



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON THE CLINICAL AND NON CLINICAL EVALUATION DURING THE
CONSULTATION PROCEDURE ON MEDICINAL SUBSTANCES CONTAINED IN DRUG-
ELUTING (MEDICINAL SUBSTANCE-ELUTING) CORONARY STENTS**

| | |
|--|-------------------|
| DRAFT AGREED BY EFFICACY WORKING PARTY AND SAFETY WORKING PARTY | 9 January 2007 |
| ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION | 21 March 2007 |
| END OF CONSULTATION (DEADLINE FOR COMMENTS) | 30 September 2007 |
| AGREED BY EFFICACY WORKING PARTY | May 2008 |
| ADOPTION BY CHMP | 30 May 2008 |
| DATE FOR COMING INTO EFFECT | 1 December 2008 |

| | |
|-----------------|---|
| KEYWORDS | Drug Eluting Stents, non-clinical safety, clinical safety, usefulness |
|-----------------|---|

| |
|---|
| <p>GUIDELINE ON THE CLINICAL AND NON CLINICAL EVALUATION DURING THE CONSULTATION PROCEDURE ON MEDICINAL SUBSTANCES CONTAINED IN DRUG-ELUTING (MEDICINAL SUBSTANCE-ELUTING) CORONARY STENTS</p> |
|---|

TABLE OF CONTENTS

| | |
|--|-----------|
| 1. LEGAL BASIS | 3 |
| 2. INTRODUCTION..... | 3 |
| 3. SCOPE..... | 4 |
| 4. BACKGROUND..... | 4 |
| 5. BENCH TESTING | 5 |
| 6. DATA FOR NON-CLINICAL EVALUATION..... | 5 |
| 6.1 BIOCOMPATIBILITY TESTING OF THE DEVICE | 5 |
| 6.2 NONCLINICAL TESTING REQUIREMENTS FOR THE DRUG-ELUTING STENT | 5 |
| 6.2.1 <i>Pharmacodynamics (proof of concept)</i> | 5 |
| 6.2.2 <i>Non-clinical pharmacokinetic testing</i> | 5 |
| 6.2.3 <i>Testing multiple overlapping stents</i> | 6 |
| 6.2.4 <i>Preclinical toxicity studies</i> | 6 |
| 6.2.5 <i>Testing of the medicinal substance if not an approved medicinal product</i> | 7 |
| 7. CLINICAL DATA..... | 7 |
| 7.1 CLINICAL PHARMACOKINETIC TESTING | 7 |
| 7.2 CLINICAL SURROGATE MEASURES AND EXPLORATORY TESTING..... | 7 |
| 7.3 CONFIRMATORY CLINICAL TRIALS | 7 |
| 7.4 CLINICAL SAFETY EVALUATION | 9 |
| 7.5 POST-MARKETING SURVEILLANCE CONSIDERATIONS | 9 |
| 8. REFERENCES (BACKGROUND GUIDANCE, NORMS AND SCIENTIFIC)..... | 10 |

EXECUTIVE SUMMARY

This Guideline is intended to harmonise the pre-clinical and clinical assessment by National Competent Authorities/ EMEA in the consultation procedure to the competent bodies of the member states or the EMEA regarding the assessment of safety of the medicinal substance (including the clinical benefit/risk profile of the incorporation of the medicinal substance into the device), which, if used separately, may be considered a medicinal product as defined in article 1 of Directive 2001/83/EC and is liable to act upon the body with action ancillary to that of the device, in a drug-eluting (medicinal substance-eluting) coronary stent (DES).

When referring to (ancillary) medicinal substance, this can include either an active pharmaceutical ingredient or a formulated medicinal product.

This Guideline is not intended to provide guidance regarding the requirements to be submitted for the quality section of the dossier.

1. LEGAL BASIS

It should be read in conjunction with Directive 93/42/EEC as amended, Annex I to Directive 2001/83/EC as amended, CETF guideline on clinical evaluation of coronary stents (ref 5) and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations (see References).

2. INTRODUCTION

The benefit of percutaneous coronary intervention is often limited by restenosis. Even with the best medical treatment, including stents, restenosis continues to occur in some patients because stents are not designed to address the process of intimal thickening that results from the cascade of events initiated by arterial injury.

The restenosis process involves local inflammation and signal transduction, mediating smooth-muscle-cell migration and proliferation which may lead to thrombus formation. The rate of restenosis after stenting varies considerably from ~10% to as much of 40% in certain patient groups. Much research has been conducted to the pathophysiology and treatment of in-stent restenosis. DES have been introduced as a potential solution for restenosis. DES are combination products composed of a medicinal substance and a medical device and since the medicinal substance has an ancillary function to the device, these combination products are classified as medical devices in accordance with the Council Directive 93/42/EEC as amended.

According to the medical device legislation, the Notified Body has to consult one of the competent authorities of the Member States or the EMEA with regards to the quality, safety of the medicinal substance incorporated as integral part of the device, including the clinical benefit/risk profile of the incorporation of the substance into the device. This ancillary medicinal substance can be an active pharmaceutical ingredient or a formulated medicinal product. When issuing its scientific opinion the competent authority or the EMEA shall take into account the manufacturing process (not addressed in this guidance) and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body. The aspect of "usefulness" relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the device. It refers to the suitability of the medicinal substance to achieve its intended action and whether the potential inherent risks (aspects of "safety") due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the device. Guidance is needed with regard to the non-clinical and clinical data required for this evaluation.

The Medical Devices Directive and its corresponding Guidelines state that in the case of implantable devices, active implantable devices and devices of Class III, evidence of the clinical performance and safety of a medical device is provided by means of clinical data. Clinical data are relevant to the

various aspects of the clinical safety and performance of the device and can be based on (1) published and/or unpublished data on market experience of the device; or a similar device for which equivalence to the device in question can be demonstrated; or (2) a prospective clinical investigation(s) of the device concerned; or (3) results from a clinical investigation(s) or other studies reported in the scientific literature of a similar device for which equivalence to the device in question can be demonstrated.

Equivalence in this context is defined as:

- Clinically: used for the same clinical condition or purpose; used at the same site in the body; used in similar population (including age, anatomy, physiology) ; have similar relevant critical performance according to expected clinical effect for specific intended use.
- Technically: used under similar conditions of use; have similar specifications and properties; viscosity, surface characteristics; be of similar design; use similar deployment methods (if relevant); have similar principles of operation.
- Biologically: use of same materials in contact with the same human tissues or body fluids.

3. SCOPE

The scope of the present document is restricted to the clinical and non-clinical aspects of the evaluation of ancillary medicinal substances contained in DES coronary stents following by analogy the methods specified in Annex I to Directive 2001/83/EC as amended. The non-clinical data refer to in vitro and animal data regarding pharmacodynamics, pharmacokinetics and toxicology. This guideline does not deal with quality aspects.

4. BACKGROUND

Different possibilities can be distinguished depending on the knowledge of the ancillary medicinal substance (although it is recognised that new emerging technologies may not be covered by the different possibilities as described below) i.e.:

1. the medicinal substance of the combination is already used in a CE marked DES with the same indication (see section 7.3) and the Manufacturer claims:
 - a. comparable medicinal substance release characteristics (**A**):
 - i. same stent material with the same surface coating and drug carrier system (**A1**);
 - ii. same stent material with a different surface coating and drug carrier system (**A2**);
 - iii. different stent material with same surface coating and drug carrier system (**A3**);
 - iv. different stent material with different surface coating and drug carrier system (**A4**).
 - b. different medicinal substance release characteristics (**B**);
2. the medicinal substance of the combination is known to the competent authority as an active pharmaceutical ingredient or formulated medicinal product in an authorised medicinal product but not as a component of a (previously) CE marked DES (**C**);
3. the medicinal substance of the combination is a new active substance and therefore not known to a Competent Authority neither as an active pharmaceutical ingredient or formulated medicinal product in an authorised medicinal product nor as a component of a CE marked DES (**D**).

These different possibilities of the DES raise important questions about the data needed for adequate evaluation in vivo and in vitro of the medicinal substances contained in DES in order to establish safety and the clinical benefit/risk profile of the incorporation of the substance into the device. The combination of DES with ancillary medicinal substances creates the potential for local as well as systemic effects not seen previously with bare metal stents (BMS). The combination exhibit properties that are obviously uncharacteristic for medical devices. As a consequence the evaluation of the

medicinal substance component cannot solely be based on conventional methods used to evaluate medicinal products, because drug release from DES is designed to be focussed at the site of stent implantation. Although it is recognised that the total amount of medicinal product incorporated in the DES is substantially lower than used systemically in clinical applications, local safety aspects are a major point of concern and should be taken into account in the (non-) clinical evaluation programme. The benefit- risk profile of medicinal substances in the context of a DES is linked with the chosen stent platform, the surface coating and drug carrier system (if present) and any interaction among these. Evaluation of the medicinal substances safety and clinical risk/benefit profile in the context of a DES in coronary stenting is complicated by the fact that in case of adverse events (e.g. Major Adverse Cardiac Events (MACE)) the influence of the medicinal substance and of the device component cannot easily be separated.

5. BENCH TESTING

In all cases (**A, B, C, D**), the Manufacturer is expected to perform a series of bench tests on the integrity of the device component of the investigational combination product. It must be demonstrated that the ancillary medicinal substance and device neither chemically nor physically interact adversely with each other. In addition, it is important for the Manufacturer to elucidate how application of the medicinal substance and drug-carrier to the device may affect its fatigue and corrosion properties, coating integrity, durability, and any other relevant combination- product specific components.

It is acknowledged that Bench-testing and Biocompatibility testing are part of the review by Notified Bodies. The NCA/EMA particularly expect to review the following data as part of their non-clinical evaluation.

6. DATA FOR NON-CLINICAL EVALUATION

6.1 Biocompatibility testing of the device

The Manufacturer must submit results of biocompatibility testing of the bare stent platform performed to support the initiation of a human clinical study as described in the Essential Requirements. The results of biocompatibility testing of all relevant materials including carrier and stent material shall be provided to the NCA/EMA. The Manufacturer should document and discuss the extent of biocompatibility testing conform ISO 10993 (**A, B, C, D**).

6.2 Nonclinical testing requirements for the drug-eluting stent

In case of the same surface coating and drug carrier system as a reference DES, in vitro testing alone might be an acceptable option (A1).

6.2.1 Pharmacodynamics (proof of concept)

The Manufacturer should elucidate the mechanism of action of the added medicinal product(s) justified by relevant data. Several biological effects, such as inhibition of cell proliferation, can be examined in cell culture utilising vascular endothelial and smooth cells. Other study endpoints, such as inhibition of inflammation and matrix deposition, can be examined by tissue histology, which is typically not possible with human subjects. Experience suggests that the coronary arteries in domestic crossbred swine and iliac arteries of rabbits are suitable in that their size, access, and injury response are similar to human vessels. However, there is no known animal model for human atherosclerotic disease. No animal model has been successful in replicating the magnitude of clinical benefit observed in humans with DES and there is poor correlation between animal and human effectiveness parameters and study results. This applies to **A, B, C, D**.

6.2.2 Non-clinical pharmacokinetic testing

Drug-eluting coronary stents present major challenges for in vivo (**B, C, D**) pharmacokinetic (PK) characterisation. The devices are designed to release medicinal substance locally, with the intent to maximise or control bioavailability within local vascular tissue. The development of a suitable in vivo

local pharmacokinetic testing model is complicated by the lack of an animal model equivalent to human atherosclerotic disease (see 6.2.1). DES pharmacokinetic testing consists of local, regional, and systemic assessments. Furthermore, factors such as stent geometry, homogeneity of stent strut apposition to the vessel wall, and drug hydrophobicity should be taken into account because of major differences in drug distribution, even within the same stent. In vitro PK studies of medicinal substance properties, such as rates of dissolution, have also been required for drug-eluting stents (**B, C, D**). In vivo pharmacokinetic studies are very important to quantify the duration of medicinal substance exposure (**B, C, D**). Ancillary medicinal substance concentrations should be measured at the local (tissue), regional (organ), and systemic levels in animals (**B, C, D**). In the case of very small doses of medicinal substance, time-release profiles usually suffice to demonstrate safety for human trials (**B, C, D**). The profiles are typically collected in an appropriate animal model and reflect besides tissue medicinal substance levels also the quantity of medicinal substance remaining on the device. These critical laboratory and animal studies can also serve as the basis for an in vivo–in vitro correlation.

6.2.3 Testing multiple overlapping stents

Treatment of large vascular lesions requires implantation of multiple stents. At sites of stent overlap, the load and release of the medicinal substance(s) are increased and substantial deposition of the medicinal substance(s) could occur because of altered flow. Within the context of clinical practice of implanting multiple overlapping stents, the effect of stent overlap on vascular healing should be evaluated (**A, B, C, D**).

6.2.4 Preclinical toxicity studies

Because prediction of efficacy is not reliable from current animal models, animal testing is primarily limited to the evaluation of safety. The proposed clinical medicinal substance dose and release characteristics should be justified by nonclinical data (**B, C, D**) (see above). Preclinical dose range finding studies are strongly recommended, showing effects across ranges from sub-therapeutic to toxic levels, where practicable (**B, C, D**). A multiple dose study should be performed in an animal model to establish safety margins, and toxicity in choosing a dose for clinical trials (**B, C, D**). The dosing studies will establish a performance margin between the sub-therapeutic dose and the therapeutic dose, and a safety margin between the therapeutic dose and the toxic dose.

Experience suggests that the coronary arteries in domestic crossbred swine and iliac arteries of rabbits are suitable in that their size, access, and injury response are similar to human vessels. A key safety concern is stent thrombosis. Animal models provide useful information regarding stent thrombosis risk in clinical trials. The porcine model can be used to determine stent safety from both thrombosis and neointimal stimulation perspectives. Adverse vascular effects showing poor healing, vessel toxicity, absent endothelialisation, or neointimal stimulation are of major concern and information on these effects should be proactively looked for. The Manufacturer should provide nonclinical safety evidence on the results from both acute and chronic studies. Stent efficacy should be assessed by an absence of thrombosis and by neointimal reduction. Data obtained at an early time point (3 or 7 days) should help determine subacute thrombosis risk. Other time points used should be at 28 days to observe neointimal hyperplasia, and at least one late time point to examine long term effects. The late time point (3 or 6 months) depends on when “healing” and medicinal substance release are both complete. Three-month follow-up is generally acceptable if no adverse effects are noted at this time. However, it is to be recognised that given the inability to extrapolate animal outcome to clinical outcome data in humans, there is currently no consensus on the duration of animal testing before testing in humans. Although it is generally agreed that the early post implantation period (from 1 week to 1 month of follow-up) is useful for gaining preliminary evidence about the tendency for acute stent thrombosis as well as the neointimal tissue formation with respect to the human condition, the total length of required follow-up should be discussed by the Manufacturer by means of the biological and release characteristics of the product and animal data. E.g. later time points are important given the impact of peri-stent late remodeling as an additional cause of peri-stent effects that would impact the clinical outcome. This applies to **A2-4, B, C, D**. All animals experiencing death or other untoward clinical events should be examined. Such deaths typically occur in the first 24 hours after implant, but may occur later if healing

is impaired. Sudden death later than 24 hours should be vigorously investigated for cause, as the ancillary medicinal substance might have interfered with healing.

Simple visual description of the histopathology is discouraged as the sole evaluation. A more rigorous (semi) quantitative and defined scale for arteriography and histopathology evaluation (inflammation, vascular healing, endothelization) should be presented as well. Full protocols, gross photographs, histologic photomicrographs, and detailed pathology reports should be made available.

When a medicinal substance is bound directly to a stent, the stent without ancillary medicinal substance can be satisfactory control. Polymer coatings by their nature typically induce inflammatory response and fibrinoid deposits. When a carrier is present, additional controls to evaluate the carrier alone, without the ancillary medicinal substance, must be included. It is key that early inflammatory reactions meet safety criteria for later time points as well.

Only one stent should be implanted per artery except when issues of stent overlap or multiple stent dosing are considered. While avoiding overlap during initial evaluation, purposeful overlap should be performed in later studies. The intended distance of overlap should be discussed by the Manufacturer.

In case of safety concerns, a non-inferiority study against an approved DES may be acceptable, provided that long-term safety concerns can be clearly ruled out. It is the key that early inflammatory reactions and changes in matrix composition meet safety criteria for later time points as well.

6.2.5 Testing of the medicinal substance if not an approved medicinal product

Additional animal toxicity studies are to be expected if the medicinal substance is not approved for the use in a stent (**C, D**). In case of “**D**”, human Phase I studies are to be expected. An additional requirement would be an initial human testing in healthy volunteers intended to determine the no observed adverse effect level. The testing typically needs to evaluate study questions that are specific to the DES device.

7. CLINICAL DATA

7.1 Clinical pharmacokinetic testing

It is recognised that generating human PK data can be difficult for these combination products because they often use very small medicinal substance doses. The Manufacturer may need to develop highly sensitive analytical methods to collect fitting PK data or to demonstrate that such studies are impractical (**B, C, D**). Human toxicity Phase I studies are to be expected to determine the no observed adverse effect level (NOEL) if the medicinal substance is not approved (**D**).

7.2 Clinical surrogate measures and exploratory testing

Improvement of angiographic, intravascular ultrasound and/or the potential value of new imaging (e.g. Optical Coherence Tomography (OCT) as well as functional testing biomarkers of luminal stenosis provides important information (**A2-4, B, C, D**). These novel techniques may be applied early on during the evaluation of new generation DES and could serve as a screening method to provide indications as to whether specific claims about safety, including the clinical benefit-risk profile of the incorporation of the substance into the device, can possibly be substantiated. The dose-related benefit and adverse effects should be characterised in randomised, controlled studies (**B, C, D**). The aim of dose-response studies is to define the most effective dose for confirmatory trials.

7.3 Confirmatory clinical trials

The clinical evaluation of drug-eluting stents is primarily aimed to demonstrate performance and safety according to the intended use as defined by the Manufacturer including the clinical benefit/risk profile of the incorporation of the substance into the device and the study design should fulfil both.

The usual standard of evidence for a DES is the randomised, controlled clinical trial. A historical control is rarely acceptable for a novel stent. Actively controlled studies where patients are treated

with a commercially available DES are expected. Choices of control groups for these trials should be critically evaluated and justified in order to ascertain that best of care approaches are being used. Randomised controlled trials utilising either a superiority or non-inferiority design and evaluating commonly used clinical endpoints will give the most reliable form of evidence in case questions remain about long term safety (**B, C, D**).

When the medicinal substance of the combination is known to the competent authority and already registered in the setting of a DES and the Manufacturer claims comparable medicinal substance release characteristics (**A2-4**) the use of clinical surrogate measures in the setting of a non-inferiority study against an approved DES may be acceptable, provided that long-term safety concerns can be clearly ruled out for the claimed target population.

The suitable target population will depend on the type of approach chosen by the Manufacturer. In the past, the approved indication for DES was in general limited to patients with symptomatic ischemic heart disease with discrete, de novo lesions in native vessels with reference vessel diameters of 2.5 to 3.5 mm of up to 30 mm in length. However, a broader or enriched predefined high risk target population is to be pursued provided that the long term safety is properly studied. In each individual case, the type of comparator and the statistical approach (superiority vs. non-inferiority) should be properly discussed. A non-inferiority design with an already approved DES would only be acceptable if patients are included according to the approved conditions of use (indications). In all cases, background therapy should be standardised according to available recommendations. Specific evidence for the usefulness and safety of the DES across more complex lesions or patients cohorts (i.e. small vessels, long lesions, lesions at bifurcations, multi vessel disease, diabetes, coronary grafts) will be requested (**A, B, C, D**).

Study endpoints

Angiographic biomarkers (in-stent/in-lesion minimal lumen diameter, percent diameter stenosis, in stent/in-lesion late lumen loss), and intravascular ultrasound biomarkers (neointima volume) provide valuable information concerning the usefulness of the antiproliferative agent being studied. They can be used as primary endpoints in the setting of a DES in which the Manufacturer claims comparable medicinal substance release characteristics with an already commercially available DES (**A2-4**). In case of the same polymer as a reference DES, in vitro testing alone might be an acceptable option (**A1**). However, a significant improvement of an angiographic/intravascular ultrasound parameter does not necessarily translate into a better clinical outcome. Conclusions regarding possible improvements of clinical outcome could be difficult since the study will be underpowered.

In terms of study endpoints for other settings of coronary drug-eluting stents (**B, C, D**), clinically meaningful endpoints are strongly recommended. Ischemia-driven revascularisation of the target lesion, cardiac death and myocardial infarction, should be used as primary endpoint. It is recommended to analyse in addition the single components and clinically relevant groups of components separately, to show consistent results.

Specific consideration should be given to the potential interference/contribution of concomitant therapy on study endpoints. Concomitant therapies; e.g. anti-platelet regimes, should be specified and justified.

Death and myocardial infarction (rates to be reported along with sensitivity analysis based on accepted thresholds), abrupt stent occlusion (ARC definitions), bleeding including stroke, should be reported in order to capture complications of anti-platelet therapy.

Duration of follow-up

Time points for acceptable pathological evaluation will depend upon the specifics of DES (i.e., polymer and medicinal substance characteristics, elution kinetics, etc). An important question that has to be answered (e.g. by means of extrapolation of animal data) is whether or not DES implantation merely delays the growth of neointimal tissue, perhaps to a time point (far) beyond the 6- or more recently used 9-month evaluation period. In this context, 9 months is an appropriate endpoint, but additional angiographic evaluation at 12 to 24 months could provide additional information on the longitudinal healing response (**A, B, C, D**).

In general, pivotal clinical studies providing data on primary endpoints should last at least one year with careful follow-up (see below).

7.4 Clinical safety evaluation

All potential adverse events should be collected and analysed using a pre-planned methodology. Identified adverse events should be carefully monitored and should be characterised in relation to the DES, patient and lesion characteristics, time course, and other relevant variables (**A, B, C, D**). Specific consideration should be given to the potential interference/contribution of concomitant therapy. The most important aspects of safety are both short- and long-term rate of major cardiac events (MACE), including those related to early and late stent thrombosis. Any sub-population at increased risk of adverse events should be identified. Appropriate ways of observing safety for trials in such vulnerable patient populations are warranted.

7.5 Post-marketing surveillance considerations

The information gathered in the post-marketing period is very important. Long-term post approval clinical follow up (e.g. 5-year) should be carried out in order to determine issues of long term safety and performance according to the requirements of MEDDEV 2.12-2. Data from this follow-up should be fed into the risk management process. Post-approval follow-up could include patients already enrolled and treated in the pivotal study(ies) and also new patients in the post-approval setting (**A, B, C, D**).

8. REFERENCES (BACKGROUND GUIDANCE, NORMS AND SCIENTIFIC)

1) *Related to Medical Devices*

- a) Guidance document MEDDEV 2. 1/3: Interface with other directives: medical devices medicinal products.
- b) Guidance document MEDDEV. 2.7: Evaluation of clinical data: a guide for manufacturers and notified bodies.
- c) Guidance document MEDDEV 2.12-2 : Post Market Clinical Follow-up.
- d) EN ISO 14971:2007 Medical devices – Application of risk management to medical devices.
- e) EN ISO 14155-1:2003 Clinical investigation of medical devices for human subjects – Part 1: General requirements.
- f) EN ISO 14155-2:2003 Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans.
- g) EN ISO 10993-1:2004 Biological evaluation of medical devices – Part 1: Evaluation and testing.
- h) EN ISO 14630:2005 Non-active surgical implants – General requirements.
- i) EN 12006-3:1998 Non-active surgical implants – Particular requirements for cardiac and vascular implants – Part 3: Endovascular devices EN 14299:2004 Non active surgical implants – Particular requirements for cardiac and vascular implants – Specific requirements for arterial stents.
- j) Pre EN ISO DIS 25539-2- Cardiovascular implants-Endovascular devices –Part 2: Vascular Stents.

2) *Related to Medicinal Products*

- a) Note for Guidance on Clinical Safety Data Management ICH E2.
- b) Schwartz RS, Chronos NA, Virmani R.: Preclinical restenosis models and drug-eluting stents: still important, still much to learn. *J Am Coll Cardiol.* 2004;44:1373-1385.
- c) Schwartz RS, Edelman ER, Carter A, Chronos N, Rogers C, Robinson KA, Waksman R, Weinberger J, Wilensky RL, Jensen DN, Zuckerman BD, Virmani R.: Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group. *Circulation.* 2002;106:1867-1873.
- d) Kereiakes DJ, Kuntz RE, Mauri L, Krucoff MW.: Surrogates, substudies, and real clinical end points in trials of drug-eluting stents. *J Am Coll Cardiol.* 2005;45:1206-1212.
- e) Muni NI, Califf RM, Foy JR, Boam AB, Zuckerman BD, Kuntz RE.: Coronary drug-eluting stent development: issues in trial design. *Am Heart J.* 2005;149:415-433.
- f) Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R.: Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus. *Circulation.* 2005 Jul 12;112(2):270-8.
- g) Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R.: Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol.* 2007 Jul;27(7):1500-10.