Safeguarding public health

MHRA

Current UK experience with trial approval in early development

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28th April 2009

Clinical Trials Directive (2001/20/EC)

from 1st May 2004:

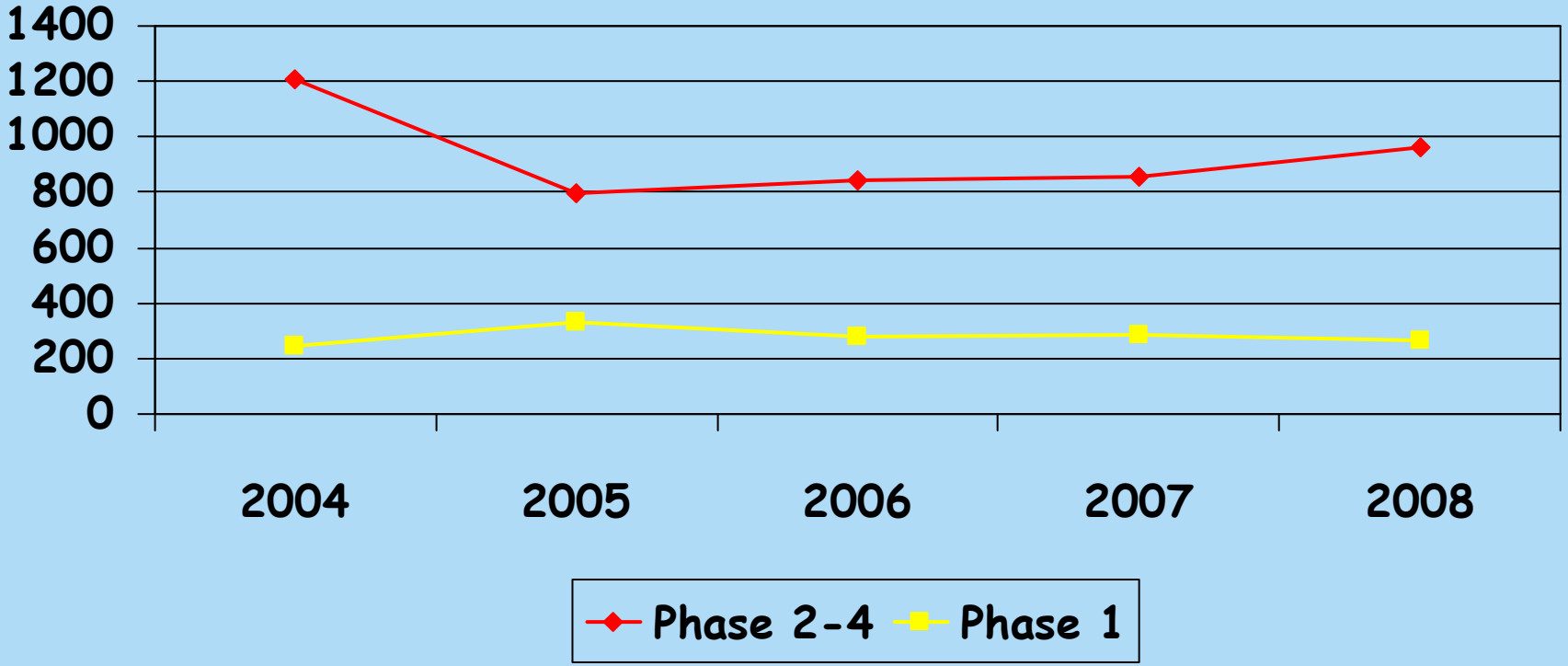
→ Regulation of healthy volunteer trials (Phase 1)

FIH trials from February 2007

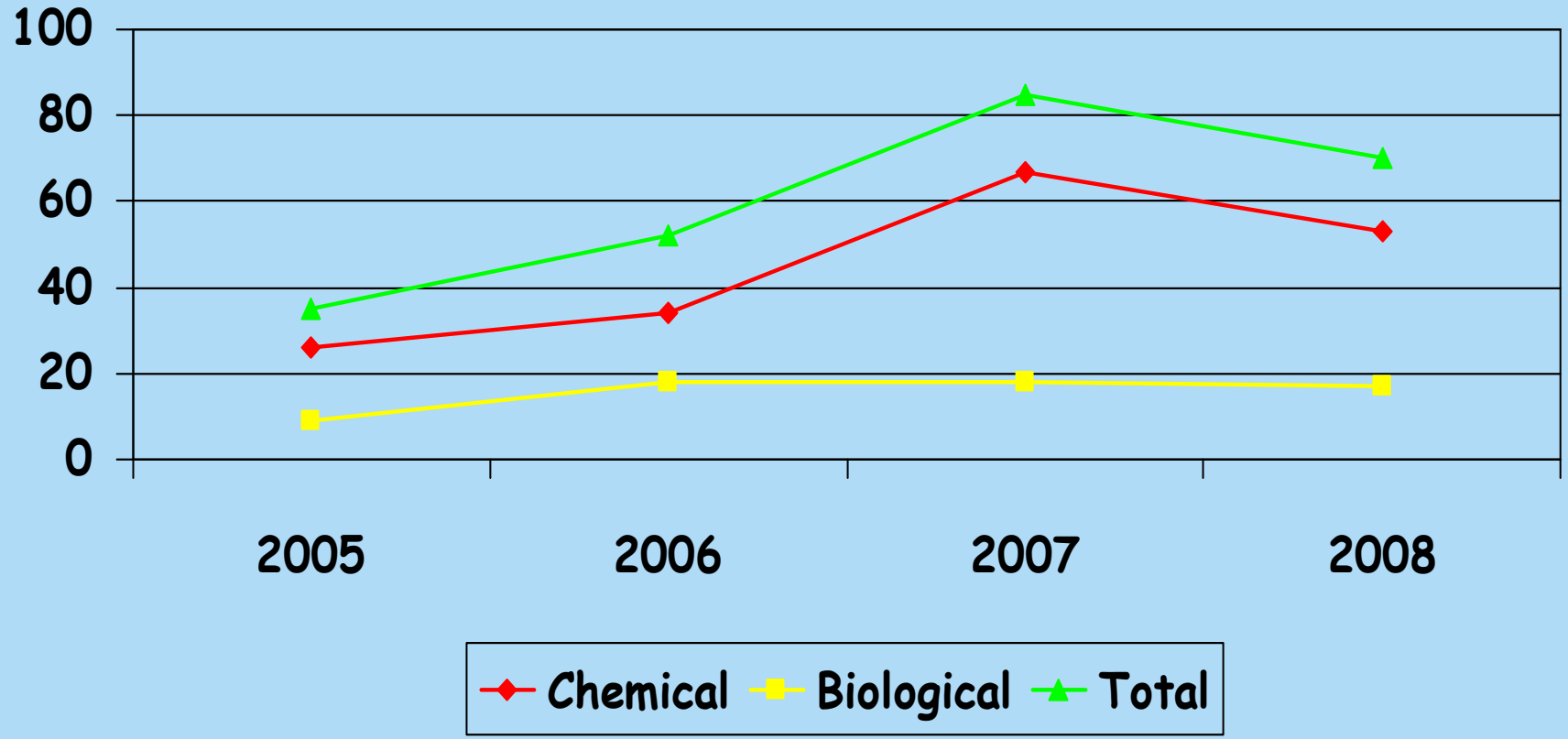
- The MHRA to seek advice from an Expert Advisory Group (EAG) and CHM before approval of trials involving certain types of molecules can be given.

- MHRA target is to provide applicants with pre-submission feedback, obtain EAG/CHM advice and provide a notification to applicants within 30 days.

UK CTA application numbers



UK First in Human CTA numbers



EAG FIH trials:

2007 6

2008 1

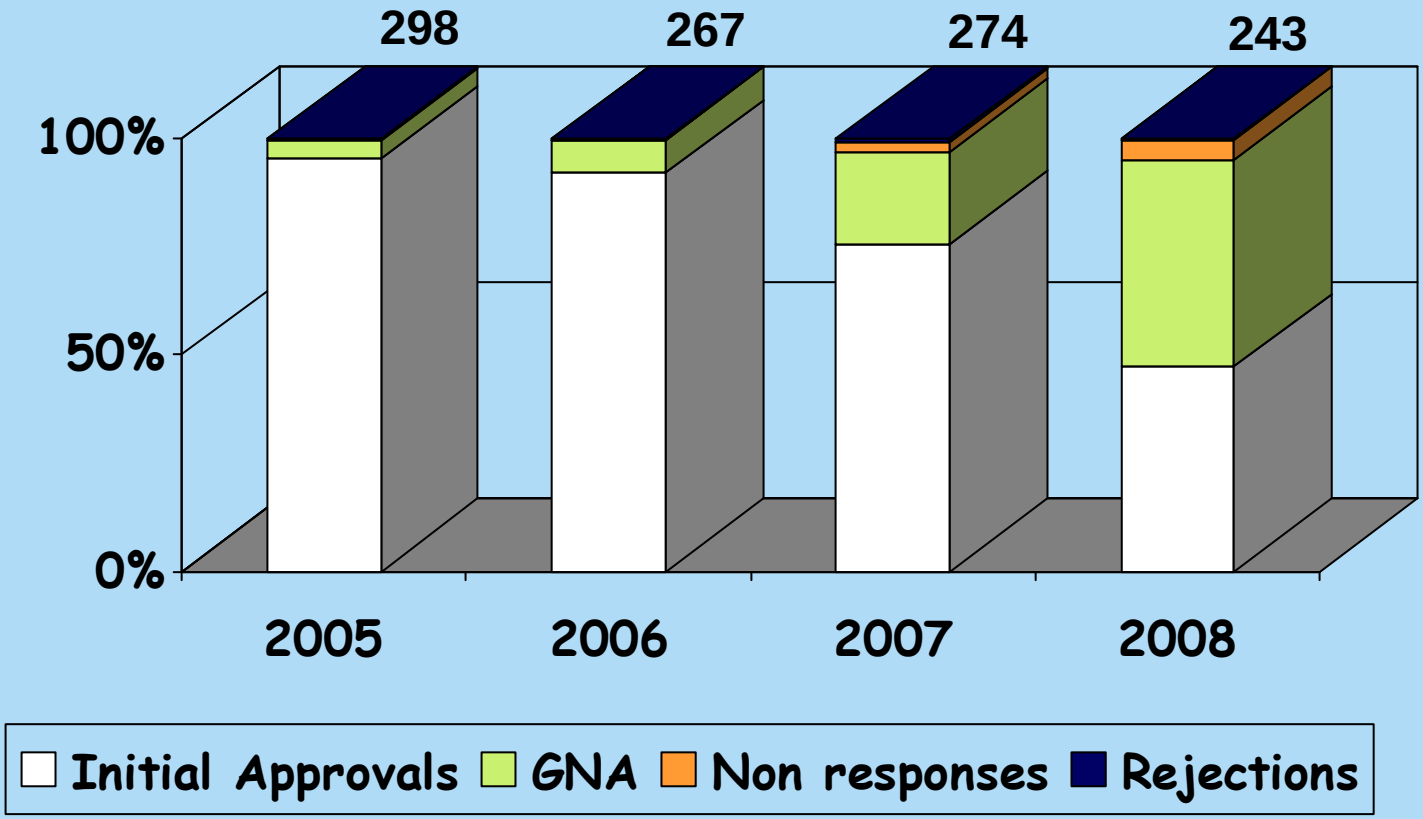
Validation issues

Approximately 15% applications fail initial validation

Main reasons:

- Paper submission (10%)
- CD errors (17%)
- Wrong application form (7%)
- Files not OCR (12%)
- Application form not signed (12%)
- No xml file (6%)
- Missing Documents (18%),
  (including missing application forms or protocol)

Phase 1 CTA outcomes



Phase 1 CTA outcomes

	2005	2006	2007	2008
Ph 1 CTAs received	298	267	274	243
Initial Approval	284	247	215	121
GNA	14	20	59	122
Non responses	1	0	6	12
Rejections	0	1	2	1

Outcome of Assessment

- The result of the assessment is either:
  - acceptance (with or without conditions) or
  - a request for further information (this request is received by the sponsor in the form of a 'Grounds for Non-Acceptance letter).
- In the almost all cases, this additional information allows the application to be accepted.
- Where the information is not acceptable (or no response is submitted) the application is rejected.

Determination Outcome

Period covered 1st March – 31st March 08

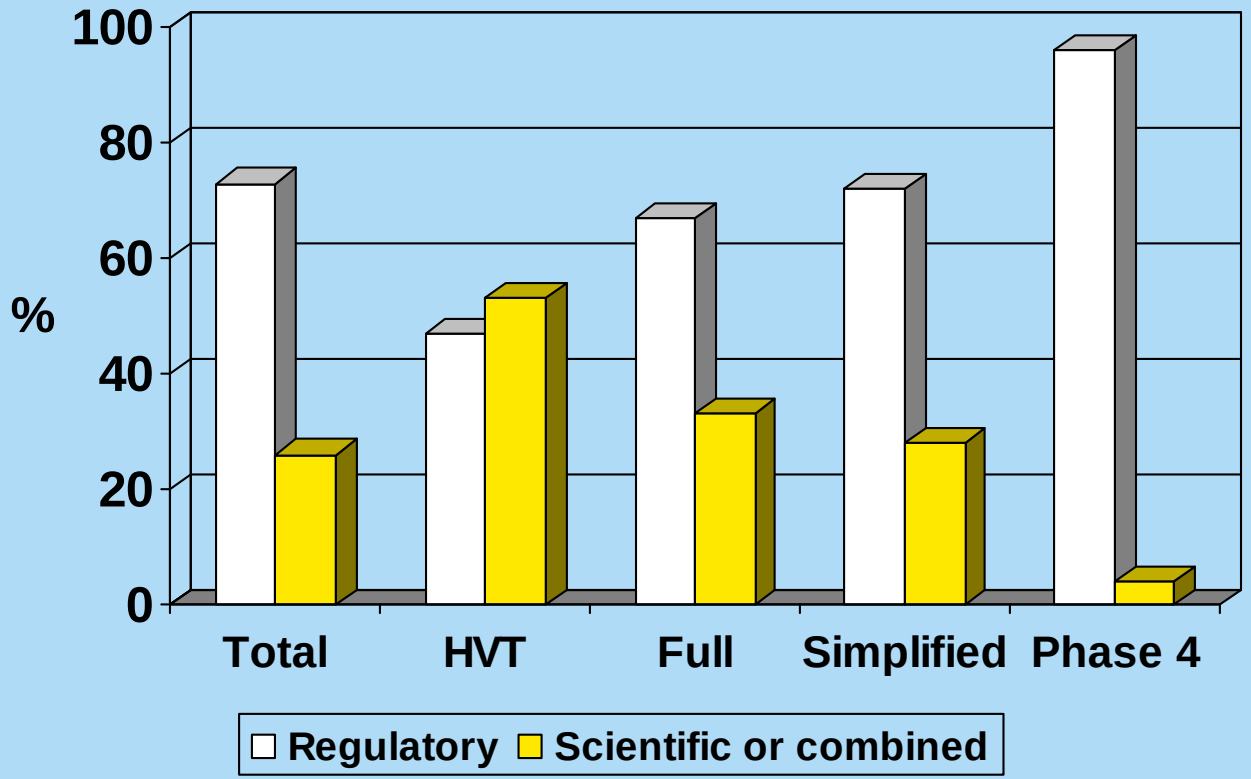
Total	109	
Approved	46	
GNA	63	(58%)
Regulatory	27	(42%)
Scientific or combined	36	(58%)

Determination Outcome

Period covered 1st July – 31st July 08

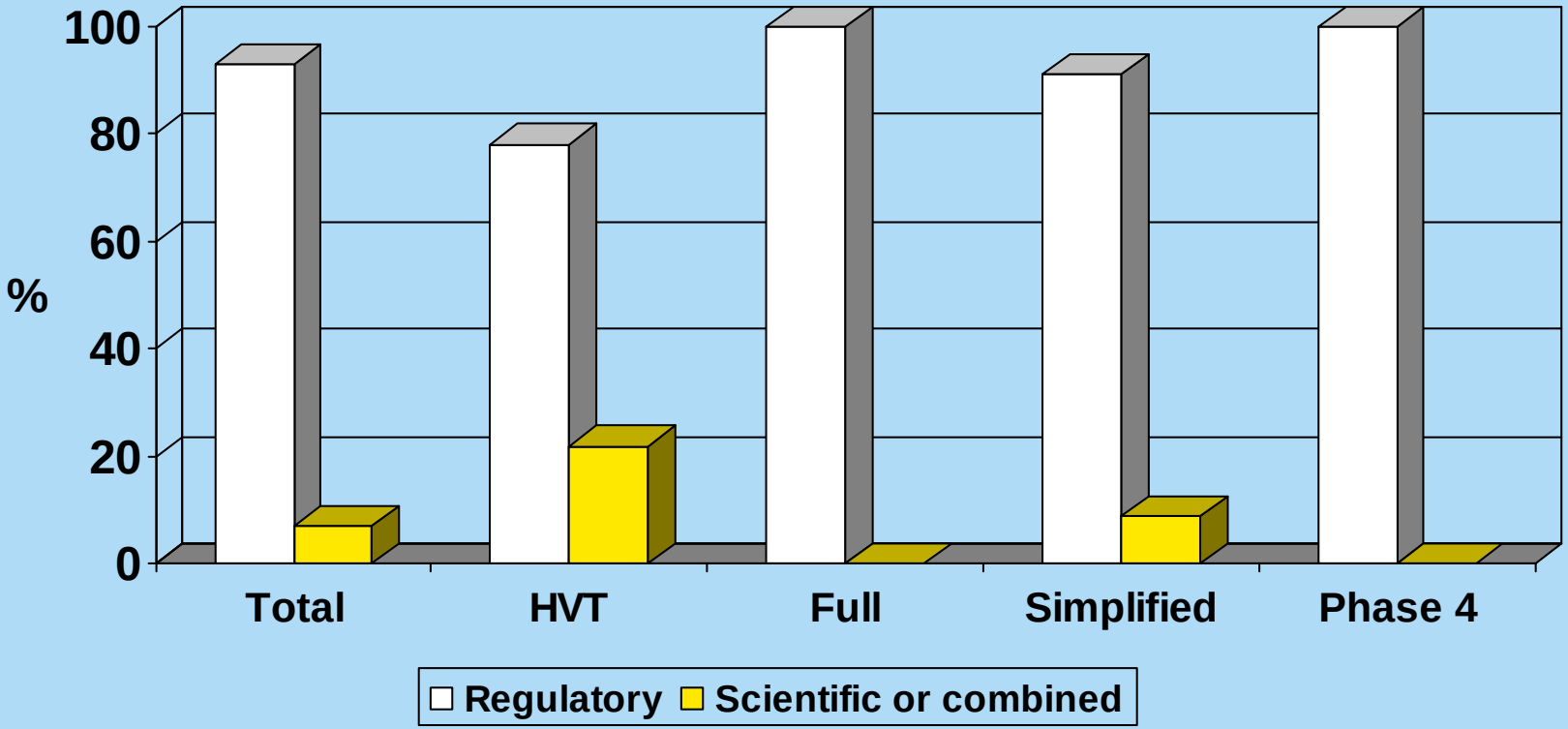
Total received	123	
Approved	52	
GNA	71	(58%)
Regulatory	52	(73%)
Scientific or combined	19	(27%)

GNAs in July 2008



Total applications - 123
58% of applications had GNA

GNAs in Nov 2008



45.5% of applications had GNA

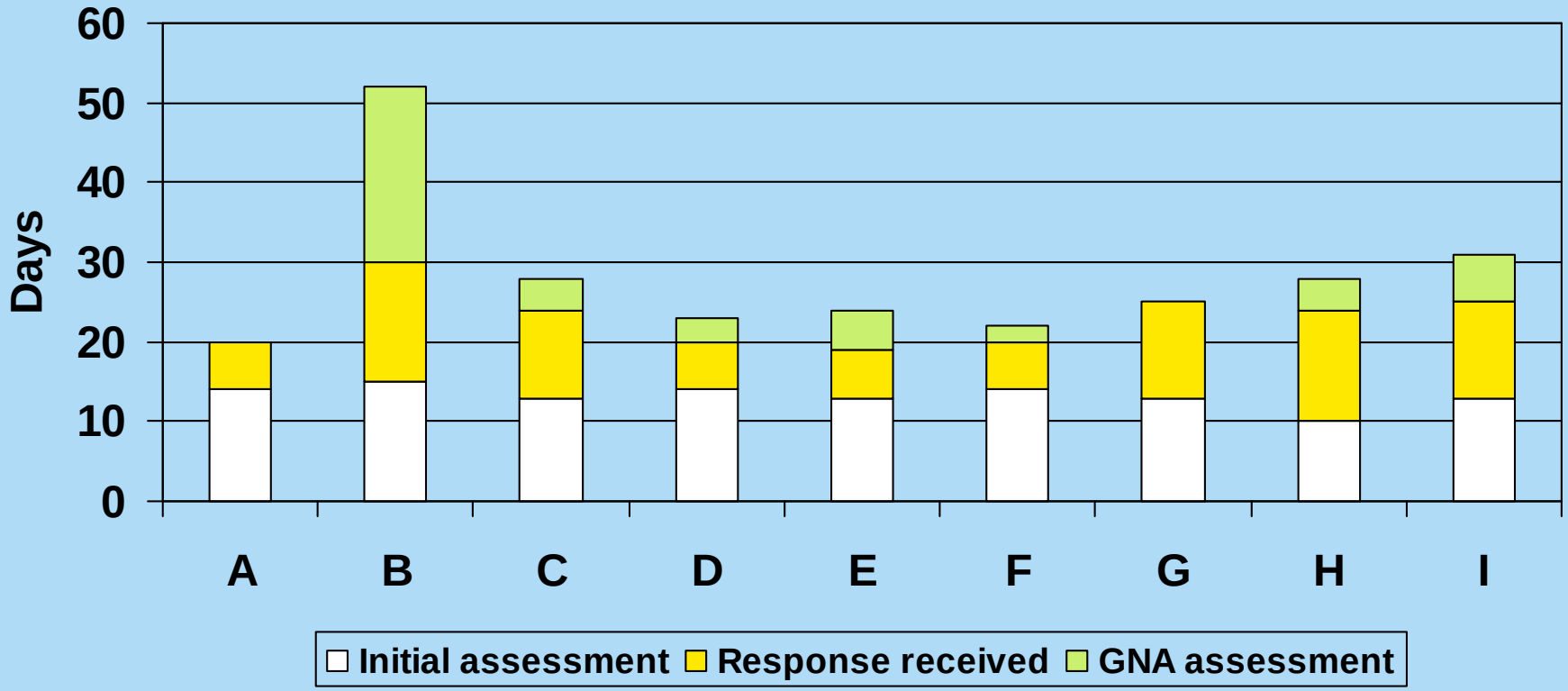
Avoidable Reasons for RFI requests (GNA)

- Of all letters sent to request further information, around half were to request basic information which should have been included in the initial application.
  - **Manufacturers Authorisation missing/clarification required (32%)**
  - **Labelling missing or requiring revision (20%)**
  - **QP declaration required (18%)**
  - **SUSAR/ADR provisions missing from protocol (12%)**
  - **Protocol inaccuracies (re IB or SmPC) (12%)**
  - **Application form inaccuracies (10%)**

Examples of RFI points for HVT trials and impact on timelines:

Sponsor type	*Initial assessment*	*Response received*	*Final decision*	*Day of approval*	*Days delayed*	*RFI Points*
Commercial	14 days	6 days	0 days	20 days	6 days	Batch analysis data missing Justification of storage conditions required
Commercial	15 days	15 days	22 days	52 days	37 days (2^{nd} response required)	Excipient information missing MIA(IMP) missing Rationale for choice of study participants and study duration required Protocol revision required
Commercial	13 days	11 days	4 days	28 days	15 days	Specification missing QP release clarification required
Commercial	14 days	6 days	3 days	23 days	9 days	Revision of contraceptive precautions required
Commercial	13 days	6 days	5 days	24 days	11 days	Protocol revision/justification required regarding stopping criteria
Commercial	14 days	6 days	2 days	22 days	8 days	Batch analysis data required Shelf life to be defined
Commercial	13 days	12 days	0 days	25 days	12 days	Clarification of storage conditions required
Commercial	10 days	14 days	4 days	28 days	18 days	Clarification required for dose escalation
Non commercial	13 days	12 days	6 days	31 days	18 days	Protocol revision required for safety monitoring/reporting

Impact on time taken to final approval



November 2008

April 2009

Scientific Reasons for RFI requests (GNAs)

IMP dossier/IB data required	23 (21.7%)
Protocol revisions	
· Safety monitoring	9 (8.5%)
· Contraception/lactating women/WOCBP	8 (7.5%)
· Follow up provisions missing/insufficient	5 (4.7%)
· Dose level or duration	5 (4.7%)
· Other major revisions	8 (7.5%)

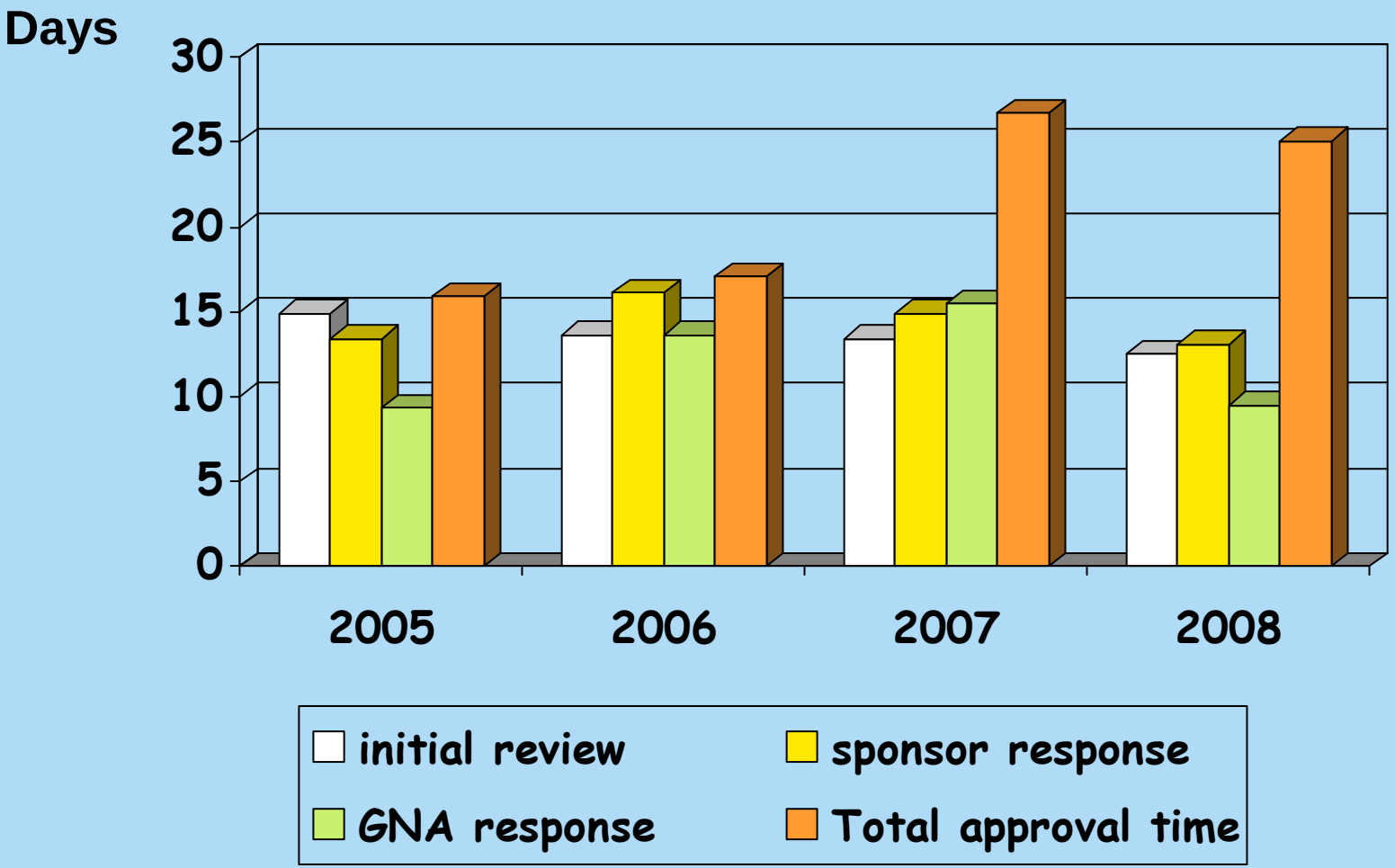
10 questions for Phase 1 applications

- A discussion of the function of the target in man.
- A discussion of the ability of the subject to maintain a normal physiological response to challenge in the presence of the investigational product.
- A discussion for the transition from preclinical to human testing, particularly with regard to highly species specific molecules
- A discussion of the potential for on-target and off-target effects and how this will be handled in the clinic
- A discussion of the doses used in the relevant animal species (particularly with regard to the use in the animal model of the starting dose to be administered to man)

10 questions for Phase 1 applications

- A rationale for the starting dose in man (including, for example receptor occupancy)
- A rationale for the study population (particularly for the use of healthy volunteers)
- A rationale for the administration schedule for the initial and subsequent cohorts. This should include the time interval between doses administered to individual subjects
- A rationale for the dose escalation particularly with regard to potential adverse effect.
- A rationale for the proposed trial site, including the facilities available.

Phase 1 review times



Phase 1 review times (days)

	2005	2006	2007	2008
Ph 1CTAs received	298	267	274	243
Initial review	14.9	13.6	13.4	12.5
Sponsor response	13.4	16.1	14.9	13.1
GNA response review	9.3	13.6	15.5	9.5
Total approval time	15.9	17.1	26.7	25.1

Phase 1 Substantial Amendments

2008	Numbers	Average Time (days)	Range (days)
Amendments requiring assessment	369	14.5	1 - 40
Admin only	102	3.6	1 - 31

Targets:

Agreed: 14 days

Statutory: 35 days

EAG Trials

	2007	2008
FIH (n)	6	1
Average assessment times:		
Initial assessment (days)	33.3	47
Sponsor response (days)	24.4	19.7
Second assessment (days)	23.7	14.3

All have required some additional information from sponsor

6 approved, 1 rejected

How to improve Early Phase applications

1. Quality control CTA application content to avoid the 'avoidable' GNA points

2. Address the 10 questions for all Phase 1 applications to help ensure all scientific points are covered