THE HUGGARD CONSULTING GROUP

Gauging the Effectiveness of the QRA

IDEA WG Meeting

Leuven, February 15, 2017

Background

- The QRA approach is:
  - "Risk-based"
  - Scientific principles are well regarded by stakeholders, including regulators and JRC
- But questioned by some stakeholders, especially in the dermatological community because:
  - Not yet demonstrated to reduce incidence of skin CA in population – no demonstration in real people

Requirements

- Industry needs to address demonstrating the effectiveness of the QRA and there are a number of criteria:
  - Must be scientifically robust
  - Must address key concerns of dermatologists
  - Must demonstrate that industry is behaving positively and responsibly

What Has Been Carried Out?

- Discussions with key dermatologists and academics
- Understanding gained of concerns, constraints and expectations
- Detailed literature review of key factors that need to be considered in developing a study
- Development of additional options to 'basic' surveillance system in clinical population
- Preliminary estimate of study sizes

Literature Review Findings

Detailed review of some 40 papers examining the role of sex, age, prevalence by population (sensitive and general), prevalence variations with time and reproducibility of testing

- Findings:
  - Incidence of skin CA is higher in women than men, possibly attributable to greater exposure
  - Incidence of fragrance-related skin CA only declines in very old age but does increase as young population ages
  - Sensitive populations exhibit approximately 6 times the prevalence of that of the general population
  - The evidence as to prevalence changes over time is ambiguous
  - Lack of inter-and intra-clinic reproducibility is a major challenge to evaluating data

Other Factors in Study Design

- Ethics committee approvals
- On market issue
  - Roll-out time from substance assessment to bathroom shelves
    - e.g., for elements of the QRA1 implementation started in 2008, the changes in the marketplace might only have taken place recently
- Costs
- Time to results
- Addressing "Absence of evidence not evidence of absence"

The Challenge

- To demonstrate the effectiveness or lack thereof of the QRA, we are faced with questions:
  - Is there a change in incidence?
    - Compared to what we would expect?
  - Can this change be linked to the QRA?

Materials and Populations are Key

- In principle, we have to identify/create a (quasi-) naïve population and monitor it.
- To create a quasi-naïve population, we have a number of options which have been examined in some detail:
  1. An interventional study created by using a unique, not-in-the-market substance
  2. Surveillance (Repeat cross-sectional) study including 'new materials' with special attention to the younger population
  3. Cohort study allied with a repeat cross-sectional study including on 'new materials' focussing on the younger population
  4. Other options:
     1. Hybrid of 2 and 3
     2. Run (2 or 3) with substances where the QRA has had a substantial impact on quantities used in relevant consumer products

Note: For options 2 or 3 there is the need to identify materials with no confounding factors to increase the likelihood of drawing conclusions on the effectiveness of the QRA

Interventional Study

Cohort Study

- Follow cohort of 3,000 drawn from young, sensitive population over 10 years to measure changes in prevalence of skin CA with 4 comparison points with cross-sectional older groups
- The primary objectives of this study are:
  - To estimate the 0-, 3-, 6-, and 9 year incidence rate
  - To demonstrate that the 3-, 6- and 9-year incidence rate is smaller than the prevalence (FM I?) in the cross-sectional group
  - Also utilise the work of Buckley (2003) which reports that the incidence doubles (2,7% -5.8%) between the 10-19 age group compared with the 20-29 age group.
  - Fundamentally, if the QRA is not working then we would expect that for the new materials incidence rates would approach that of FM I in the older population with an adjustment for the fact that we are potential dealing with individual/fewer (?) materials.

Sample Size Considerations

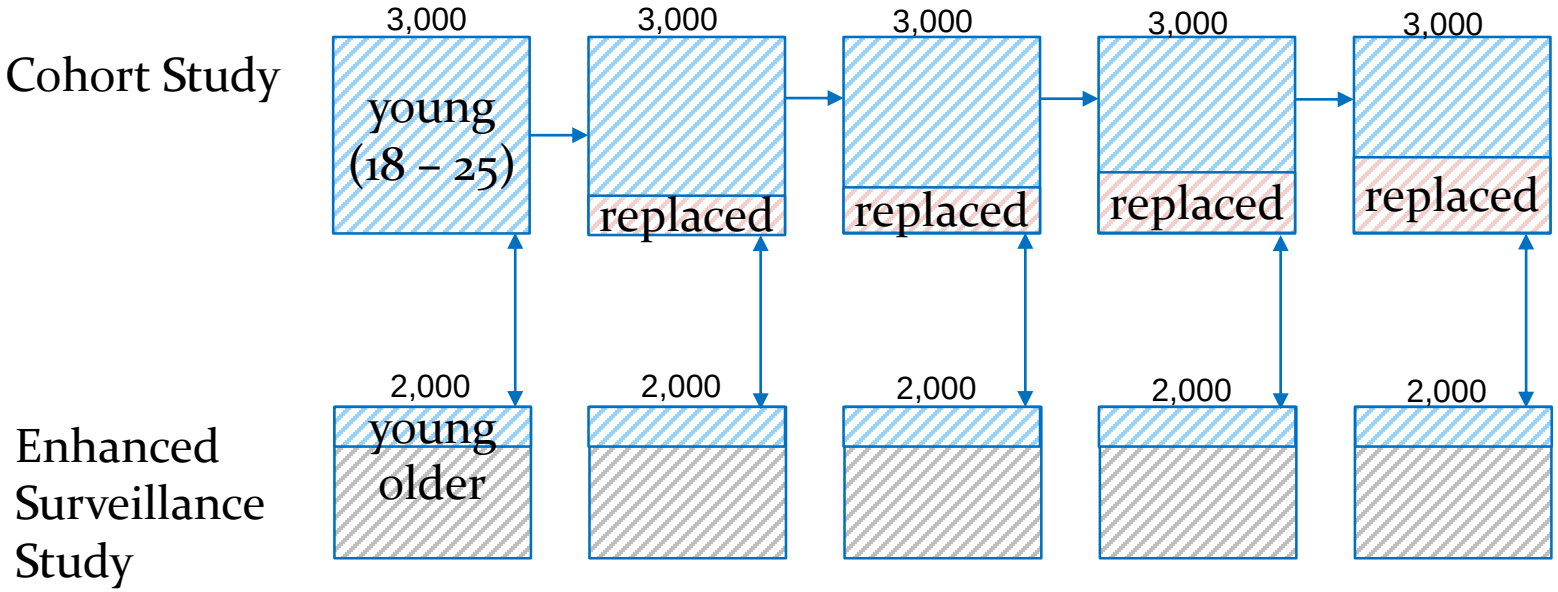
- Plan for 3000 subjects at conclusion for the cohort to have sufficient precision of estimation at end
- 6000 to 9000 subjects at beginning due to expected dropout, which would also result in a better precision of the incidence rates in the first years of the cohort study.
- A sample size of 3000 subjects results in a two-sided 95% confidence interval of 0.7% – 1.4% when the sample incidence is 1%.

Enhanced Surveillance Study

- Provide new materials when they enter into broad use to clinics to enhance surveillance of 2,000 -4,000 patients per year over 10 years
- Effectively a repeat cross-sectional study
- Fundamentally, if the QRA is not working then we would expect that for the new materials incidence rates would approach that of FM I with an adjustment for the fact that we are potential dealing with individual/fewer materials.
- Sizing is 2,500 subjects from a sensitive population – e.g., those presenting for testing because of eczema
  - Incidence based on FM I would be approximately 7%, adjusted for number and potency of new materials
  - Assumed under QRA methodology incidence would be 0.5% to 1.0%

Other Options - Hybrid Study Design

(Combination of Cohort and Enhanced Surveillance Study with Panel Methods)



Additional Options – Existing Material

- Material that:
  - Has had or will have its levels in products significantly reduced as a result of the QRA assessment
  - Is in broad use

Conclusions

- Demonstrating effectiveness of QRA is difficult but necessary to support it as a management tool for engaging with (EU) regulators
- Each study has various advantages and drawbacks – time, uncertainty/confounders, costs and need to agree detailed study design
- No study will deliver absolute certainty
- All give additional insights which can be feed into the continued enhancement of QRA

The Huggard Consulting Group S.A.R.L.
94, rue de l'Horizon
L-5960, Luxembourg
Phone: +352 305544
Fax: +352 305773
www.HuggardConsulting.com