Biomedical regulation for product safety and manufacturing quality in Europe

Laboratorio di Tecnologie Biomediche A.A. 2017/2018

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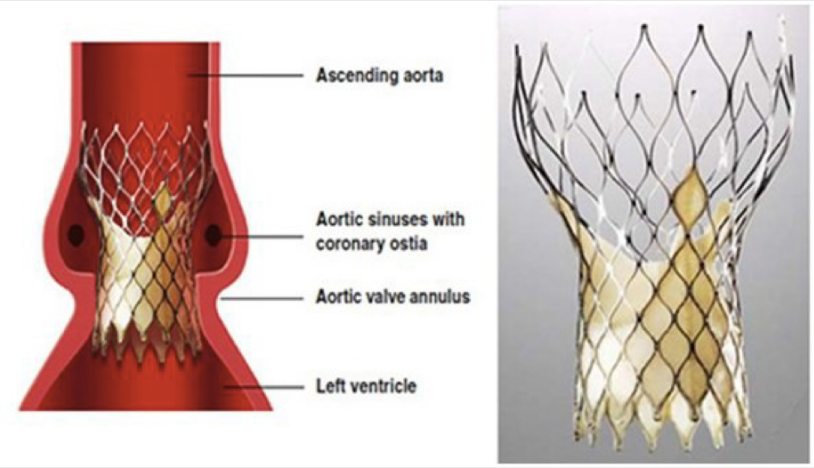
Topics:

- European Union Regulation for Medical Devices
- Bringing your medical device to the EU market: CE-marking step-by-step
  - What is the product?
  - Classification
  - Meet Safety and Performance Requirements
  - Conformity Assessment Procedure
  - Assemble Technical Documentation
  - Affix a CE Marking
  - Draw up a Declaration of conformity

Legislation on Medical Device in the European Union

What do they have in common?



Yesterday – Medical Device Directive

- Three Directives (”current directives”)
  - Council directive 93/42/EEC of 14 June 1993 concerning medical devices (“MDD”)
  - Council directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the member states relating to active implantable medical devices (“AIMD”)
  - Directive 98/79/EC of the European parliament and of the council of 27 October 1998 on in vitro diagnostic medical devices (“IVDD”)

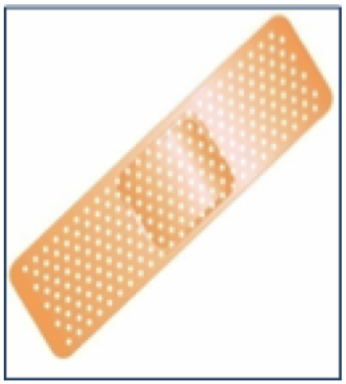
The Medical Device Directive is a law that regulates the marketing of Medical Devices in the EU

Covered Medical Devices (1/3)

Medical Devices (MD)

(Directive 93/42/EEC)

"Medical Device means any instrument, apparatus, appliance, software, material or other article (...) including the software (...) intended by the manufacturer to be used for human beings " for several purposes such as diagnosis, monitoring, treatment and "which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means";

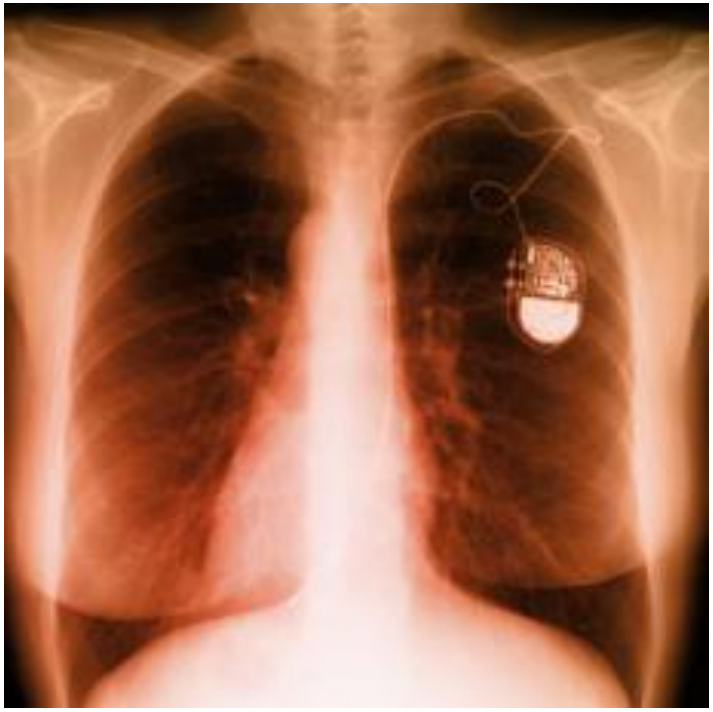



Covered Medical Devices (2/3)

Active Implantable Medical Devices (AIMD)

(Directive 90/385/EEC)

«Any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure;"



Example: heart pacemakers

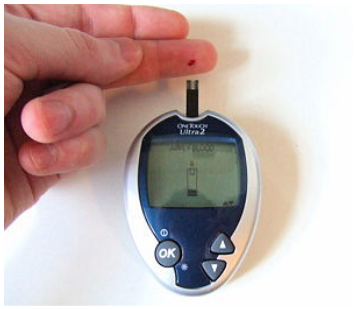
NB: "active" = relying for its functioning on a source of electrical energy or any source of power

Covered Medical Devices (3/3)

In Vitro Diagnostic Medical Devices (IVD)

(Directive 98/79/EEC)

"Reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system (...) intended by the manufacturer to be used in vitro for the examination of specimens (...) derived from the human body (...) for the purpose of providing information" concerning a pathological state, a congenital abnormality, or to determine the compatibility with potential recipients, or to monitor therapeutic measures.



Today – Medical Devices Regulations

- Directive 90/385/EEC on active implantable medical devices
- Directive 93/42/EEC on medical devices

Regulation on medical devices: **Regulation (EU) 2017/745**

http://eur-lex.europa.eu/legal-content/ENG/TXT/PDF/?uri=CELEX:32017R0745&from=EN

Directive 98/79/EC on in vitro diagnostic medical devices

Regulation on in vitro diagnostic medical devices:

Regulation (EU) 2017/746

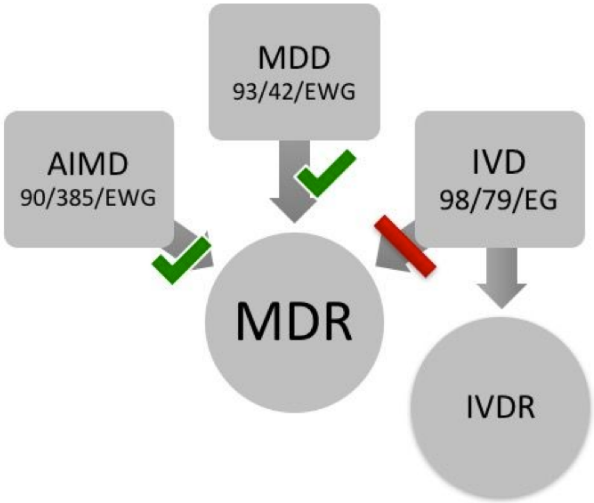
http://eur-lex.europa.eu/legal-content/ENG/TXT/PDF/?uri=CELEX:32017R0746&from=EN

The Medical Device Regulation is a law that regulates the marketing of Medical Devices in the EU

Transitional period: MDR and IVDR (1/2)

- Entry into force ("EIF") of both regulations takes place 20 days after their publication → As of 25 May 2017

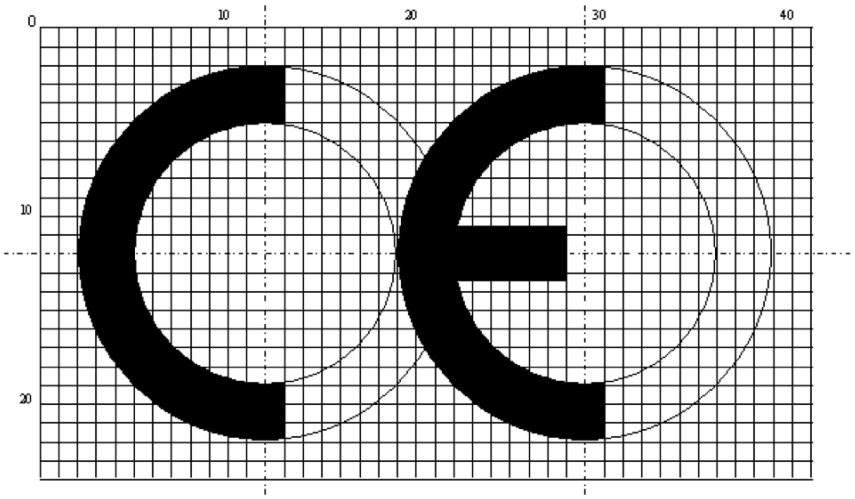
- The regulations do not apply directly ("Application Date"):



- **MDR** applies 3 years after EIF
- **IVDR** applies 5 years after EIF

Transitional period: MDR and IVDR (2/2)

Bringing your medical device to the EU market: CE-marking step-by-step



Step 1: what is the product? (1/2)

- Is the product a medical device according to the medical devices directives/regulations?
- What kind of medical device is the product (IVD, AIMD, MD)?

Depends on the intended purpose and whether the product fits the definition of the directives.

Step 1: what is the product? (2/2)

Borderline issues

It may sometimes be difficult to determine:

- If a product is a medical device (whether MD, IVD or AIMD)

  Examples: thermomixers intended to control the temperature of liquids in closed micro test tubes, gold implants for treatment of osteoarthrosis...

- If a medical device is an MD, or an IVD, or an AIMD:

  Example: bone-anchored hearing aids...

Step 2: classification (1/10)

- Medical devices (MD, IVC and AIMD) fall into various risk categories

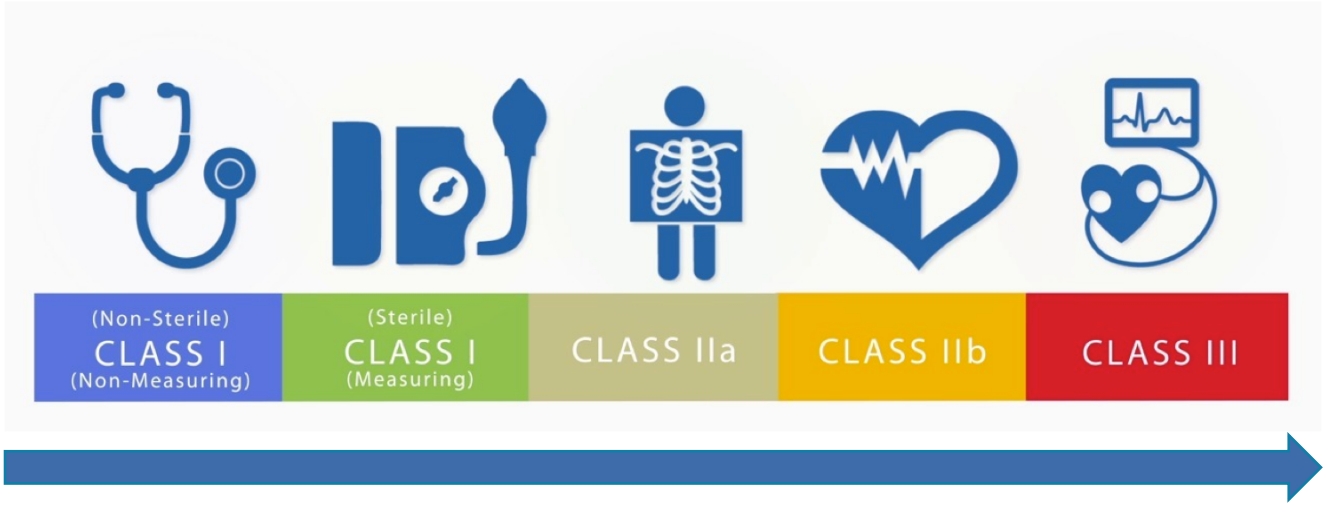
Compliance procedures depend on classification → Important to classify properly

NB. US and EU classification system don't match perfectly

Step 2: classification (2/10)

Classification of MD

- A **'risk based'** system based on the vulnerability of the human body
- Four risk classes:



Step 2: classification (3/10)

Annex IX of Medical Device Directive 93/42/EEC contains the classification rules for the Medical Device

Annex VIII of Medical Device Regulation 2017/745 contains the classification rules

http://134t7045rwgf19lpbh29libk9d3.wpengine.netdna-cdn.com/wp-content/uploads/sites/11/2017/05/EC-MDR-Annex-VIII-Classification-Rules.pdf

Step 2: classification (4/10)

Class I

All invasive devices with respect to body orifices, other than surgically invasive devices, which are not intended for connection to an active device or which are intended for connection to a class I active device if they are intended for transient use;

All non-invasive devices which come into contact with injured skin or mucous membrane if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates;

All invasive devices with respect to body orifices, other than surgically invasive devices, which are not intended for connection to an active device or which are intended for connection to a class I active device for transient use;

Step 2: classification (5/10)

Class IIa

All invasive devices in relation with body orifices, other than surgically invasive devices, which are not intended for connection to an active device or which are intended for connection to a class I active device.

All surgically invasive devices intended for transient use.

All active therapeutic devices intended to administer or exchange energy.

Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes

All active devices intended to administer and/or remove medicinal products, body liquids or other substances to or from the body

All devices incorporating or consisting of nanomaterial with a negligible potential for internal exposure.

Step 2: classification (6/10)

Class IIb

All non-invasive devices intended for modifying the biological or chemical composition of human tissues or cells, blood, other body liquids or other liquids intended for implantation or administration into the body

All non-invasive devices which come into contact with injured skin or mucous membrane are classified as: class IIb if they are intended to be used principally for injuries to skin which have breached the dermis or mucous membrane and can only heal by secondary intent;

All implantable devices and long-term surgically invasive devices

All active devices intended to emit ionizing radiation for therapeutic purposes, including devices which control or monitor such devices, or which directly influence their performance

All devices used for contraception or prevention of the transmission of sexually transmitted

All devices intended specifically to be used for disinfecting, cleaning, rinsing or, where appropriate, hydrating contact lenses

Step 2: classification (7/10)

Class III

All surgically invasive devices in direct contact with the heart or central circulatory system or the central nervous system,

Active implantable devices or their accessories

Breast implants or surgical meshes

All active devices that are intended for controlling, monitoring or directly influencing the performance of active implantable devices

All devices incorporating or consisting of nanomaterial are classified as: — class III if they present a high or medium potential for internal exposure;

Active therapeutic devices with an integrated or incorporated diagnostic function which significantly determines the patient management by the device, such as closed loop systems or automated external defibrillators,

Step 2: classification (8/10)

Classification of AIMD

High risk, invasive: one single risk class

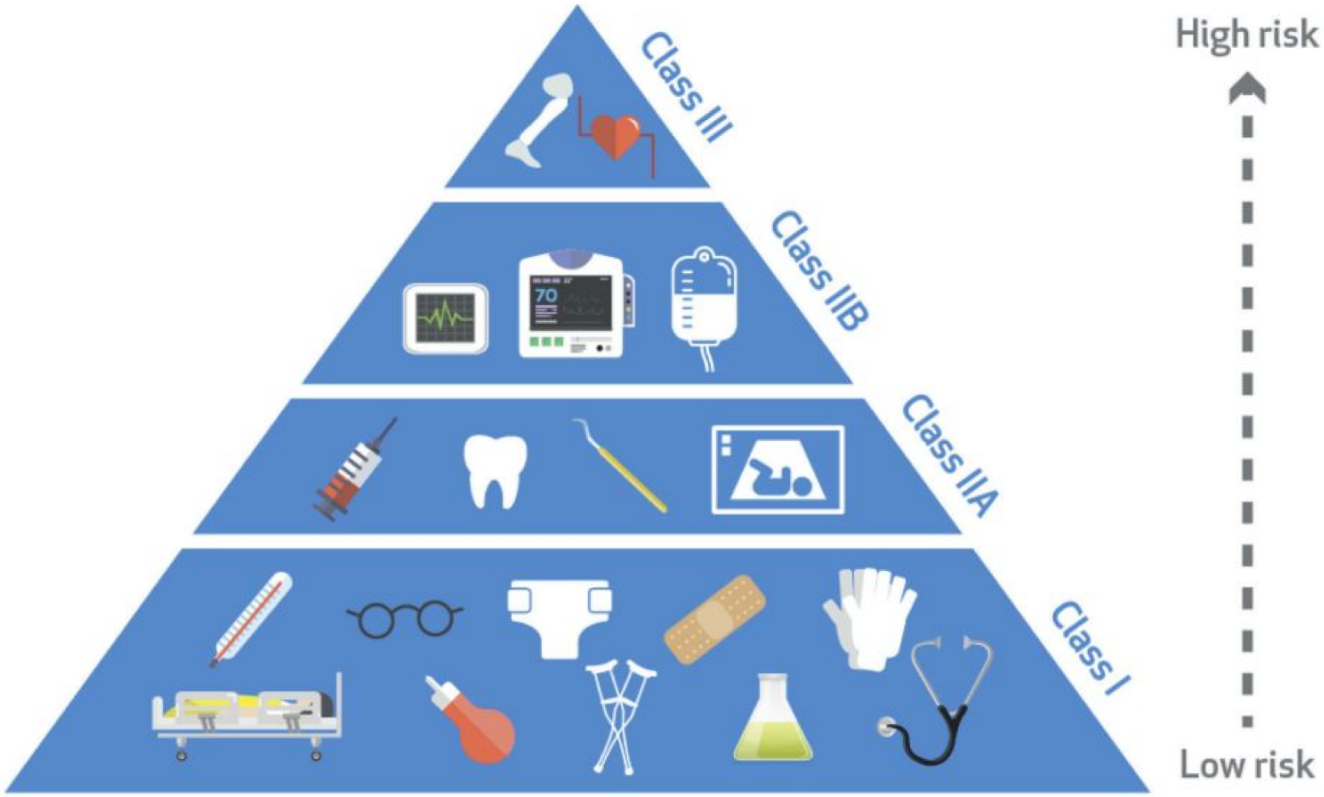
Medical Device Directive 90/385/EEC contains the classification rules for the AIMD

Annex VIII of Medical Device Regulation 2017/745, Chapter III, Rule 8

http://134t7045rwgf19lpbh29libk9d3.wpengine.netdna-cdn.com/wp-content/uploads/sites/11/2017/05/EC-MDR-Annex-VIII-Classification-Rules.pdf

Step 2: classification (9/10)

Examples



Step 2: classification (10/10)

Classification of IVD

Class	Risk level	Device Examples
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyser, prepared selective culture media
B	Moderate Individual Risk and /or Low Public Health Risk	Vitamin B12, Pregnancy self testing, anti-Nuclear Antibody, Urine test strips
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self testing, HLA typing, PSA screening, Rubella
D	High Individual Risk and High Public Health Risk	HIV Blood donor screening, HIV Blood Diagnostic

Step 3: Meet Safety and Performance Requirements (1/4)

Safety and Performance requirements for the protection of health and safety

Form the core of the 2 Regulations.

- Are set out in general terms.
- Cover risks and hazards that may occur at the design, production and handling stages.
- Are listed in **Annex I** of each Regulation.

The Safety and Performance Requirements (SPRs) of the Medical Devices Regulation (MDR) replace the previous Directives' Essential Requirements (ERs) and outline the key areas to address within the Technical Documentation

Step 3: Meet Safety and Performance Requirements (2/4)

EU-wide Harmonized standards

Compliance with harmonized standards provides a presumption of conformity with the corresponding requirements of the directive.

Official Journal L 117

of the European Union

English edition — Legislation — Volume 60 — 5 May 2017

Contents

I *Legislative acts*

REGULATIONS

- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (1) 1
- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (1) 176

Regulation (EU) 2017/745: «References in this Regulation to harmonised standards shall be understood as meaning harmonised standards the references of which have been published in the Official Journal of the European Union.»

Step 3: Meet Safety and Performance Requirements (3/4)

A few examples EU-wide Harmonized standards

- EN ISO 14971:2009 (Risk management)
- EN 980:2008 (Symbols for use in the labeling of MD)

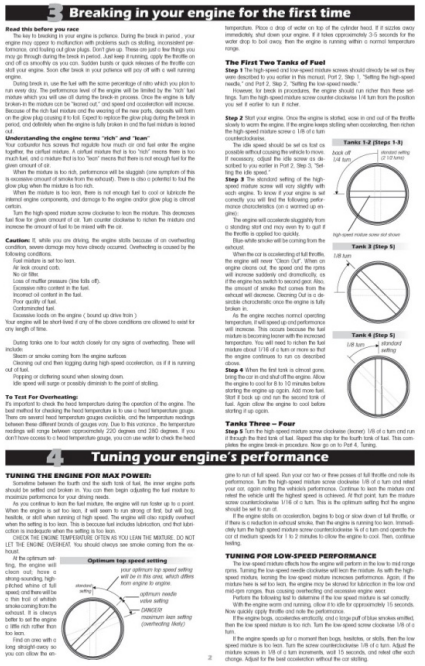
List of EU Harmonized Standards for MD/IVD/AIMD:

https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards_it

Step 3: Meet Safety and Performance Requirements (4/4)

Language requirements

- Information to users plays a critical role in reducing risks.
- Detailed provisions for Instructions for Use (IFU) and label
- Use of symbol (standards)
- National language must be used for packaging, label and IFU



3 Breaking in your engine for the first time

Read this before you race

The key to breaking in your engine is patience. During the break-in period , your engine may appear to malfunction with problems such as stalling, inconsistent performance, and fouling out glow plugs. Don't give up. These are just a few things you may go through during the break-in period. Just keep it running, apply the throttle on and off as smoothly as you can. Sudden bursts or quick releases of the throttle can shut your engine. Soon after break in your porteus will pop off with a well running engine.

During break in, use the fuel with the some percentage of nitro which you plan to run every day. The performance level of the engine will be limited by the "rich" fuel mixture which you will use all during the break-in process. Once the engine is fully broken-in the mixture can be "leaned out," and speed and acceleration will increase. Because of the rich fuel mixture and the wearing of the new parts, deposits will form on the glow plug causing it to foil. Expect to replace the glow plug during the break-in period, and definitely when the engine is fully broken in and the fuel mixture is leaned out.

Understanding the engine terms "rich" and "lean"

Your carburetor has screws that regulate how much air and fuel enter the engine together, the carfuel mixture. A carfuel mixture that is too "rich" means there is too much fuel, and a mixture that is too "lean" means that there is not enough fuel for the given amount of air.

When the mixture is too rich, performance will be sluggish (one symptom of this is excessive amount of smoke from the exhaust). There is also a potential to foul the glow plug when the mixture is too rich.

When the mixture is too lean, there is not enough fuel to cool or lubricate the internal engine components, and damage to the engine and/or glow plug is almost certain.

Turn the high-speed mixture screw clockwise to lean the mixture. This decreases fuel flow for given amount of air. Turn counter clockwise to richen the mixture and increase the amount of fuel to be mixed with the air.

Caution: If, while you are driving, the engine stalls because of an overheating condition, severe damage may have already occured. Overheating is caused by the following conditions.

Fuel mixture is set too lean.
Air leak around carb.
No air filter.
Loss of muffler pressure (line falls off)
Excessive nitro content in the fuel.
Incorrect oil content in the fuel.
Poor quality of fuel.
Contaminated fuel.
Excessive loads on the engine (bound up drive train)

Your engine will be short lived if any of the above conditions are allowed to exist for any length of time.

During tanks one to four watch closely for any signs of overheating. These will include:

Steam or smoke coming from the engine surfaces.
Cleaning out and then logging during high-speed acceleration, as if it is running out of fuel.
Popping or stuttering sound when slowing down.
Idle speed will surge or possibly diminish to the point of stalling.

To Test For Overheating:

It's important to check the head temperature during the operation of the engine. The best method for checking the head temperature is to use a head temperature gauge. There are several head temperature gauges available, and the temperature readings between these different brands of gauges vary. Due to this variance, the temperature readings will range between approximately 220 degrees and 280 degrees. If you don't have access to a head temperature gauge, you can use water to check the head temperature. Place a drop of water on top of the cylinder head. If it sizzles away immediately, shut down your engine. If it takes approximately 3-5 seconds for the water drop to boil away, then the engine is running within a normal temperature range.

The First Two Tanks of Fuel

Step 1 The high-speed and low-speed mixture screws should already be set as they were described to you earlier in this manual, Part 2, Step 1, "Setting the high-speed needle valve" and Part 2, Step 2, "Setting the low-speed needle valve."

However, for break in procedures, the engine should run richer than these settings. Turn the high-speed mixture screw counter-clockwise 1/4 turn from the position you set it earlier to run it richer.

Step 2 Start your engine. Once the engine is started, ease in and out of the throttle slowly to warm the engine. If the engine keeps stalling when accelerating, then richen the high-speed mixture screw a 1/8 of a turn counterclockwise.

The idle speed should be set as fast as possible without causing the vehicle to move. If necessary, adjust the idle screw as described to you earlier in Part 2, Step 3, "Setting the idle speed."

Step 3 The standard setting of the high-speed mixture screw will vary slightly with each engine. To know if your engine is set correctly you will find the following performance characteristics (on a warmed up engine):

The engine will accelerate sluggishly from a standing start and may even try to quit if the throttle is applied too quickly.

Blue-white smoke will be coming from the exhaust.

When the car is accelerating at full throttle, the engine will never "Clean Out". When an engine cleans out, the speed and the rpms will increase suddenly and dramatically, as if the engine has switch to second gear. Also the amount of smoke that comes from the exhaust will decrease. Cleaning Out is a desirable characteristic once the engine is fully broken in.

As the engine reaches normal operating temperature, it will speed up and performance will increase. This occurs because the fuel mixture is becoming leaner with the increased temperature. You will need to richen the fuel mixture about 1/16 of a turn or more so that the engine continues to run as described above.

Step 4 When the first tank is almost gone, bring the car in and shut off the engine. Allow the engine to cool for 8 to 10 minutes before starting the engine up again. Add more fuel. Start it back up and run the second tank of fuel. Again allow the engine to cool before starting it up again.

Tanks Three – Four

Step 5 Turn the high-speed mixture screw clockwise (leaner) 1/8 of a turn and run it through the third tank of fuel. Repeat this step for the fourth tank of fuel. This completes the engine break-in procedure. Now go on to Part 4, Tuning.

Tanks 1-2 (Steps 1-3)
Tank 3 (Step 5)
Tank 4 (Step 5)

4 Tuning your engine's performance

TUNING THE ENGINE FOR MAX POWER:

Sometime between the fourth and the sixth tank of fuel, the inner engine parts should be settled and broken in. You can then begin adjusting the fuel mixture to maximize performance for your driving needs.

When the engine is set too rich, the engine will run faster up to a point. When the engine is set too lean, it will seem to run strong of fast, but will bog, hesitate, or stall when running of high speed. The engine will also rapidly overheat when the setting is too lean. This is because fuel includes lubrication, and that lubrication is inadequate when the setting is too lean.

CHECK THE ENGINE TEMPERATURE OFTEN SO YOU LEAN THE MIXTURE, DO NOT LET THE ENGINE OVERHEAT. You should always see smoke coming from the exhaust.

At the optimum setting, the engine will clean out, have a strong-sounding, high-pitched whine of full speed, and there will be a thin fruit of whitish smoke coming from the exhaust. It is always better to set the engine a little rich rather than too lean.

Find an area with a long straight-away so you can allow the engine to run at full speed. Run your car two or three passes at full throttle and note its performance. Turn the high-speed mixture screw clockwise 1/8 of a turn and retest your car, again noting the vehicle's performance. Continue to lean the mixture and retest the vehicle until the highest speed is achieved. At that point, turn the mixture screw counterclockwise 1/16 of a turn. This is the optimum setting that the engine should be set to run at.

If the engine stalls on acceleration, begins to bog or slow down at full throttle, or if there is a reduction in exhaust smoke, then the engine is running too lean. Immediately turn the high speed mixture screw counterclockwise 1/4 of a turn and operate the car at medium speeds for 1 to 2 minutes to allow the engine to cool. Then, continue testing.

TUNING FOR LOW-SPEED PERFORMANCE

The low-speed mixture affects how the engine will perform in the low to mid range rpms. Turning the low-speed needle clockwise will lean the mixture. As with the high-speed mixture, leaning the low-speed mixture increases performance. Again, if the mixture here is set too lean, the engine may be starved for lubrication in the low and mid-rpm ranges, thus causing overheating and excessive engine wear.

Perform the following test to determine if the low speed mixture is set correctly:

With the engine warm and running, allow it to idle for approximately 15 seconds. Now, quickly apply throttle and note the performance.

If the engine bogs, accelerates erratically, and o large puff of blue smokes emitted, then the low speed mixture is too rich. Turn the low-speed screw clockwise 1/8 of a turn.

If the engine speeds up for a moment then bogs, hesitates, or stalls, then the low speed mixture is too lean. Turn the screw counterclockwise 1/8 of a turn. Adjust the mixture screws in 1/8 of a turn increments, wait 15 seconds, and retest after each change. Adjust for the best acceleration without the car stalling.

Optimum top speed setting
your optimum top speed setting will be in this area, which differs from engine to engine.
standard setting
optimum needle valve setting
DANGER maximum lean setting (overheating likely)

Step 4: Follow a CAP (1/5)

Conformity Assessment procedures (CAP)

- **CAPs allow manufacturers to demonstrate the conformity of their device with the provisions of the regulation.**
- **The choice of the CAP is determined by the classification of the device and the preference of the manufacturer for a given CAP.**
- **CAPs address the design and production stages**

Step 4: Follow a CAP (2/5)

Range of CAP

- Low-risk products (e.g. class I MD) generally allow **self- certification**.
- CAPs applicable to higher-risk products will require the services of a **third party** ("EU Notified Body") depending on the classification of the device.

Step 4: Follow a CAP (3/5)

CAP for different Medical Device's class

MDR 2017/745 (60)

The conformity assessment procedure for:

- **class I** devices should be carried out, as a general rule, under the sole responsibility of manufacturers in view of the low level of vulnerability associated with such devices.
- For **class IIa**, **class IIb** and **class III** devices, an appropriate level of involvement of a notified body should be compulsory.

Step 4: Follow a CAP (4/5)

Role of Notified Bodies (NBs)

- **For all AIMD, certain IVD and MD (Class IIa and above).**
- **NB are accredited test laboratories based in the EU.**
- **Only an accredited EU NB can make the final assessment of conformity with the directives and deliver a certificate.**

Step 4: Follow a CAP (5/5)

Quality Management System

- **Required for all devices (except Class I non sterile/ non measuring).**
- **Most companies apply EN ISO 13485 to comply with QMS requirements (not mandatory).**
- **Implementation of a QMS may take 3-4 months to a year.**

Step 5: Assemble the Technical Documentation

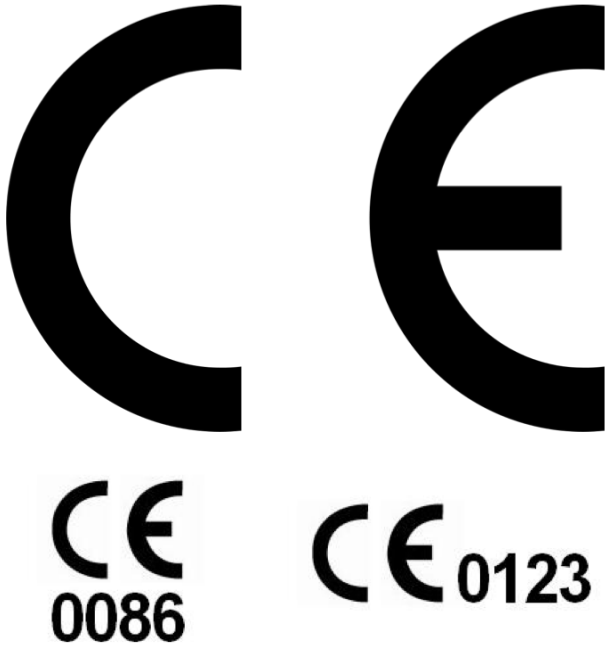
The Technical Documentation

- Contains all relevant information to support the claims of compliance with the requirements of the directive.
- Must be kept at the disposal of national surveillance authorities.

Step 6: Affix CE Marking

The **CE-marking symbol**:

- Is affixed to the device and accompanying documents.
- Demonstrates that the manufacturer has complied with the applicable directive(s)/regulation(s) and is not a quality sign



When a NB intervenes, its ID number must appear below/next to the CE-marking.

Step 7: draw up a Declaration of Conformity

- **For all devices**
- **One-page document on which the manufacturer of a medical device "declares" his product's "conformity" with the:**
  - **Essential Requirements of the Directive.**
  - **Safety and Performance Requirements of the Regulation**
- **To be kept at the disposal of authorities.**