideration. A strong answer will show understanding about two areas and give a detailed explanation about each one.

For example, as it is asked about the design of a clinical trial by researchers, it is likely that candidates will refer to the Declaration of Helsinki because it defined rules for ‘research combined with clinical care’. One aspect that will likely be referred to is that to run a trial, a research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This independent review is a key aspect of the Declaration.

Another likely answer will be focused more on the recruiting of participants, and will be around the concept of 'consent'. While precise wording from the notes is not required, it is anticipated that candidates show an understanding of consent being linked to:
Communicating information by the clinician and its comprehension by the patient.
Ensuring the patient’s ability to understand the information and to appreciate consequences
The patient’s right to come to a decision freely without influence.

(ii) A basic answer will note two valid areas where sets of tests are required and note very briefly challenges anticipated for this device. A good answer will give some details about the types of tests under each area noted and link these tests to the likely areas the product could fail. A strong answer will show a very good understanding of two areas where tests are required as a device goes through conformity assessment on its way to market, will describe in detail an example test in each and will give clear reasons why this particular device will face challenges.
While any valid answers will be considered, it is anticipated that the majority will refer to biocompatibility and sterilisation tests.

For example, under sterilisation, it is anticipated that the candidates will identify the need to measure bioburden, tests of the sterilisation technique that lead to a valid sterility assurance level. They may note that upon establishing a good sterilisation technique that parametric release will require regular tests using biological or chemical devices. A detailed description may note the approach taken when looking at bacterial contamination, with washing the sample with a broth and monitoring bacterial growth from these samples. Because this device will need to have very specific mechanical properties and release properties, a strong answer may note that depending on the sterilisation technique chosen, this may impact the material functionality. For example, gamma radiation may lead to polymer degradation. As it is a completely new material, the researchers will not be able to refer quickly to existing methods.
In terms of biocompatibility, it is anticipated that a strong answer will give a brief overview of tests where cells likely to be in contact in the body will be exposed to this new material. There may be a sketch or brief description of tests with direct contact, and with indirect contact (i.e. through a gel layer or through contact with washings from the material). It is important that through the descriptions the candidates show an understanding that biocompatibility is tested to look for biosafety, avoiding deleterious effects such as cytotoxicity, but also ensuring the biofunctionality is maintained. While there are many potential areas this could fail, it is anticipated that most answers will refer to the fact that this is a composite material with nanomaterials embedded, and will be experiencing applied loads. It is known that composites can have poor biocompatibility within the body as wear leads to the release of nano and microparticles that are on the same lengthscale as the cells. These can readily interact and lead to issues.

Q3

(a)

							Sum
Chain molecular weight (kDa)	20	60	100	120	140		
Number of chains at the specified molecular weight	50	300	800	350	100		**1600**
n*Mi	**1000**	**18000**	**80000**	**42000**	**14000**		**155000**
n*Mi^2	**20000**	**1080000**	**8000000**	**5040000**	**1960000**		**16100000**

Number average molecular weight

$$M_n = \sum x_i M_i = \frac{\sum n_i M_i}{\sum n_i}$$

n_i= number of chains
x_i= number fraction of chains
M_i= chain molecular weights

Weight average molecular weight

$$M_w = \sum w_i M_i = \frac{\sum n_i M_i^2}{\sum n_i M_i}$$

w_i= weight fraction of chains

M_n=155000/1600≈96.9 kDa

M_w=16100000/155000≈103.8 kDa

PI=103.8/96.9≈1.1

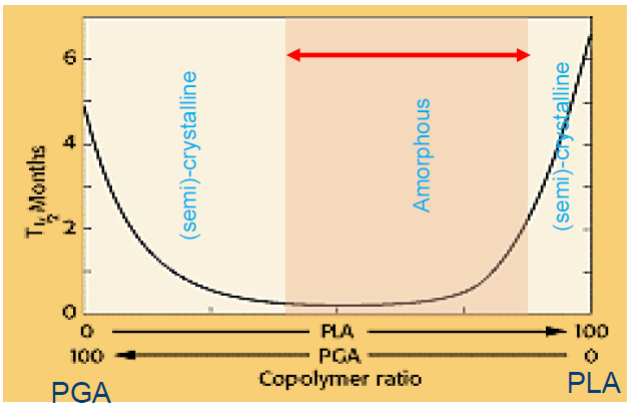
(b)

(i) Polyethylene glycol (PEG). PEG is relatively biocompatible. PEG has highly hydrophilic chains which "stealth" the drug carrier like coating the drug particle with a layer of water. It is generally thought that coating of PEG allows particulate delivery systems and biomaterials to evade the immune system and thereby prolong circulation lifetimes. The PEG should have a relatively small number of molecular weight (repeated units smaller than 1000) to allow PEG to remain in a liquid state for the 'sheath' application.

(ii) Ultrahigh molecular weight polyethylene (UHMWPE). PE can be considered as bioinert in the proposed application. PE offers low coefficient of friction, thus acting as a articulation couple for moving components in the hip replacement. High molecular weight PE has improved toughness, strength and wear resistance compared to low molecular weight PE. Wear is a particular concern as the wear particles can cause a cellular response leading to bone resorption, aseptic loosening, and implant failure.

(iii) Nylon (or polyamide) suture. The cornea has low regeneration capacity, but it is sitting on the surface of the body (thus easily accessible for surgery). A biodegradable/ hydrolysable system 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.

(iv) PLG:PLA. This is a hydrolysable polymer with its main chain/backbones formed by chemical linkages which can undergo hydrolysis reaction. The key advantages of using co-polymerisation to form a hydrolysable polymer is that tuning the co-polymerisation ratio, tuneable polymer properties can be resulted, such as in rate of hydrolysis (degradation rate), material mechanical properties, and surface hydrophilicity. For drug delivery application, the labelled 'amorphous' co-polymer composition region is normally used. The biodegraded products can be safely eliminated by the body.

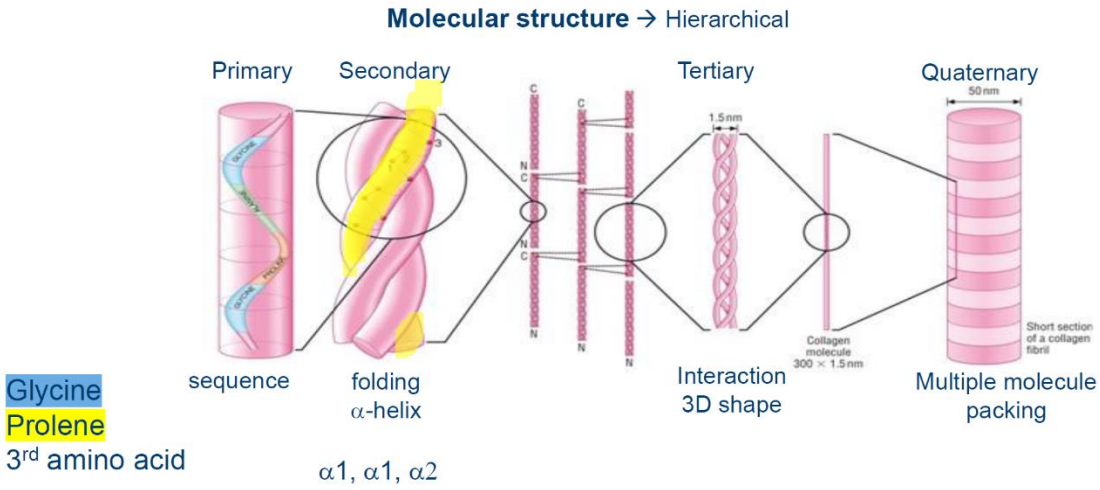


(c) Fibrin is a natural biopolymeric material that are used in both tissue engineering (as a cell support scaffold), and wound repair (as a haemostat) applications. Fibrin (also called Factor Ia) is a fibrous, non-globular protein involved in the clotting of blood. It is formed by the action of the protease thrombin on fibrinogen, which causes it to polymerize.

Q4

(a)

(i) The secondary structure of collagen is an alpha fold (alpha-helix) of the collagen polypeptide chains; the tertiary structure is a triple helix (i.e. three alpha chains twisted together) which leads to a collagen molecule; the quandary structure consists of packing of multiple collagen molecules forming a collagen fibril.



(ii)

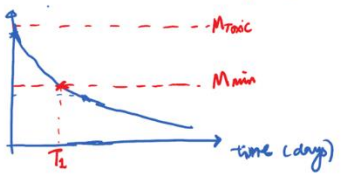
Example 1: Acid treatment dissolve the collagen fibril, thus disintegrate the collagen fibre quaternary structure while the collagen's tertiary structure remains. In this case, collagen can be used as a hydrogel/ scaffold to support cell growth. The acid treated collagen has weak mechanical property thus needs to be post-crosslinked. Acid treated collagen has some exposed cell attachment sites (e.g. RGC sequence), and is thromboresistant. For acid extracted collagen, crosslinking of collagen fibres lead to decelerated degradation rate.

Example 2: Heat treatment can cause complete denature of the collagen, thus the collagen can lose its tertiary and secondary structure and become amorphous (i.e. gelatine). Gelatine is hydrolysed, highly charged, have a smaller chain length than collagen. It has large water uptake, and weak mechanical properties; but it is more biocompatible, less antigenic than collagen. The RGD-amino acid sequence are exposed than collagen. Application of gelatine is such as a hydrogel/scaffold for supporting cell growth, or digestible carrier for oral drug delivery.

(b)

(i)

Single injection:



unit = hour

$T_{\frac{1}{2}} = 2$

$T_{\frac{1}{2}} = \frac{0.69}{\lambda}$

$\lambda = \frac{0.69}{T_{\frac{1}{2}}} = 0.345\ hr^{-1}$

$M = M_0 \exp(-\lambda t)$ ①

Criteria ① : $M_{tox} = 4M_{min}$

② 1st Injection time, T_1 : $M_{min} = M_0 \exp(-\lambda T_1)$

$\ln\left(\frac{M_{min}}{M_{max}}\right) = -\lambda T_1$

$T_1 = \frac{1}{\lambda} \ln\left(\frac{M_{max}}{M_{min}}\right)$ ②

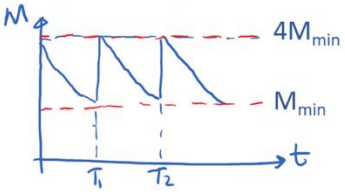
$= 4\ hr$

Injection does:

$\Delta M_1 = M_{max} - M_{min} = 3M_{min}$

(thus the drug level is brought back to M_0)

multiple injection



First injection $4M_{min}$

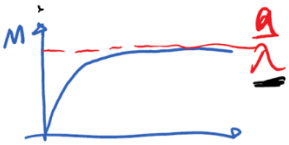
Then inject every 4hrs with $3M_{min}$

$$\langle M \rangle = \frac{\int_0^{T_1} M\,dt}{T_1} = \frac{\int_0^{T_1} M_{max} \exp(-\lambda t)\,dt}{T_1} = \frac{M_{max}\left[\exp(-\lambda t)\right]_0^{T_1}}{-\lambda T_1}$$

$$= \frac{\frac{M_{max}}{\lambda}\left(1 - \frac{M_{min}}{M_0}\right)}{T_1} = \frac{M_{max} - M_{min}}{T_1 \lambda}$$

$$\langle M \rangle = \frac{M_{max} - M_{min}}{\ln\left(\frac{M_{max}}{M_{min}}\right)} = \frac{3M_{min}}{\ln 4} = 2.16 M_{min}$$

(ii)



$\frac{\partial M}{\partial t} = \frac{\partial M_1}{\partial t} - \lambda M$, $\frac{\partial M_1}{\partial t} = a$

$M = \frac{a}{\lambda}\left(1 - exp(-\lambda t)\right)$

If we only look at the steady state

$t \to \infty$

$M_{s.s} = \frac{a}{\lambda}$

$M_{s.s} = \frac{a}{\lambda} = \langle M \rangle$.

$a = \lambda \cdot \langle M \rangle = 0.345 \times 3M_{min} = 1.035\, M_{min}/hr$

An external digital pump can be used to control the flow rate of the drug injection.

(c)

(i) A biofilm is an architectural colony of microorganisms, within a matrix of extracellular polymeric substance that they produce. Biofilms contains microbial cells adherent to one-another and to a static surface (living or non-living).

(ii) Biofilm can cause the premature failure of ureteral stent, by blocking the flow of urine through the stent. Biofilm formation on acetabular cup of the hip implant can lead to septic loosening, and hence implant failure.