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University of Siena Medical School

Novartis Vaccines and Diagnostics S.r.l.

Novartis Vaccines Institute for Global Health S.r.l., part of the Novartis Institutes for Biomedical Research

“Advanced Immunization Technologies” (ADITEC) - Project funded by the European Commission
Technical-Scientific Committee

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President Technical – Scientific Committee
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Dean Medical School, University of Siena

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Prof. Pediatric Infectious Diseases
Director Novartis Vaccines Academy

Dr. Audino Podda, M.D., PhD
Head Clinical Development and Regulatory Affairs, Novartis Vaccines Institute for Global Health

Dr. Emanuela Palla, PhD
Head Global Early Projects, Novartis Vaccines and Diagnostics

Dr. Giovanni Della Cioppa, M.D.
Head, Global Clinical Research and Development, Vaccines Development, Novartis Vaccines and Diagnostics
Organization, Venue and Duration

**Organization**

Novartis Vaccines Academy (Master coordination)

**Venue**

- University of Siena Medical School - Hospital and Laboratories
- Novartis Vaccines and Diagnostics S.r.l., Siena - Development departments, Research Center and Laboratories
- Novartis Vaccines Institute for Global Health S.r.l., Siena

**Duration**

May 2013 – November 2014
Vaccination has improved health in the world in an unparalleled way and has saved over 20 million lives in the last two decades. And yet, every year more than 3 million people, mostly children, die from vaccine preventable diseases. Preventable infectious diseases present a daily risk especially in countries where poverty and economic issues are the root cause for poor health care.

Immunization has proven to be one of the most cost effective interventions in health care systems. But it must be well planned, implementation must ensure high coverage, must be sustainable, and must have a reliable surveillance system. Just a few years ago immunization programs used few vaccines that had been developed decades ago. Major advances in immunology and biotechnology over the last decade have brought several new vaccines to reality.

This Master Program aims to provide to physicians with interest in public health and infectious diseases the opportunity to learn about vaccine preventable diseases, immunization impact, vaccine development and the roles of various stakeholders such as academia and governing authorities in vaccine policy setting and immunization programs, focusing in developing countries.

Sue Ann Costa Clemens
Prof. Pediatric Infectious Diseases
Director Novartis Vaccines Academy
Goals & Concept

First references to the University of Siena date back to 1240, making it one of the most ancient academic institutions in Europe. In 1357 Emperor Charles IV included Siena among the official universities of the Holy Roman Empire. Today, the University of Siena runs a wide selection of graduate and postgraduate courses, including doctoral degree programs, specialization schools and master programs.

In 2009 the University of Siena and Novartis Vaccines and Diagnostics established a novel specialization program for medical graduates, “The Master Program in Vaccinology and Pharmaceutical Clinical Development”.

“Knowing is not enough; we must apply. Willing is not enough, we must do.”

Goethe

Goals

- Capacity building in vaccinology and vaccine development in developing countries;
- To prepare students for a career in academia, public health and research and development in public and private vaccine institutes in developing countries.

Concept

- To provide graduates in Medicine with training in epidemiology and disease burden of vaccine preventable infectious diseases, vaccine development from research to licensure and vaccine policy and funding;
- Is a collaborative effort between academia and vaccine industry;
- Combines theoretical and practical training in immunology, infectious diseases and vaccinology, from research to licensure. The training is given by worldwide experts from academia, well known international universities, supranational organizations (e.g., EMA, Sabin Institute, Gates Foundation) and industry;
- The master course is conducted in English and is composed by:
  - a complete one-year course which includes lectures on all relevant disciplines of vaccinology and clinical development and a practical training at the University Hospital of Siena;
  - a 6-month internship within different departments of the Novartis Vaccines and Diagnostics (development and research departments); field training at various investigational sites and at the University of Siena laboratories involved in vaccine trials.

At the end of the Master program, following submission and discussion of a thesis, the students will receive a second level Master degree from the University of Siena.
Entry Requirements

- University degree in Human Medicine;
- Minimum 2 years, maximum 5 years post-graduation or residency in clinical medicine;
- Excellent command of English, written and spoken;

*Only ADITEC sponsored candidates must be:
  - Currently working in a European Union or Associated Member state or
  - Currently working in a vaccine development project funded by the European Commission or EDCTP.

Funding

- A 18-month grant will be provided to students who are accepted.
Application to the University of Siena

The III Edition of the Master Program in Vaccinology will start on May 2013.

The Application process is explained in the University of Siena announcement (bando) that is available at [http://www.unisi.it/didattica/corsi-post-laurea/master-universitari](http://www.unisi.it/didattica/corsi-post-laurea/master-universitari), (under the heading "Il livello" [2nd level], courses are ordered by date [05/feb/2013]) from October 2012. Candidates must send the official application form to the University of Siena by **February 05, 2013**.

Assistance or further information to the candidates will be provided by Novartis Vaccines Academy - Master Program Coordination. Please send an e-mail to vaccines_master.nvdit@novartis.com by **November 20, 2012**

Further Information

**Master Coordination:** Mrs. Roberta Bianchi, +39 0577 24 5253, +39 0577 24 3217, +39 328 76 04 987 (mobile)

**Web:** [http://www.novartisvaccines.it/ricerca/clinical-development-eng.shtml](http://www.novartisvaccines.it/ricerca/clinical-development-eng.shtml)

**E-mail:** vaccines_master.nvdit@novartis.com
Program Overview

First year
- Module I: Public Health and Vaccine Development Process;
- Module II: Vaccine Immunology and Preclinical Research;
- Module III: Infectious Diseases and Vaccine Prevention;
- Module IV: Vaccine Manufacturing and Quality Control Processes;
- Module V: Clinical Development Methodology, Biostatistics and Clinical Data management;
- Module VI: Pharmacovigilance;
- Module VII: Epidemiology, Health Systems and Economics;
- Module VIII: Good Clinical Practices, Clinical Quality Assurance and Clinical Trial Operations;
- Module IX: Regulatory Affairs;
- Module X: Policies and Recommendations for Vaccines in the World;
- Extra Curriculum Modules: Special Topics.

Second year (6 months)
- Internship:
  - Novartis development and research departments;
  - Investigational site training;
  - Training at University of Siena hospital and laboratories;
- Master thesis (writing and discussion).

Students Evaluation

- Written exams after each module and a cumulative one at the end of the first year;
- Internship: students performance is assessed by supervisors and master coordination based on activities and overall training and deliverables during the 6 month internship period.

Thesis
- Each student will select a subject for a written thesis;
- The thesis will be submitted to University of Siena and discussed at the end the Master Program.
Module Directors

- Prof. Emanuele Montomoli - Dept. of Physiopathology Experimental Medicine, Public Health, University of Siena
- Prof. Sue Ann Costa Clemens - Prof. Pediatric Infectious Diseases, Director Novartis Vaccines Academy

Aim

To get a general overview on immunization and public health in the world and to understand the overall principles of pharmaceutical development process from research to the market.

Contents

- Public Health basic concepts;
- The role of vaccines in public health;
- Role of stakeholders;
- Governments, NGO's, Supranational Organizations;
- Academia;
- Vaccine industry;
- Vaccine development process;
- From research to licensure and recommendations;
- How vaccine companies function;
- How to manage projects in vaccine companies;
Module Directors

- Prof. Gian Maria Rossolini - Dean Medical School, University of Siena, Italy
- Dr. Giuseppe Del Giudice - Global Head Translational Medicine, Novartis Vaccines and Diagnostics
- Dr. Emanuela Palla - Head Early Development Projects, Novartis Vaccines and Diagnostics

Aim

To understand the basic concepts of immunology, immune response to vaccines and how to translate this into vaccine development and licensing.

Contents

- Historical background to vaccination:
  - Human Immune response:
    o Innate immunity;
    o B-cell and T-cell responses;
    o How to measure B and T cell function.
- Identification of vaccine targets:
  - Antigen structures as potential vaccine candidates;
  - Conventional and novel approaches to vaccine development.
- Type of vaccines;
- The role of adjuvants;
- Pre clinical evaluation of vaccine immunology and safety;
- Analysis of immune response to vaccines in humans:
  - Antibody response;
  - Functional assays versus quantitative assays.
Module Directors

- Prof. Roberto Gasparini - Director Public Health Department, University of Genoa, Italy
- Dr. Audino Podda - Head Clinical Development & Regulatory Affairs, Novartis Vaccines Institute for Global Health

Aim

To learn about vaccine preventable infectious diseases, their epidemiology and vaccine available, or under development, for their prevention.

Contents

- Vaccine preventable infectious diseases;
- Epidemiology of vaccine preventable diseases;
- Licensed vaccines;
- New vaccines under development.
Module Directors

- Prof. Emanuele Montomoli - Dept of Physiopathology Experimental Medicine, Public Health, University of Siena
- Dr. Massimo Bugnoli - Technical Operations, Novartis Vaccines and Diagnostics

Aim

To get an understanding of concepts, methods and challenges of technical operations and quality of vaccine manufacturing.

Contents

- History of vaccine production, challenges and advances;
- Production processes in bacterial and viral vaccines:
  - Working seed, bulk formulation, filling and packaging;
  - Products in development;
  - Industrialization (scale-up);
  - From idea to product.
- Organization:
  - Procedures and flows in manufacturing and control vaccines;
  - Plant structure and layout; shifts.
- Importance of Good Manufacturing Practices (GMP) to guarantee an immunogenic and safe product:
  - Selection of raw materials;
  - Systems as tools to monitor and control quality.
- Labeling and packaging;
- Differences between vaccine and pharmaceutical production.
Module Directors

- Prof. Stefania Rossi - Department of Physiopathology Experimental Medicine & Public Health, University of Siena
- Dr. Giovanni Della Cioppa - Head, Global Clinical Research and Development, Vaccines Development, Novartis Vaccines and Diagnostics
- Dr. Uwe Nicolay - Head Biostatistics, Novartis Vaccines and Diagnostics

Aim

To understand the basic principles of clinical trial methodology, especially in vaccine development. To understand basic concepts of statistics and data management for clinical trials.

Contents

- Overview of the clinical development:
  - Clinical development plans;
  - Phases of the clinical development process: Phase I - II - III - IV trials;
  - Experimental studies (clinical trials) vs. epidemiological (observational) studies;
  - Life-cycle of a product;
  - Geographical, logistical & economic considerations.
- Clinical trial methodology and protocol development:
  - Why clinical trials? Variability of biological phenomena and measurement errors;
  - Defining the treatment effect: from measurements to end-points;
  - The choice of the sample: which subjects, how many subjects;
  - The choice of treatments: study treatments, concomitant treatments;
  - Experimental designs;
  - The protocol approval processes: internal, external, amendments.
Vaccine trial methodology:
- Safety, immunogenicity, efficacy and effectiveness;
- Surrogate end-points, correlates of protection and constrains of serological end-points;
- Ethical considerations in clinical development.

Statistical methodology for clinical trials:
- Basics, ICH guidelines (E8, E9, E10), EMEA/FDA guidelines;
- Descriptive vs. inferential statistics;
- Importance of randomization to avoid bias;
- Power & sample size calculations for hypothesis testing;
- Superiority, equivalence, non-inferiority;
- Designs & analytical approaches;
- Endpoints (measures and variables), surrogate, markers;
- P-values: statistical and clinical significance;
- Statistical analysis plan;
- Interim analyses, meta analyses;
- Alignment of protocol, data collection and reports.

Clinical Data Management:
- Case Report Form (CRF) design;
- Electronic Data Capture and paper CRF processes and systems;
- Database design and setup with edit checks, rules and derivations;
- Validation of computerized systems for data management;
- Data collection and data cleaning;
- Data integration (e.g. lab data transfers);
- Data quality, database lock, post database lock changes;
- Adverse Event reporting;
- Coding dictionaries (MedDRA, WHO-drug).
Module Directors

- Prof. Franco Laghi Pasini - Department of Medicine and Immunological Sciences, University of Siena
- Dr. John Ferguson - Global Head Pharmacovigilance & Medical Safety - Novartis Vaccines and Diagnostics

Aim

To understand main rational, best practice and present overview on Pharmacovigilance systems in the world. The learning is focused on: how to write an individual case narrative, how to assess causality and expectedness of cases, how to determine certainty of diagnosis according to Brighton collaboration guidelines.

Contents

- Introduction to clinical safety, Pharmacovigilance and benefit-risk management;
- Clinical safety in the Developing World;
- Statutory basis for safety in humans:
  - Historical basis;
  - Governing bodies and Health Authorities: ICH, CIOMS, WHO;
- Safety data collection in clinical trials;
- Spontaneous adverse events;
- Adverse Events:
  - Definitions and classification;
  - Processing, archiving and retrieval;
  - Assessment: expectedness, listedness, causality and reference documents
  - Analysis and decision-making;
- Regulatory Reporting;
- Life-Cycle Clinical Product Safety:
  - Discovery and pre-clinical science;
  - Pre and post authorization clinical safety;
  - Structured benefit-risk assessment and management
- Safety strategy, issue management and crisis prevention
- Communication in Pharmacovigilance
Module Directors

- Prof. Felice Petraglia – Department of Pediatrics, Obstetrics and Reproductive Medicine – University of Siena
- Dr. John Weil - Head Epidemiology – Novartis Vaccines and Diagnostics

Aim

To understand basic principles of Epidemiology and Health Economics and the relevance for vaccine development.

Contents

- Epidemiology:
  - Principles of infectious diseases epidemiology;
  - Measures of disease occurrence;
  - Measures of impact;
  - Sensitivity – specificity;
  - Observational studies: cohort and case-control, alternative designs, how to write a study protocol, choice of a reference group, synthesis causal inference, sampling;
  - Methodology: matching, bias, confounding, third factor, disentangling;
  - Calculations - analysis: sample size calculation, significance, logistic regression;
  - Surveillance: principles of surveillance, event based surveillance, analytical tools in surveillance, lab-based surveillance, evaluation of surveillance.
- Health Systems and Economics:
  - Overview of key patterns and issues of health systems mainly in Low Income Countries;
  - Key concepts of the economics of health;
  - Student will simulate tools for allocating resources in local health systems assessing population health needs.
Module Directors

- Prof. Stefano Gonelli - Department of Internal Medicine, University of Siena
- Dr. Elisa Marchetti - Head Clinical Operations and Training, Novartis Vaccines Institute for Global Health

Aim

To understand the requirements and to ensures quality in clinical trials execution and the operational requirements for planning and executing vaccines clinical trials.

Contents

- Introduction to Good Clinical Practice (GCP):
  - Regulatory requirements, ICH and GCP and regional differences;
  - Roles and responsibilities of sponsors, investigators and monitors;
  - The importance of the Informed Consent;
  - Essential documents.
- Elements of the Clinical Quality System:
  - Quality Policies and Quality Manual;
  - Standard Operating Procedures (SOPs);
  - Qualification and training of staff;
  - Qualification of third parties (Contract Research Organizations CROs);
  - Trial Master File;
  - Auditing: Internal and external auditing, system audits.
• Regulatory inspections:
  - Preparation of an inspection (sponsor and site);
  - Types, procedure, reports;
  - Frequent findings.
• Introduction to CTO:
  - From protocol to clinical study report;
  - Clinical project management & planning.
• Clinical trials preparation:
  - Protocol, Informed Consent Form and related documents;
  - Labeling & packaging of vaccines;
  - Site qualification;
  - Clinical research organizations (CRO);
  - Documentation.
• Clinical trial execution:
  - Initiation visit;
  - Monitoring;
  - Safety;
  - Study closure.
• Database lock and close-out data management activities;
• Operational systems and processes:
  - Trial management systems;
  - Efficiencies and quality control in process;
• Clinical Study Report.
Module Directors

- Prof. Franco Laghi Pasini - Department of Medicine and Immunological Sciences, University of Siena
- Dr. Anne Marie Georges, Independent Consultant, Chairperson - Regulatory Affairs Working Group of European Vaccine Manufacturers Association - Brussels, Belgium
- Dr. Jochen Auerbach, Head Regulatory Affairs - Novartis Vaccines Institute for Global Health

Aim

To understand international regulatory environment and requirements related to obtaining approval for marketing vaccines and the maintenance of these licenses.

Contents

- Introduction:
  - General overview of main Competent authorities (FDA, EMA, MHLW);
  - International Conference on Harmonization (ICH).
- Drug development life cycle from a regulatory perspective:
  - Preclinical;
  - Phase I – initial safety
  - Phase II – proof of concept, dose ranging;
  - Phase III – efficacy, large scale safety;
  - Regulatory constrains of serological endpoints;
  - Post Approval Commitments – studies to detect rare vaccine adverse events, impact studies; epidemiology;
  - Health Authority review and approval procedures.
• Regulatory systems:
  – US regulatory system;
  – EU regulatory system;
  – WHO prequalification process;
  – Other selected regulatory systems.
• Product labeling:
  – US Package Insert;
  – EU Summary of Product Characteristics;
  – Package Inserts and labels, what needs to be included.
• Regulatory differences between classical drugs and biologics;
• Promotional compliance;
• Regulatory Inspections
MODULE X - Policies and recommendations for vaccines in the world

Module Directors

- Prof. Paolo Bonanni - Department of Public Health, University of Florence
- Dr. Audino Podda - Head Clinical Development & Regulatory Affairs, Novartis Vaccines Institute for Global Health

Aim

To understand that the introduction of new vaccines into the immunization calendars of different countries is dependent on a number of local and international factors.

Contents

- Key elements of Vaccination Systems and Policies in different countries and geographical areas:
  - Vaccination systems: centralized vs. decentralized;
- Policies for vaccine licensure, recommendation and implementation:
  - data requested (epidemiological, clinical, economical etc.);
- Factors influencing introduction of new vaccines;
- Procedures for vaccine purchasing and supply;
- Public acceptance of Vaccination;
- Health Technology Assessment (HTA) as a tool for prioritization;
- Economic analysis applied to vaccination programs:
  - Priority settings;
  - National Immunization Committees;
  - Vaccine schedules;
  - National budgets;
- Financing mechanisms: GAVI, AMCs, Revolving Fund, PAHO, others.
Specials Topics

Aim

To provide tools for the students personal and professional growth.

First and second semester

- How to read and interpret scientific papers;
- How to write a clinical trial protocol and a protocol synopsis;
- How to write an epidemiology protocol;
- How to write grant applications and where to apply;
- How to write a thesis;
- How to write a paper to be published;
- Presentation skills;
- Communication: crisis management (clinical studies, SAEs, marketed products).